

Single Technology Appraisal

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

Contents:

The following documents are made available to stakeholders:

Access the [final scope](#) and [final stakeholder list](#) on the NICE website.

- 1. Company submission** from Ipsen
- 2. Company summary of information for patients (SIP)** from Ipsen
- 3. Clarification questions and company responses**
 - a. Clarification response
 - b. Clarification addendum
- 4. Patient group, professional group and NHS organisation submissions** from:
 - a. Insulinoma Support Network
 - b. Neuroendocrine Cancer UK
 - c. UK & Ireland Neuroendocrine Tumour Society
- 5. Expert personal perspectives** from:
 - a. Dr Charlotte Fribbens – clinical expert, nominated by UK & Ireland Neuroendocrine Tumour Society
 - b. Dr Debashis Sarker – clinical expert, nominated by Ipsen
 - c. Clinical expert, nominated by Ipsen
 - d. Enola Wright – patient expert, nominated by Insulinoma Support Network
- 6. External Assessment Report** prepared by BMJ Technology Assessment Group
- 7. External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment

ID6474

Company evidence submission

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Abbreviations

Abbreviation	Definition
1L/2L	First line/second line
¹⁷⁷ Lu-dotatate	¹⁷⁷ Lutetium-dotatate
5-FU	5-fluorouracil
ADTTE	Analysis of Delayed Time-to-Event
AE	Adverse event
AIC	Akaike Information Criterion
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BIC	Bayesian Information Criterion
BIRC	Blinded Independent Review Committee
BNF	British National Formulary
BOR	Best overall response
BSA	Body surface area
BSC	Best supportive care
CAP	Capecitabine
CAPTEM	Capecitabine and temozolomide
CCT	Concomitant therapy
CE	Conformité Européenne
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Cycle length
CMH	Cochran–Mantel–Haenszel
CR	Complete response
CRF	Case report form
CS	Carcinoid syndrome
CSR	Clinical study report
CT	Computed tomography
DCO	Data cut-off
DCR	Disease control rate
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSMB	Data and Safety Monitoring Board
DSU	Decision support unit
DTC	Differentiated thyroid cancer
EAG	External assessment group
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture

Abbreviation	Definition
EMA	European Medicines Agency
ENETS	European Neuroendocrine Tumor Society
EORTC	European Organisation for Research and Treatment of Cancer
pNET	Extra-pancreatic neuroendocrine tumour
EQ-5D	EuroQol-5 dimension
ESMO	European Society for Medical Oncology
ETM	Event to monitor
FDA	Food and Drug Administration
FOLFOX	Folinic Acid, Fluorouracil, and Oxaliplatin
G	Grade
GEP NET	Gastroenteropancreatic neuroendocrine tumour
GI NET	Gastrointestinal neuroendocrine tumour
HCC	Hepatocellular carcinoma
HCRU	Healthcare and resource use
HPF	High-power field
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HSE	Health Survey England
ICER	Incremental cost-effectiveness ratio
IFN- α	Interferon alpha
IM	Intramuscular
INHB	Incremental net health benefit
IP	Investigational product
IPCW	Inverse probability of censoring weights
IPD	Individual patient data
IQR	Interquartile range
IRP	International Recognition Procedure
ITT	Intention-to-treat
IWRS	Interactive web response system
IxRS	Interactive voice/web response system
KM	Kaplan-Meier
LAR	Long-acting release
LCNEC	Large cell neuroendocrine carcinoma
LMWH	Low molecular weight heparin
LR	Log-rank test
LYG	Life-years gained
MAIC	Matching-adjusted indirect comparison
MET	Mesenchymal-epithelial transition
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	Magnetic resonance imaging

Abbreviation	Definition
mTOR	Mammalian target of rapamycin
NA	Not applicable
NCI	National Cancer Institute
NCRAS	National Cancer Registration and Analysis Service
NEC	Neuroendocrine carcinoma
NEN	Neuroendocrine neoplasm
NET	Neuroendocrine tumour
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
NPACT	Non-protocol anticancer therapy
NSCLC	Non-small cell lung cancer
ONS	Office for National Statistics
OPEN	Oncology Patient Enrollment Network
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressed disease
PF	Progression-free
PFS	Progression-free survival
PGIC	Patient Global Impression of Change
PH	Proportional hazards
PICO	Population, intervention, comparator, outcome
pNET	Pancreatic neuroendocrine tumour
PPE	Palmar-plantar erythrodysesthesia
PPS	Post-progression survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROs	Patient reported outcomes
PRRT	Peptide receptor radionuclide therapy
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal social services
PSSRU	Personal social services research unit
QALE	Quality-adjusted life expectancy
QALY	Quality-adjusted life year
QD	Once daily
QLQ	Quality of Life Questionnaire
QoL	Quality of life
RCC	Renal cell carcinoma

Abbreviation	Definition
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response evaluation criteria in solid tumors
RET	Rearranged during transfection
RoB	Risk-of-bias
RPSFTM	Rank preserving structural failure time model
RTK	Receptor tyrosine kinase
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SCLC	Small cell lung cancer
SD	Stable disease
SD	Standard deviation
SEER	Surveillance, epidemiology, and end results
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SOC	Standard of care
SSA	Somatostatin analogue
SSTR	Somatostatin receptor
STM	State transition model
STZ	Streptozotocin
TA	Technology appraisal
TEM	Temozolomide
TH	Time horizon
TKI	Tyrosine kinase inhibitor
TLR	Targeted literature review
TNM	Tumour, node, metastasis
ToT	Time on treatment
TRAE	Treatment-related adverse event
TSD	Technical support document
TTD	Time to treatment discontinuation
TTO	Time trade-off
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WBC	White blood cell
WHO	World Health Organization
WTP	Willingness to pay

1 Decision problem, description of the technology and clinical care pathway

1.1 *Decision problem*

The anticipated marketing authorisation extension for cabozantinib in the indication under consideration is [REDACTED]

[REDACTED] The target population addressed in this submission is in line with the full marketing authorisation.

In line with the Phase III CABINET randomised controlled trial (RCT), which provides the pivotal evidence base for this submission, systemic therapy with regards to the marketing authorisation is defined as:²

- pNET: everolimus, sunitinib, or peptide receptor radionuclide therapy (PRRT); the PRRT regimen approved in the UK is lutetium oxodotreotide (¹⁷⁷Lu-dotatate)
- epNET:
 - GI (gastrointestinal) NET: everolimus or PRRT
 - Lung NET: everolimus

Prior treatment with somatostatin analogues (SSAs) alone is not sufficient to meet the definition of prior systemic treatment. The decision problem addressed within this submission is outlined in Table 1.

Cabozantinib offers a new systemic therapy to delay disease progression and improve prognosis in a patient population that has limited treatment options post-progression. Unlike existing targeted therapies, the broad anticipated marketing authorisation means cabozantinib offers a treatment option that is not restricted to any specific subgroup.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with advanced pancreatic or extra-pancreatic neuroendocrine tumours (pNETs or epNETs) that have progressed after systemic treatment	As per the NICE final scope	N/A. The target population addressed in this submission is in line with the full marketing authorisation and the population enrolled in the Phase III CABINET trial.
Intervention	Cabozantinib	As per the NICE final scope	N/A
Comparator(s)	Established clinical management without cabozantinib, including but not limited to: • Best supportive care (BSC) • Chemotherapy • Other systemic treatments	Best supportive care	BSC represents the appropriate comparator for cabozantinib in this indication. Chemotherapy and other systemic treatments are not considered appropriate comparators for cabozantinib. NETs are heterogenous with treatment informed by a broad range of characteristics such as functional status, somatostatin receptor (SSTR) status, differentiation (well/moderate or poor), the location of primary tumour site, Ki-67 scores and tumour grade (G1, G2 or G3).³⁻⁵ This heterogeneity is reflected in the relatively narrow labels of the currently licensed systemic treatment options.^{3, 4} Somatostatin analogues (SSAs), such as lanreotide, are licensed for the treatment of Grade 1 and a subset of Grade 2 (Ki-67 index up to 10%) gastroenteropancreatic neuroendocrine tumours (GEP-NETs) of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable or metastatic disease.⁸⁵ SSAs are typically administered at first-line, except in the case of Grade 3 NETs, and are typically continued concomitantly alongside other systemic therapies.⁶⁻¹¹ Subsequent systemic therapies are restricted to specific subgroups on the basis of primary tumour site, grade, SSTR expression status and functional status, and can include everolimus (for progressive pNETs and non-functional progressive GI and lung NETs), sunitinib (for progressive pNETs only) and peptide receptor radionuclide therapy (PRRT) ¹⁷⁷Lu-dotatate (for SSTR-positive progressive GEP NETs).^{3, 4}

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			Given the heterogeneity of the disease and the narrow labels for available systemic treatment options, systemic therapy after progression on SSAs is highly individualised and driven by specific patient characteristics, and there is no clear or consistent treatment pathway. Chemotherapy regimens such as capecitabine and temozolomide (CAPTEM) are considered for off-label use, with the evidence base for their use made up of retrospective or small trials with diverse patient populations. The high treatment burden associated with chemotherapy, as well as the lack of robust efficacy data, means chemotherapy is not commonly used in the wider well-differentiated NETs population for which cabozantinib is indicated (largely Grade 1 and 2). Chemotherapy was not considered an appropriate comparator in both TA449 and TA539 based on clinical feedback that its use is typically reserved for higher-grade NETs (e.g., Grade 3 tumours with high Ki-67).^{3, 4, 12} As such, for many patients who have progressed on SSAs and subsequent systemic therapy, the only remaining treatment option is BSC. Cabozantinib is anticipated to be used in UK clinical practice in line with the population enrolled in the CABINET trial, which informed the anticipated marketing authorisation for cabozantinib in this indication and which reflects the population with the highest unmet need for new treatment options. The inclusion criteria for CABINET specified that patients were eligible if they had progressed on at least one prior systemic therapy such as everolimus, sunitinib or PRRT.¹³ CABINET enrolled heavily pre-treated patients with pNETs and epNETs (patients in the cabozantinib arms had received a mean of 2.7 and 1.9 prior systemic treatments, excluding SSAs, in the pNET and epNET cohorts, respectively).^{2, 13} The trial otherwise had broad eligibility criteria, including patients irrespective of SSTR status, functional status and tumour grade. In line with the CABINET trial population, cabozantinib is anticipated to be considered as a treatment option after other targeted systemic

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			treatments in UK clinical practice, with the number and type of prior treatments differing according to individual patient characteristics (for example, everolimus is the only systemic treatment currently recommended in lung NETs). Accordingly, clinical experts experienced in the treatment of NETs consulted for this submission confirmed that the appropriate comparator for cabozantinib on the basis of its marketing authorisation and the CABINET trial is BSC. Furthermore, no relevant randomised controlled trials (RCTs) investigating other systemic therapies were identified in the systematic literature review (SLR) (with the exception of two small studies based in China investigating surufatinib versus everolimus or sunitinib); RCTs investigating other systemic treatments used in UK clinical practice were excluded on the basis that less than 70% of patients had received a relevant prior line of therapy, and thus the enrolled population could not be considered comparable to CABINET.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • symptom control • adverse effects of treatment • health-related quality of life	As per the NICE final scope	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness	• The cost-effectiveness of cabozantinib versus BSC has been evaluated, in line with the NICE reference case • The time horizon for assessing costs was set to a lifetime horizon, which is sufficiently long to capture the majority of costs and benefits associated with the	N/A

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	should be sufficiently long to reflect any differences in costs out outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services (PSS) perspective.	use of cabozantinib - Costs were considered from an NHS and PSS perspective - A patient access scheme (PAS) for cabozantinib was included in the analysis	
Subgroups to be considered	If the evidence allows the following subgroups will be considered: - Pancreatic NETs - Extra-pancreatic NETs (including by tumour location) - Other characteristics of NETs (for example, functioning status, differentiation status, Ki-67 index and somatostatin receptor expression)	The following subgroups are considered in the economic model, informed by the randomised, ITT cohorts of the CABINET trial: - Pancreatic NETs - Extra-pancreatic NETs Prespecified subgroup analyses for the primary endpoint (progression-free survival [PFS]) are presented for key patients characteristics, including primary tumour site in epNETs (midgut GI/unknown versus non-midgut GI/lung/other), tumour grade and differentiation status. Post-hoc subgroup analyses are presented for PFS by specific tumour location in epNETs (i.e. lung, GI tract or other) for completeness, but are not sufficiently robust to inform decision-making. Subgroup analysis by other characteristics of NETs (functional status, Ki-67 index and somatostatin	The CABINET trial included separate cohorts of patients with pNETs and epNETs populations, which form the ITT populations and for which the trial was powered. Clinical and cost-effectiveness evidence has been presented for these cohorts separately throughout the submission. Randomisation in the pNET cohort was stratified according to concurrent SSA use (yes or no) and receipt of prior sunitinib therapy (yes or no). Randomisation in the epNET cohort was stratified according to primary tumour site (midgut GI/unknown versus non-midgut GI/lung/other) and concurrent SSA use (yes or no). Subgroup analyses were prespecified for the primary endpoint (PFS) to determine how the treatment effect varied across different key subgroups and are presented in the submission. Notably, however, these subgroup analyses were not powered to show differences between cabozantinib and placebo. Subgroup analysis of the epNETs cohort by specific tumour location (i.e. lung, GI tract or other) was not pre-specified. Post-hoc subgroup analysis for PFS and OS by specific tumour location have been presented for completeness but are subject to high risk of bias due to small patient numbers and breaking of randomisation, and results are inconsistent with the stratified subgroup analysis by primary tumour site (midgut GI/unknown versus non-midgut GI/lung/other). Therefore, these subgroup analyses are not sufficiently robust for decision-making and are not included in the economic model.

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		receptor expression) were not pre-specified and are not available.	Subgroup analysis by other characteristics of NETs, including functional status, Ki-67 index (or grade) and somatostatin receptor expression, were not pre-specified and are not available. However, the SSTR negative population is very small, and thus any subgroup analysis based on SSTR status would be limited by small patient numbers. Unlike the SSAs and PRRT, the mechanism of action of cabozantinib does not target SSTR-expressing tumour cells, so there is no clinical rationale that SSTR status is treatment effect-modifying. Approximately one in six patients in the pNET cohort and one in three patients in the epNET cohort had known functional tumours, respectively. Cabozantinib demonstrated statistically significant PFS in both cohorts, demonstrating compelling efficacy irrespective of functional tumour status.
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	Ipsen do not consider there to be any equality concerns related to this appraisal. Cabozantinib does not present any issues to the NICE's commitment of promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.	N/A

Abbreviations: BSC: best supportive care; CAPTEM: capecitabine and temozolomide; epNET: extra-pancreatic neuroendocrine tumour; G1: Grade 1; G2: Grade 2; G3: Grade 3; GEP NET: gastroenteropancreatic neuroendocrine tumour; GI: gastrointestinal; ITT: intention-to-treat; Ki-67: antigen Kiel-67; NET: neuroendocrine tumour; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PAS: Patient Assessment Scheme; PFS: progression-free survival; PRRT: peptide receptor radionuclide therapy; pNET: pancreatic neuroendocrine tumour; PSS: Personal Social Services; SSA: Somatostatin analogue; SSTR: somatostatin receptor; TA: Technology Assessment.

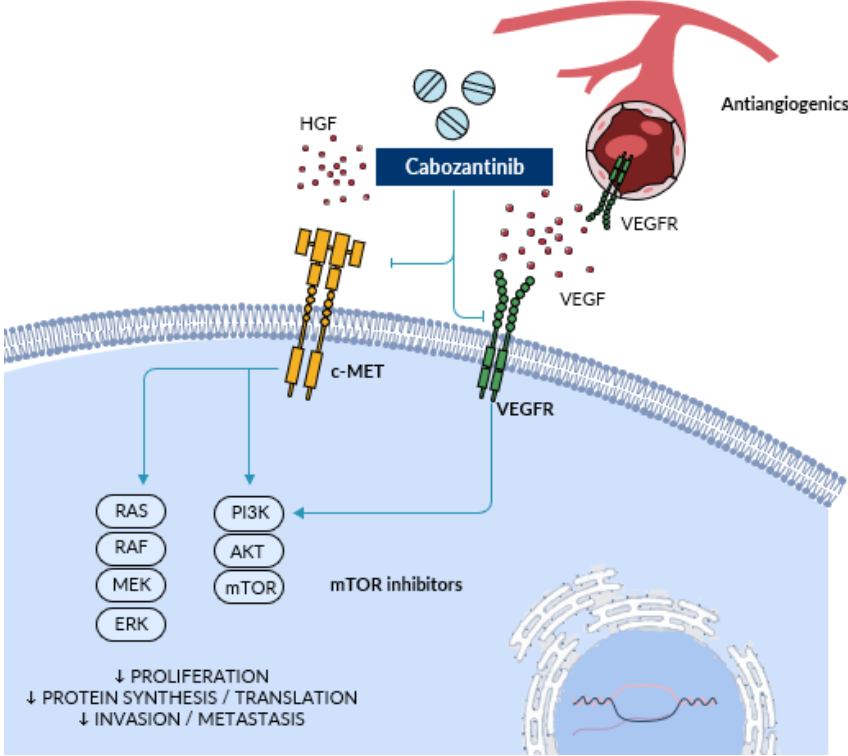
Source: Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID11613]. Final Scope.¹⁴

1.2 Description of the technology being evaluated

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements associated with cabozantinib are presented in Table 2.

Table 2: Technology being evaluated

UK approved name and brand name	Cabozantinib (Cabozantinib Ipsen)
Mechanism of action	Cabozantinib is an orally administered, third-generation small molecule that inhibits the enzymatic activity of multiple tyrosine kinases with a broader target profile than other tyrosine kinase inhibitors (TKIs) currently available for treatment of patients with neuroendocrine tumours (NETs). The molecular pathways that lead to the development and metastasis of NETs are not well defined. Several studies have demonstrated a key role for angiogenesis and vascular endothelial growth factor (VEGF) signalling pathways across NET populations, which make the NETs highly vascularised.^{15, 16} Over-expression of VEGF has been demonstrated in pNETs and epNETs.^{16, 17} c-MET signalling may additionally be involved in the molecular pathways that are characteristic of NETs. Preclinical studies have confirmed the role of c-MET activation in stimulating the growth of NETs and demonstrated that inhibition of c-MET is a potential pathway for treatment.¹⁸⁻²¹ Other signalling pathways such as mTOR and RET have also been shown to be involved in the development of NETs.^{22, 23} Cabozantinib has a unique mechanism of action by targeting receptor tyrosine kinases (RTKs) including VEGFR2, RET, MET, and AXL. These RTKs are implicated in tumour growth, angiogenesis and cancer cell invasion or metastasis.^{18, 19, 21, 24} Pre-clinical models in NETs have demonstrated a potent inhibition of VEGFR2, RET, MET and AXL by cabozantinib.^{18-21, 25} NETs are highly vascularised tumours, and the combined inhibition of angiogenesis and receptor TKIs, particularly VEGFR, has been shown to be an effective strategy in the treatment of advanced NETs.^{15, 16} Figure 1 further illustrates the mechanism of action of cabozantinib, including downstream signalling pathways. The simultaneous targeting of these multiple key pathways by cabozantinib may provide enhanced anti-tumour effects and reduce the risk of progressive disease compared to agents that target only one of these pathways.²⁶ Cabozantinib is already used as a targeted treatment across multiple indications including renal cell carcinoma (RCC), hepatocellular carcinoma (HCC) and differentiated thyroid cancer (DTC).¹

	Figure 1: Mechanism of action of cabozantinib  Adapted from Corti 2023.²⁷ Sources: Adapted from Bai 2022²⁸ and Corti 2023,²⁷ Garcia-Alvarez 2021.²⁹
Marketing authorisation/CE mark status	A marketing authorisation IRP Route A application to the MHRA for a license in Great Britain will be made in [REDACTED] for [REDACTED]. The anticipated marketing authorisation from the MHRA is expected in [REDACTED]. Positive opinion from the CHMP is due in [REDACTED], with marketing authorisation from the EMA expected in [REDACTED].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Indication of interest in this evaluation Cabozantinib is anticipated to be indicated as a monotherapy for [REDACTED] Other current indications: <u>Renal cell carcinoma</u> - As monotherapy for patients with advanced RCC, for the first line (1L) treatment of adult patients with intermediate or poor risk, or in adults following prior VEGF-targeted therapy (i.e. 2L treatment) - In combination with nivolumab for 1L treatment of adult patients with advanced RCC <u>Hepatocellular carcinoma</u> - Cabozantinib is indicated as monotherapy for HCC in adults who have previously been treated with sorafenib <u>Differentiated thyroid carcinoma</u> - Cabozantinib is indicated as monotherapy for adult patients with locally advanced or metastatic DTC, refractory or not eligible to radioactive iodine who have progressed during or after prior systemic therapy

	Restrictions Contraindications include hypersensitivity to the active substance or to any of the excipients. For full details of the warnings and precautions for the use of cabozantinib, please refer to the SmPC. ¹
Method of administration and dosage	Cabozantinib 60 mg tablet orally administered once daily. Management of suspected adverse drug reactions may require temporary treatment interruption and/or dose reduction. When dose reduction is necessary, it is recommended to reduce to 40 mg daily, and then to 20 mg daily.
Additional tests or investigations	NA.
List price and average cost of a course of treatment	The list price of cabozantinib is: £5,143.00 (30 x 60 mg tablets) per 30 day pack. Cabozantinib is flat-priced meaning the other available strengths (20 mg and 40 mg) in the 30 tablet pack also have this list price. ³⁰
Patient access scheme (if applicable)	A confidential simple patient access scheme is available. The pack price under this scheme is [REDACTED] (a [REDACTED]).

Abbreviations: 1L: first line; 2L: second line; CHMP: Committee for Medicinal Products for Human Use; c-MET: transmembrane tyrosine kinase; CE: Conformité Européenne; DTC: differentiated thyroid carcinoma; EMA: European Medicines Agency; epNETs: extra-pancreatic neuroendocrine tumour; HCC: hepatocellular carcinoma; IRP: International Recognition Procedure; mg: milligram; MHRA: Medicines and Healthcare products Regulatory Agency; NET: neuroendocrine tumour; pNET: pancreatic neuroendocrine tumour; RCC: renal cell carcinoma; RET: rearranged during transfection; RTK: receptor tyrosine kinase; SmPC: summary of product characteristics; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor.

1.3 *Health condition and position of the technology in the treatment pathway*

Disease overview

- Neuroendocrine tumours (NETs) are a heterogeneous group of malignancies which typically present asymptotically,^{7, 31} and thus the majority of patients are diagnosed at an advanced stage of disease^{31,32}
- NETs can develop in most organs throughout the body with primary tumour sites often grouped into categories, such as pancreatic (pNETs) and extra-pancreatic (epNETs)
- Although NETs are considered to be rare, their incidence is increasing across most demographics, primary tumour sites and tumour grades^{33,34}
- Patients with progressive NETs have a poor prognosis in terms of survival, regardless of the primary tumour site³²
- The complex nature of NETs means disease classification involves a considerable number of clinicopathological assessments which are determined by tumour site, histologic characteristics and functional status^{7, 31}

Disease burden

- Advanced progressive NETs are associated with a significant disease burden due to symptomatic burden and the health-related quality of life (HRQoL) detriment associated with progression^{35, 36}
- Typically, NET patients often progress through multiple lines of therapy, with options often limited at later lines³⁷
- Existing treatments are also associated with burdens (e.g. toxicity associated with chemotherapy and ¹⁷⁷Lu-dotatate, as well as the negative impact on daily life caused by the administration of ¹⁷⁷Lu-dotatate)³⁸⁻⁴¹

Treatment pathway

- The aim of treatment for patients with unresectable or metastatic NETs is to control symptoms and delay disease progression⁷
- Somatostatin Analogues (SSAs) are often prescribed at first-line, except in the case of Grade 3 NETs, regardless of primary tumour location⁶⁻¹¹
- Due to the heterogeneity of NETs, the treatment pathways are complex and individualised and are based on disease characteristics such as primary tumour site, tumour growth rate, somatostatin receptor (SSTR) expression and functional status^{6, 7, 31}
- Subsequent systemic therapies are restricted to specific subgroups on the basis of primary tumour site, tumour grade, functional status and SSTR expression status, and can include everolimus (for progressive pNETs and non-functional progressive gastrointestinal [GI] or lung NETs), sunitinib (for progressive pNETs only) and lutetium oxodotreotide (¹⁷⁷Lu-dotatate, for SSTR-positive progressive well-differentiated Grade 1 and 2 gastroenteropancreatic [GEP] NETs)⁶⁻¹¹
- Given the heterogeneity of the disease and the narrow labels for available systemic treatment options, systemic therapy after progression on SSAs is highly individualised and driven by specific patient characteristics, and there is no clear or consistent treatment pathway^{6, 7, 31}
- Chemotherapy regimens such as capecitabine and temozolomide (CAPTEM) are considered for off-label use, but are typically reserved for higher-grade NETs (e.g., Grade 3 tumours with high Ki-67), and are not commonly used in Grade 1 and 2 well-differentiated NETs due to high treatment burden and lack of robust efficacy^{3, 4}
- There are limited treatment options following progression on SSAs and further systematic treatment, and for many patients the only remaining option is best supportive care (BSC)^{6, 7, 38, 41}

Unmet need

- Whilst there are several recommended systemic treatment options after SSAs, these are often restricted to specific subgroups^{3, 4}
- Furthermore, 55% of patients progress to second-line systemic therapy and 31% progress to

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third-line systemic therapy,³⁷ meaning there is a significant need for more, effective treatment options for patients who have progressed on prior therapies

- For patients with unresectable and metastatic NETs who have progressed after SSAs and subsequent systemic therapy, there is a significant unmet need for therapies that extend progression-free survival (PFS) post-progression regardless of primary tumour site, tumour grade and SSTR expression status (i.e. without restrictions to specific subpopulations)
- An effective treatment that delays progression would also delay the HRQoL detriment associated with further progression³⁶

Proposed position of cabozantinib

- The proposed indication for cabozantinib in this submission is for adult patients with [REDACTED]

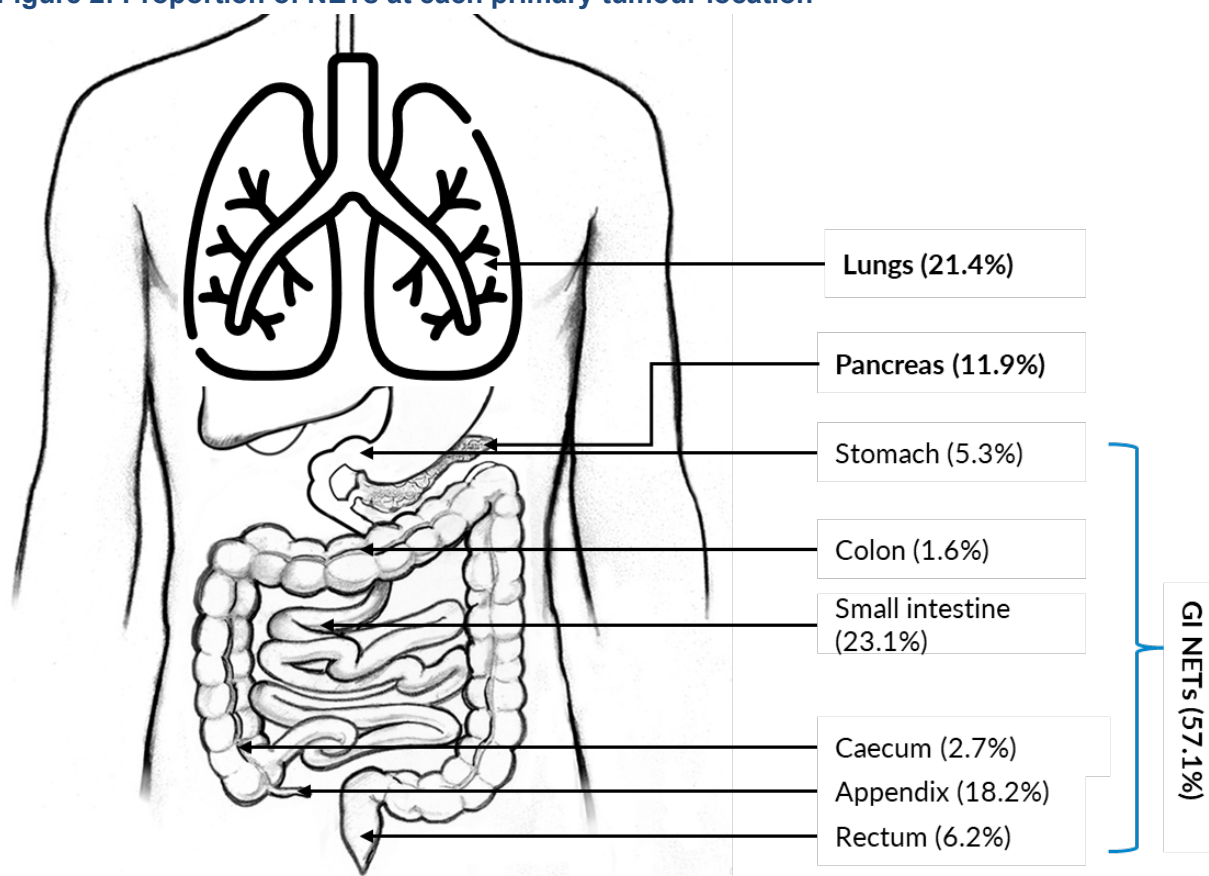
1.3.1 Disease Overview

Neuroendocrine neoplasms (NENs) are a rare and heterogenous group of malignancies arising from secretory cells of the neuroendocrine system in various organs.^{7, 31} NENs encompass both well-differentiated neuroendocrine tumours (NETs) and poorly differentiated neuroendocrine carcinomas (NECs).³¹ Well-differentiated tumours contain cancerous cells that mimic normal body cells whereas poorly differentiated tumours contain cancerous cells that look and behave differently to normal body cells.⁴² Further information on disease classification can be found in Section 1.3.2. Throughout this submission, where data specifically reporting on NETs relevant to the UK population were not available, data for NENs have been reported.

NETs are commonly indolent at onset, with a prolonged disease course and lower risk of distant metastasis than NECs. However, NET prognosis depends on several factors and varies between subpopulations. NECs, on the other hand, are always high-grade aggressive carcinomas with rapid disease progression.³¹ The majority of NENs are NETs, with NECs making up only 10–20% of all NENs.⁷

Due to the extensive presence of neuroendocrine cells in the human body, NETs can develop in most organs, as shown in Figure 2. NETs arise most often in the GI tract, lung, and pancreas,^{7, 31, 43} and may also occur in the breast, prostate, thymus and skin.³¹ Primary tumour sites can be grouped into categories, such as pNETs and epNETs (including lung NETs and GI NETs). GI NETs can be further stratified into midgut (jejunum, ileum and cecum) and non-midgut subtypes.^{44, 45} Midgut NETs are typically associated with classical carcinoid syndrome (classical symptomatic presentation, CS) and are the most common type of metastatic GI NETs.^{44, 45} The term epNETs is often used in the literature and refers to all NETs outside of the pancreas (e.g. GI NETs, lung NETs and other/unknown NET locations). In some cases, pNETs and epNETs (excluding lung NETs) can be grouped together and termed gastroenteropancreatic NETs (GEP NETs).

Figure 2: Proportion of NETs at each primary tumour location



Please note that the percentages presented above do not add up to 100%; the locations of the remaining ~31.7% of tumours were reported as other.

Abbreviations: GI: gastrointestinal; NET: neuroendocrine tumour.

Source: White, 2022 (Supplementary table MMC4).⁴⁶

Aetiology

The molecular pathways that lead to the development and metastasis of NETs are not well defined. However, angiogenesis, along with vascular endothelial growth factor (VEGF), mesenchymal-epithelial transition factor (cMET), mammalian target of rapamycin (mTOR) and rearranged during transfection (RET) signalling pathways, have been implicated in NET development and growth.^{15-22, 47}

Despite the uncertainty in the underlying molecular pathways for the development of NETs, there are several risk factors that can contribute to their development. A systematic review and meta-analysis of risk factors for NENs identified a family history of cancer as the most relevant risk factor across all sites analysed (including lung, stomach, pancreas, small intestine, colon and appendix). Body mass index, diabetes, cigarette smoking and alcohol consumption were also identified as potential risk factors for developing NENs.⁴⁸

Symptoms

pNETs and epNETs have distinct molecular genetics, and due to the complex and diverse origins of NETs, symptom presentation is varied and often non-specific. Symptoms depend on the location of the tumour: for example, bowel NETs may cause pain, diarrhoea, constipation, nausea, sickness and rectal bleeding. Lung tumours may cause (bloody) cough, wheezing,

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shortness of breath, chest pain and tiredness, whilst stomach NETs may cause pain, weight loss, tiredness and weakness.⁴⁹

The non-specific symptom presentation of NETs in early stages of the disease means the majority of NETs are diagnosed in older patients and at an advanced stage of the disease. A 2018 web-based survey of 303 NET patients in the UK reported the time from first symptom prior to diagnosis was 53.8 months, with 80% experiencing symptoms prior to diagnosis.⁵⁰ Furthermore, a 2014 global survey of 1,928 patients with NETs, predominantly based in North America (48%) and Europe (40%), reported that the median time from symptom onset to diagnosis was 52 months, with 29% of patients waiting over five years for an accurate diagnosis.³² Due to this delay in diagnosis, the majority (58%) of patients in this survey presented with metastatic disease at the time of diagnosis, demonstrating the need for effective treatment options in this advanced population who have poorer prognosis (see Section 1.3.5).³² This also means that a substantial proportion of patients with NETs may be diagnosed incidentally; a retrospective analysis of 399 German patients with GEP NETs treated between 1980 and 2004 estimated that 12.8% of patients were diagnosed incidentally.⁵¹ Similar studies have identified incidental diagnosis of NETs in up to 17% of patients.⁵²

Functional status

Some NETs may be functional, which contributes to the symptom burden of disease, or non-functional. Functional NETs are characterised by the hypersecretion of bioactive proteins and hormones from neuroendocrine cells, including serotonin, glucagon, insulin and gastrin. The presence of these excessive hormones in patients with functional NETs can lead to CS and other syndromes related to hormone excess.⁵³ These commonly cause symptoms including flushing and diarrhoea, as well as more serious complications such as heart failure.⁵³ A survey of 303 patients with NETs in the UK found that the first symptoms to appear across pNETs and small bowel NETs were pain (36%), flushing (24%) and diarrhoea (24%).⁵⁰

Functional NETs, and symptoms associated with CS, manifest in a substantial number of patients across pNET and epNET subpopulations. Studies have shown that CS occurs in ~20% of patients with epNETs and ~70% have functional tumours;^{7, 54, 55} meanwhile, it is estimated that 30–40% of patients with pNET have functional tumours.^{7, 54, 56} Midgut NETs are also associated with classical CS in comparison to non-midgut NETs which can either be functioning or non-functioning.⁴⁴ This results in a huge symptomatic burden for patients and an associated with a reduction in quality of life.

Epidemiology

NETs are rare, with a prevalence of 34.9 per 100,000 people in England. NENs, have an incidence of approximately 4.8 per 100,000 people.^{33, 57} However, their incidence is steadily increasing globally across most demographics, disease subtypes, primary tumour sites and tumour grades.^{33,34} In England, the age-adjusted incidence of NENs increased 3.7-fold between 1995 and 2018 from 2.35 to 8.61 per 100,000.⁴⁶

The median age for patients with NETs in England, estimated from National Cancer Registry and Analysis Service (NCRAS) data, is 62 (interquartile range [IQR]: 64-73).⁴⁶ Although the NET population is 52.2% female, certain primary tumour sites such as GI NETs, have been shown to be more prevalent in males.⁴⁶

1.3.2 Disease classification, staging and diagnosis

Due to the complex nature of NETs, disease classification is multifaceted, involving various clinicopathological assessments.^{7, 31} NETs are initially classified by primary tumour site (such as pNETs), followed by histologic characteristics (which determine tumour grade), tumour stage (as determined by the tumour, node metastasis [TNM] staging system, defined below) and functional status.⁷ Combinations of these factors define heterogeneous and individualised treatment pathways and influence rates of progression and survival.^{6, 7, 31, 46}

Tumour grade

Histological characteristics for the classification of NETs includes somatostatin receptor (SSTR) expression, mitotic count and Ki-67 index.^{7, 31} SSTR is commonly expressed on NET cells and is implicated in cell growth.⁵⁸ SSTR expression is therefore widely used as a marker for treatment selection, with tumours expressing SSTR denoted as SSTR-positive and tumours lacking SSTR expression considered SSTR-negative.⁷ Mitotic count and Ki-67 index are also both measures of cellular proliferation. Mitotic count measures the rate of cancer cell growth and division by identifying the number of dividing cells in a tumour sample. Ki-67 index measures Ki-67 protein levels: this protein is only found in dividing cells.^{59, 60}

Based on the histological characteristics described above, well-differentiated NETs are classified by tumour grade:

- GEP NETs are classified as low-grade (G1), intermediate-grade (G2) or high-grade (G3) based on mitotic count and Ki-67 index as outlined in Table 3 and Table 4.⁷ Most NETs are low-grade (G1).
- In lung NETs, disease is classified based on mitotic count. G1 lung NETs are slow-growing and do not usually result in distant metastases. On the other hand, G2 lung NETs are classified as atypical carcinoids, and are typically faster growing than G1 lung NETs with a higher rate of metastases in the liver and bones.⁶¹

As discussed previously, poorly differentiated tumours are classified as NECs and are not relevant for the indication presented in this submission.^{62, 63}

Table 3: WHO 2019 classification for GEP NENs

WHO Grade	Morphology	Mitotic count (2 mm ²) ^a	Ki-67 index (%) ^b
G1: low-grade	Well-differentiated	<2	<3
G2: intermediate-grade	Well-differentiated	2–20	3–20
G3: high-grade	Well-differentiated	>20	>20
G3: <i>high-grade</i> ^c	<i>Poorly-differentiated</i>	>20	>20

^a 10 HPF 1/4 2 mm², at least 40 fields (at 40 magnification) evaluated in areas of highest mitotic density; ^b MIB1 antibody; percentage of 500–2000 tumour cells in areas of highest nuclear labelling; ^c G3 poorly-differentiated tumours are classified as NECs, rather than NETs.

Abbreviations: G: grade; GEP: gastroenteropancreatic; HPF: high power field; NEC: neuroendocrine carcinoma; NEN: neuroendocrine neoplasm; NET: neuroendocrine tumour; WHO: World Health Organization.

Source: Pavel 2020.⁷

Table 4: WHO 2021 classification for lung NENs

WHO Grade	Morphology	Carcinoid status	Mitotic count (2 mm ²) ^a
G1: low-grade	Well-differentiated	Typical carcinoid	<2
G2: intermediate-grade	Well-differentiated	Atypical carcinoid	2–10
G3: <i>high-grade^b</i>	<i>Poorly-differentiated</i>	<i>Large cell and small cell</i>	>10

^a 10 HPF ¼ 2 mm², at least 40 fields (at 40 magnification) evaluated in areas of highest mitotic density; ^b High-grade neuroendocrine carcinomas include LCNEC and SCLC; these are poorly differentiated and as such are not classified as NETs.

Abbreviations: G: grade; LCNEC: large cell neuroendocrine carcinoma; NEN: neuroendocrine neoplasm; NET: neuroendocrine tumour; SCLC: small-cell lung cancer; WHO: World Health Organization.

Sources: Nicholson 2022,⁶² Trucco, 2024.⁶³

Tumour stage

TNM staging of the disease is based on assessment of the size and spread of the primary tumour, lymph node involvement and occurrence of distant metastasis. TNM staging is used to classify tumours based on anatomical extent of the spread of malignant tumours. Generally, Stage I refers to tumour invasion of the mucosa and/or submucosa, Stage II refers to tumour invasion into the muscle or surrounding tissues, Stage III refers to regional lymph node metastasis (locally advanced) and Stage IV refers to distant metastasis. This system has been adapted for the classification of NETs by primary tumour site, including pancreas, stomach, GI tract and lung (under the lung TNM staging criteria).^{64–67}

Diagnosis of NETs

Diagnosis aims to determine the NET primary tumour site, disease distribution and tumour grade. Due to the wide range of potential primary NET sites, a combination of diagnostic tests based on individual patients' symptoms are required. These may include endoscopic procedures, radiological (e.g. computed tomography [CT] scan, magnetic resonance imaging [MRI]) and/or radionuclide (e.g. SSTR imaging) scans, biochemical testing (e.g. blood and urine analyses), and histopathologic assessments (e.g. Ki-67 index, mitotic count).^{7, 68} Diagnosis is confirmed by histological analysis of core biopsy. If a diagnosis is confirmed, classification is carried out in line with the World Health Organization (WHO) Grade standards (see Table 3 and Table 4 in Section 1.3.2).⁷ Finally, disease stage is determined by the TNM staging system (see Section 1.3.2).⁷ This multidimensional diagnosis profile then allows for personalised treatment pathways to be offered to patients, as treatment options for patients with NETs are guided by factors including primary tumour location, Ki-67 index and SSTR expression status.

1.3.3 Disease burden

Clinical burden

The low prevalence and asymptomatic nature of NETs as well as the presentation of non-specific symptoms means there is a significant delay in diagnosis in clinical practice.^{31, 32, 50} For example, 80% of patients typically visit their GP an average of 11 times prior to diagnosis for reasons related to NET-related symptoms.⁵⁰ Due to the heterogeneity of symptoms, there is greater difficulty in recognising that something may be wrong as well as attaining a diagnosis compared to other cancer types with patients often receiving a misdiagnosis.^{69, 70} Only 44% of NET patients visit their GP before referral compared to 75% of other cancer patients, and only 58% visiting a doctor within 3 months of noticing symptoms compared to 78% of patients presenting with other

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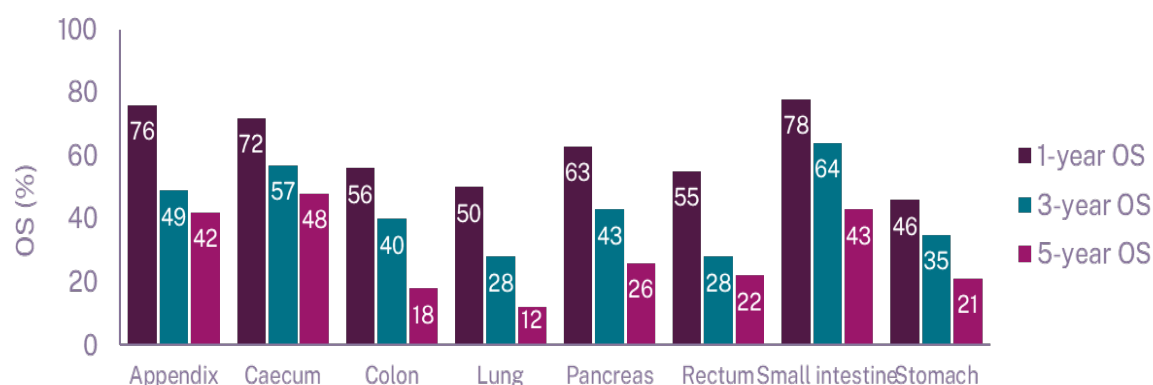
cancer types.⁶⁹ Approximately 80% of patients experience a symptom prior to diagnosis, with 55% experiencing a severe or very severe symptom.⁷¹ As a result, NET patients report a decline in health in the period between first attending primary care and starting treatment compared to other cancers (38% versus 20%).^{50, 69, 71} Further details regarding the diagnosis of NETs are outlined in Section 1.3.2. Typically, patients are only diagnosed at later stages when symptoms may be present. Particularly, advanced and metastatic NETs are incurable and portend poor prognosis for patients, particularly those with pNETs and lung NETs.⁴⁶

Overall survival

The mortality associated with NETs is influenced by multiple factors including disease stage, primary tumour site and tumour grade. Patients with advanced NETs have very poor prognosis, irrespective of primary tumour site. This was demonstrated by a large-scale observational study of retrospective data on 14,834 patients with NETs and NECs, collected by the NCRAS in England between 2012 and 2018. Based on Kaplan–Meier (KM) estimates, fewer than 25% of patients with Stage IV NETs were expected to survive at the five-year landmark, compared with over 75% of patients with Stage I and Stage II disease, and over 50% of patients with Stage III disease.⁴⁶

Furthermore, the five-year survival for patients with Stage IV NETs is consistently <50% regardless of site, as shown in Figure 3. This is lowest in patients with NETs originating in the lung (12%), colon (18%), stomach (21%), rectum (22%) and pancreas (26%).⁴⁶

Figure 3: 1-, 3- and 5- year OS of patients with Stage IV NETs in England from 2012 to 2018



Abbreviations: NET: neuroendocrine tumour; OS: overall survival.

Source: Adapted from White, 2022,⁴⁶

Furthermore, survival in patients with NETs has also been shown to decrease with increasing tumour grade in several European studies. In a retrospective study of patients with NETs (of any disease stage) (N=233), five-year overall survival (OS) decreased with advancing grade, from G1 (81%), to G2 (34%) to G3 (9%).⁷² Similarly, in a population-based study of 9,697 patients with GEP NENs from the Netherlands Cancer Registry diagnosed between 1989 and 2016, five-year OS rates were lower with increasing tumour grade amongst patients with metastatic GEP NEN (47%, 38% and 5% for G1, G2 and G3 tumours, respectively).⁷³ Therefore, as with other late-stage oncology indications across disease areas, extending OS for these patients, whilst maintaining quality of life (QoL), is a key treatment goal.

Progression-free survival

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While five-year survival rates amongst patients with NETs are generally poor, particularly for those with late stage or high-grade tumours, they are relatively high compared with those observed in other oncology areas.⁴⁶ This results in challenges in demonstrating OS benefit within limited trial durations.

Due to this, the NET Task Force, sponsored by the National Cancer Institute (NCI) GI Steering Committee, stated that progression-free survival (PFS) is a suitable and relevant primary endpoint for Phase III NET studies, where there is likely to be a delay in progression.^{32, 74} The indolent nature of NETs, coupled with their low prevalence, means power to detect OS benefit may be impossible without exceeding the local incidence of disease.⁷⁵ Given the challenges in demonstrating a significant OS benefit, PFS is often considered as the primary outcome in Phase III trials as longer PFS is associated with OS improvements.⁷⁶

While improvements in PFS are correlated with OS benefit, the likelihood of experiencing a progression on initial systemic therapy gives rise to a need for multiple PFS-extending treatment options for patients with NETs, who may need to undergo more than one line of therapy. This was evidenced by a US-based study of patients with metastatic GEP NETs treated at a tertiary centre between 2003 and 2015, where 55% of patients progressed to second-line systemic therapy and 31% progressed to third-line systemic therapy.³⁷ There is a clear need for treatments that demonstrate efficacy following progression after systemic therapy; such therapies can control tumour growth and delay further disease progression.

Humanistic burden

Patients with advanced NETs experience a substantial and persistent symptom burden that negatively impacts their health-related quality of life (HRQoL) compared to the general population.³⁶ This is particularly notable in patients with functional disease which occurs in around 30–40% of pNET patients and ~70% of epNET (specifically GI and lung NET) patients.^{7, 55, 56} 80% of patients report experiencing symptoms prior to diagnosis with 55% reporting a severe symptom.⁷¹ Of these, 80% of GI NET, 90% of pNET and 60% of lung NET patients describe their most severe symptoms as very severe.⁷¹

A significant HRQoL decrement is also observed in patients with progressive disease compared to those with stable disease, and therefore treatments should delay progression to maintain HRQoL for as long as possible. This was demonstrated by the CLARINET trial, an RCT investigating use of lanreotide (an SSA) in metastatic enteropancreatic NETs, where a significant ($p < 0.05$) difference in utility values was identified when comparing patients with stable disease (0.776) to those with progressive disease (0.726).³⁶ Similarly, a study that developed health state vignettes from published literature and clinical opinion in neuroendocrine tumours recorded a notable utility decrement between stable disease (0.771) and progressed disease (0.612).³⁵

While delaying disease progression is a priority treatment goal for most patients, a global discrete choice experiment in 242 patients with advanced NETs revealed that avoidance of treatment toxicity and convenience in mode of administration are also key patient-relevant treatment goals.⁷⁷ The current treatment options for patients with advanced NETs impose a high impact on daily life of patients and caregivers (particularly ¹⁷⁷Lu-dotatate) and are associated with considerable tolerability burden (¹⁷⁷Lu-dotatate and chemotherapy).³⁸⁻⁴¹ Furthermore, a cross-sectional study of 60 NET patients in the US reported that maintaining independence was the most valued health outcome, ranking this as more important than overall survival.⁷⁸ Therefore,

there is a clear need to not only improve survival outcomes but delay HRQoL decrements associated with NETs and, in particular, progressed disease.

Economic burden

The economic burden of cancer in the UK is substantial, encompassing high direct medical costs, productivity losses and informal care, and imposing financial burden on individual patients. However, the economic burden of NETs specifically is not well-documented, owing partly to the rarity and heterogeneity of the disease. Patients typically receive multiple lines of active treatments. In these pre-treated populations, the majority receive concurrent SSAs, which are associated with substantial acquisition and administration costs as well as considerable resource use.^{12, 79} Furthermore, primary care costs for NETs are high with 80% of patients will visit their GP an average of 11 times prior to diagnosis for reasons related to NET symptoms.⁵⁰ Around a third of patients also report their first experience of secondary care to be unplanned A&E visits.⁵⁰

Amongst the current systemic treatment options available for patients with advanced/metastatic NETs, ¹⁷⁷Lu-dotatate is particularly resource- and cost-intensive, driven by substantial administration costs for physician time and hospital admissions.⁸⁰ There are also indirect societal costs associated with in-centre administration, such as travel and productivity loss. Patients may need to take time off work to receive treatment (including an overnight hospital stay for most patients), as well as post-therapy to minimise radiation exposure (up to six days in the UK).⁸¹ A healthcare resource use (HCRU) study analysing 199 patients with GEP-NET records in England found that the number of hospital days were 195 for ¹⁷⁷Lu-dotatate and 80 for other treatments (SSAs, chemotherapy, everolimus or sunitinib) across two years of use.⁸²

There is also considerable economic burden to patients with 30% of people living with NETs report income loss and this disease-related financial loss contributes to the emotional stress that patients experience.⁸³ Two-thirds of patients with NETs report having a caregiver (a close family member or friend to help them manage day-to-day NET-associated activities), and caregiver burden is likely to be increased for patients with progressive disease.⁸³

1.3.4 *Current treatment pathway*

The aim of treatment for patients with unresectable or metastatic NETs is to control tumour-associated clinical symptoms and tumour growth with systemic therapy as well as to delay disease progression and the associated HRQoL decrement.⁷ The treatment pathways for patients are complex and individualised, with different pathways depending on primary tumour site, tumour growth rate, SSTR expression and functional status, as outlined in Section 1.3.2.^{6, 7, 12, 31}

Clinical guidelines for the management of unresectable or metastatic NETs are available from the European Neuroendocrine Tumour Society (ENETS, 2023) and the European Society for Medical Oncology (ESMO, 2020 for GEP NETs and 2021 for lung NETs).⁶⁻¹¹ The ENETS guidelines are typically considered to be most relevant for UK clinical practice with the ESMO publications used in a supportive of supplementary manner.¹² These have been used to develop the treatment pathway diagram outlined in Figure 4 which was later validated by clinical experts in NETs.¹²

The therapeutic options for patients fall into three main categories:

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- **Somatostatin analogues (SSAs**, including lanreotide and octreotide): for treating patients with SSTR-positive tumours only, for disease modification and symptom control. SSAs are typically administered at first line, except in the case of G3 NETs, and can be used concomitantly alongside the targeted therapies below or alongside best supportive care (BSC).
- Other targeted systemic therapies are restricted to specific subgroups on the basis of primary tumour site (see Table 5), grade, functional status and SSTR expression status including:^{3, 4}
 - **Everolimus (TA449)**: for treating patients with progressive pNETs and non-functional progressive GI or lung NETs. This is the only approved therapy post-progression in patients with lung NETs
 - **Sunitinib (TA449)**: for treating patients with progressive pNETs only
 - ¹⁷⁷**Lu-dotatate (TA539)**: a form of PRRT for treating patients with SSTR-positive progressive GEP NETs

Table 5: Reimbursement of systemic therapies in each NET subpopulation in the UK by NICE

	Pancreatic	Extra-pancreatic	
		GI	Lung
Everolimus (TA449)	✓	✓ G1 or G2 and non-functional)	✓ (G1 or G2 and non-functional)
Sunitinib (TA449)	✓	x	x
¹⁷⁷ Lu-dotatate (TA539)	✓ (G1 or G2 and SSTR positive)	✓ (G1 or G2 and SSTR positive)	x

Abbreviations: G: grade; GI: gastrointestinal; ¹⁷⁷Lu-dotatate: ¹⁷⁷Lutetium-dotatate; NETs: neuroendocrine tumours; SSTR: somatostatin receptor; TA: technology appraisal.

Source: TA449; TA539.^{3, 4}

- **Chemotherapy regimens** (including temozolomide +/- capecitabine [TEM +/- CAP], streptozocin/5-fluorouracil [STZ/5-FU] and folinic acid + fluorouracil + oxaliplatin [FOLFOX]) are included in guidelines for all tumour site subpopulations; however, this represents off-label use as there is a lack of robust clinical efficacy data. Clinician feedback highlighted that CAPTEM is more widely used in NET patients, with FOLFOX only prescribed for patients at higher grades or with highly aggressive tumours.¹² Given the high treatment burden associated with chemotherapy, as well as the lack of robust efficacy data, chemotherapy is not commonly used in the broader well-differentiated NETs population (largely Grade 1 and 2) for which cabozantinib is indicated (see Section 1.3.5) and is primarily used as a first-line option for patients with G3 NETs.⁸⁴

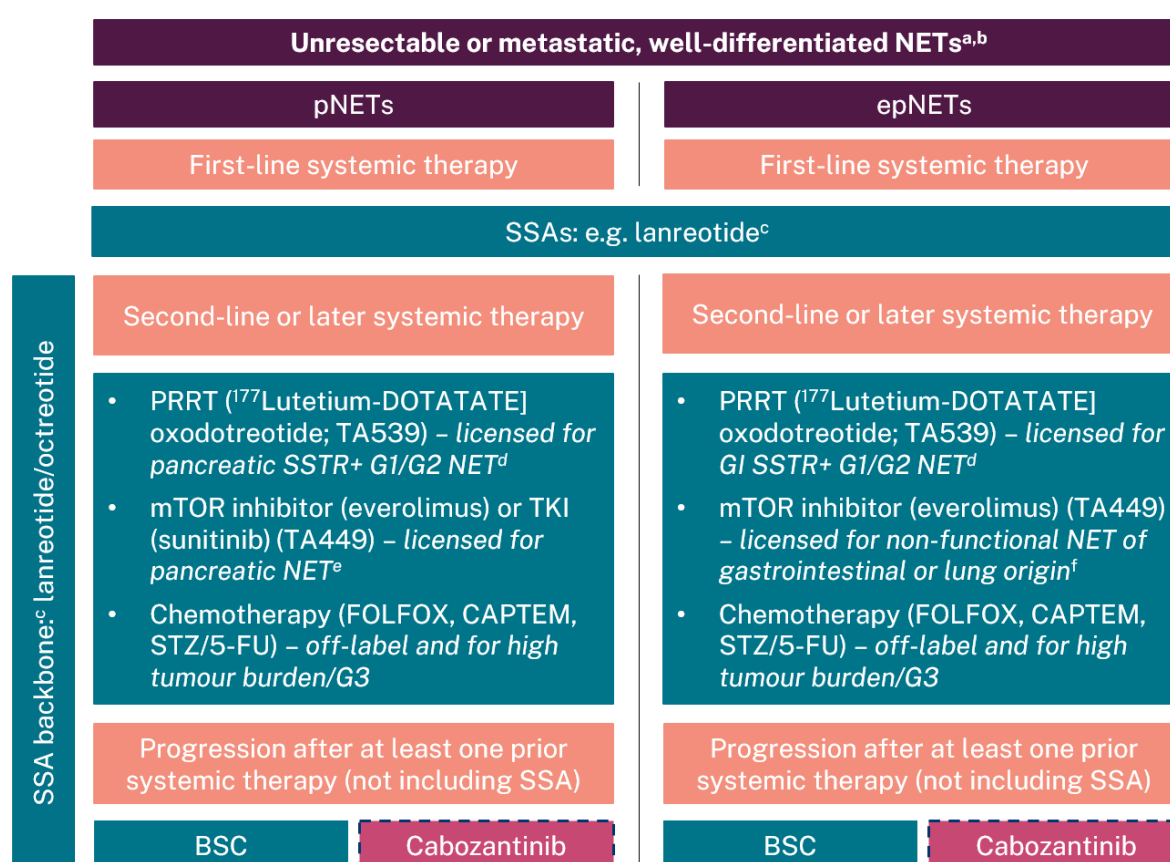
Prior NICE appraisals have indicated that interferon alpha is not widely used in UK clinical practice and is therefore not considered a relevant therapy in the current treatment pathway.^{3, 4} Although noted in the ESMO guidelines as being approved for symptom control, it is not included in the ENETs guidelines which were confirmed to be more widely used in the UK by clinical experts in NETs.⁶⁻¹²

Although treatment options can vary depending on primary tumour site, NET patients will typically be prescribed first-line SSAs irrespective of primary tumour location (except in the case of G3 NETs, where chemotherapy regimens may be considered, but including lung NETs where it is used off-label).⁶⁻¹¹ SSAs may also be prescribed concomitantly to the targeted therapies

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listed above. After SSAs, the available targeted therapies are restricted to specific subgroups, limiting treatment options. In certain subpopulations treatment options are extremely limited; for example, only everolimus is reimbursed in patients with lung NETs.^{3, 4} Given the heterogeneity of the disease and the narrow labels for available systemic treatment options, systemic therapy after progression on SSAs is highly individualised and driven by specific patient characteristics.^{6, 7, 31} There is no clear or consistent treatment pathway for the broad population of patients with pNETs or epNETs who have progressed on prior systemic therapies, and for many patients there are no treatment options remaining other than BSC. On the basis of the marketing authorisation for cabozantinib and the CABINET trial population, clinical experts experienced in the treatment of patients with NETs in the UK considered BSC to represent the most appropriate comparator for this appraisal.¹²

Figure 4: Current treatment pathway for NETs in the UK, adapted from the ENETS guidelines



^a Patients with G3/poorly differentiated tumours typically have a truncated treatment pathway, mostly with chemotherapy at first line; ^b The NHS does not reimburse re-treatment with the same treatment class; ^c Somatostatin analogues (lanreotide/octreotide) are not licensed for use in Lung NETs and they are used off-label; ^d ¹⁷⁷Lutetium-DOTATE is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (Grade 1 or Grade 2), somatostatin receptor-positive gastroenteropancreatic NETs in adults. ^e Everolimus and sunitinib are recommended, within their marketing authorisations, as options for treating well- or moderately differentiated unresectable or metastatic NETs of pancreatic origin in adults with progressive disease; ^f Everolimus is recommended, within its marketing authorisation, as an option for treating well-differentiated (Grade 1/2) non-functional unresectable or metastatic NETs of gastrointestinal or lung origin in adults with progressive disease.

Abbreviations: BSC: best-supportive care; CAPTEM: capecitabine and temozolomide; epNET: extra-pancreatic neuroendocrine tumour; FOLFOX: folinic acid + fluorouracil + oxaliplatin; G: Grade; GI: gastrointestinal; ¹⁷⁷Lu-DOTATATE; mTOR: mammalian target of rapamycin; NET: neuroendocrine tumour; pNET: pancreatic neuroendocrine tumour; PRRT: peptide receptor radionuclide therapy; SSA: somatostatin analogue; SSTR: somatostatin receptor; STZ: streptozocin; TA: Technology Appraisal; TKI: tyrosine kinase inhibitor.

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1.3.5 Unmet need

The often asymptomatic nature of NETs results in delays in diagnosis, with 29% of patients waiting at least five years for an accurate diagnosis, or receiving this diagnosis incidentally (12–17%).^{32,51,52, 70} Patients are also often misdiagnosed due to the complexity of presentation with many also reporting that limitations of the currently available diagnostic and therapeutic tools affect referral, diagnosis and treatment.^{70, 85} This also means a substantial portion of patients (58%) are diagnosed in more advanced or metastatic settings (see Section 1.3.2).³² Due to the poor prognosis of patients at later disease stages (five-year survival is below 50% in patients with Stage IV NETs regardless of tumour site), there is a clear need for treatments that extend PFS, and which could improve OS (see Section 1.3.3).⁴⁶ Additionally, extending PFS delays the HRQoL detriment associated with the large symptomatic burden observed in patients with progressed disease (shown in one study to decrease from 0.771 in stable disease to 0.612 in progressed disease).^{35, 36}

All targeted systemic treatment options are restricted to specific subgroups on the basis of primary tumour site, grade, functional status and SSTR expression status, and in some subgroups there are very few approved treatment options.^{3, 4, 6} Consequently, the treatment pathway is highly individualised and can sometimes lead to inconsistent care in NETs across the healthcare system.⁷⁰ A substantial proportion of patients progress to second (55%) and third-line therapies (31%), and thus there is a need for more treatment options without restrictive eligibility criteria.³⁷

Beyond targeted systemic treatments, the only alternative option is chemotherapy, which is used off-label and for which there is no robust efficacy data.^{6-11, 41} Chemotherapy is associated with high treatment toxicity, an inconvenient mode of administration, and an associated high healthcare recourse use burden (as discussed Section 1.3.3).⁸² Avoidance of treatment toxicity and convenience in route of administration are key patient-relevant treatment goals.⁷⁷ As such, chemotherapy is not commonly used in patients with Grade 1 and 2 well-differentiated NETs.⁸⁴

As such, patients who progress on prior systemic therapy face very few therapeutic options, and for many patients BSC represents the only available option.^{6, 7} There is a clear need for novel post-progression systemic therapy that extends progression-free survival, whilst providing a convenient mode of administration and a manageable safety profile, and which can be used regardless of disease characteristics or subgroup.³⁷

A positive NICE recommendation for cabozantinib for patients with advanced pNETs or epNETs that have progressed after systemic treatment (other than SSAs) would provide clinicians with a much-needed, effective and convenient treatment option post-progression across the wider NET population.

1.3.6 Proposed positioning of cabozantinib

Cabozantinib is an orally administered treatment that is proposed to be used as a monotherapy for the treatment of adult patients with progressive pNETs and epNETs after prior systemic therapy. Prior systemic therapies may include ¹⁷⁷Lu-dotatate, sunitinib or everolimus depending on individual patient characteristics. On the basis of the marketing authorisation for cabozantinib and the population included in the CABINET trial, clinical experts experienced in the treatment of patients with NETs in the UK considered BSC to represent the most appropriate comparator for this appraisal.¹²

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1.4 *Equality considerations*

It is not considered that the introduction of cabozantinib is likely to lead to recommendations which differentially impact any patients protected by equality legislation or disabled persons. Given the broad anticipated label of cabozantinib, reimbursement could improve the equity of access to effective treatment options across the NETs population.

2 Clinical effectiveness

Summary of clinical effectiveness of cabozantinib: CABINET

- CABINET (Alliance A021602; NCT03375320) was a high quality, multicentre, Phase III, double-blind, placebo-controlled randomised controlled trial (RCT) that evaluated the efficacy, safety and tolerability of cabozantinib in patients with progressive pancreatic or extra-pancreatic neuroendocrine tumour (pNETs or epNETs), whose disease had progressed after prior systemic therapy¹³
 - The CABINET trial enrolled a broad population of progressive patients with pNETs and epNETs (inclusive of all primary NET locations and irrespective of somatostatin receptor [SSTR] expression status and functional status)¹³
 - 95 patients with pNETs and 203 patients with epNETs were randomised within each cohort in a 2:1 ratio to receive cabozantinib (60 mg once daily) or placebo.¹³ Randomisation in the pNET cohort was stratified according to concurrent somatostatin analogue (SSA) use (yes or no) and receipt of prior sunitinib therapy (yes or no).¹³ Randomisation in the epNET cohort was stratified according to primary tumour site (midgut gastrointestinal [GI]/unknown versus non-midgut GI/lung/other) and concurrent SSA use (yes or no)¹³
 - Treatment was continued until disease progression or unacceptable toxicity²
 - Patient baseline characteristics and demographics were well-matched between arms¹³

Efficacy

- CABINET demonstrates that cabozantinib monotherapy significantly improved the efficacy outcomes of patients with progressive pNETs or epNETs, whose disease had progressed after prior systemic therapy.¹³ Progression-free survival (PFS) was selected as the primary endpoint due to being a well-accepted endpoint for other treatments in progressive NETs.⁸⁶ At the primary analysis of PFS, (data cut-off [DCO] 24th August 2023) patients treated with cabozantinib demonstrated a statistically significant and clinically meaningful improvement in blinded independent review committee (BIRC)-assessed PFS versus placebo:
 - In the pNET cohort, median PFS in patients receiving cabozantinib was ~9.4 months longer versus placebo (median PFS: 13.83 months versus 4.47 months; hazard ratio (HR): 0.23; 95% CI: 0.12, 0.42; stratified 2-sided p<0.0001) and risk of disease progression or death was 77% lower²
 - In epNETs, median PFS versus placebo was 4.5 months longer with cabozantinib than with placebo (median PFS: 8.48 months versus 3.98 months; HR: 0.38; 95% CI: 0.25, 0.58; stratified 2-sided p<0.0001) and risk of disease progression or death was 62% lower¹³
 - Based on compelling efficacy in terms of PFS observed during the interim analyses, CABINET was terminated early and unblinded to enable potential crossover for patients on the placebo treatment arms to receive cabozantinib²
 - Notably, cabozantinib demonstrated PFS improvements versus placebo across all key patient subgroups of the pNET cohort and epNET cohort, regardless of primary tumour location and receipt of prior therapies^{2, 13}
 - Cabozantinib induced a higher response rate and deeper and more durable responses versus placebo. The objective response rate (ORR) treatment difference between the cabozantinib and placebo arms was 18.8% (95% CI: 9.2%, 28.3%; p=0.0115) and 5.2% (95% CI: 1.5%, 9.0%; p=0.0524) in the pNET and epNET cohorts, respectively²
- Despite potential confounding due to crossover, a numerical benefit in OS was observed for cabozantinib versus placebo in the pNET cohort and epNET cohort. In both cohorts, overall survival (OS) HRs were <1, favouring the cabozantinib arm over the placebo arm^{2, 13}
 - 34% of patients (n=32) in the pNET cohort and 48% of patients (n=97) in the epNET cohort had died across the cabozantinib and placebo arms. OS results were also confounded by 39% of patients with pNETs in the placebo arm (n=12) and 29% of patients with epNETs in the placebo arm (n=20) crossing over to open-label cabozantinib treatment after progression^{2, 13}
- The efficacy benefits of cabozantinib are achieved without compromising patient health-related quality of life (HRQoL), with similar European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) overall and global health domain scores observed between cabozantinib and placebo arms in both the pNET and epNET

cohorts³

Safety

- Cabozantinib is associated with a predictable and manageable safety profile
 - Overall, no new safety concerns were identified in patients studied in CABINET and the safety events reported in this study were consistent with the known safety profile of cabozantinib¹
 - Adverse events (AEs) were effectively managed through dose modifications, with dose reductions reported for 68% and 66% of patients treated with cabozantinib in the pNET and epNET cohorts, respectively¹
 - In the pNET cohort, Grade 3 or 4 AEs were reported for 73% of patients in the cabozantinib arm and 45% of patients in the placebo arm²
 - In the epNET cohort, Grade 3 or 4 AEs were reported for 67% of subjects in the cabozantinib arm and 39% in the placebo arm²

Comparative effectiveness evidence

- Cabozantinib is anticipated to be used in UK clinical practice in line with the population enrolled in the CABINET trial, which informed the anticipated marketing authorisation for cabozantinib in this indication. Given that BSC represents the only relevant comparator, and the CABINET trial provides direct efficacy and safety evidence for cabozantinib versus placebo which can be considered a proxy for BSC, indirect or mixed treatment comparisons are not required

Conclusion

- Cabozantinib would provide a valuable treatment option for patients with pNETs or epNETs who have received a prior systemic therapy, providing a significant benefit to patients through prolonging progression-free survival, inducing superior response rates and maintaining HRQoL compared with placebo

2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify published interventional studies reporting clinical efficacy and safety data in patients with advanced pNETs or epNETs who have experienced treatment failure or disease progression following previous systemic treatment. Previous systemic treatments included everolimus, sunitinib, PRRT such as ¹⁷⁷Lu-dotatate, CAPTEM, STZ/5-FU, FOLFOX and interferon alpha (IFN-α). In line with the eligibility criteria of the CABINET trial (see Section 2.3), prior treatment with SSAs alone was not sufficient to meet the definition of previous systemic treatment. Initial searches of electronic databases were performed in May 2024. Hand searching of conference proceedings, clinical trial registries and bibliographies were also performed. Searches were updated in January 2025.

Overall, the searches identified a total of 42 relevant publications, reporting on 21 clinical trials. Of these, 32 publications reporting on 16 unique studies were prioritised for extraction. Only individual patient data were reported for seven publications (four unique studies), and three publications (one study) only presented relevant data graphically. These studies were deprioritised for extraction. All included studies (n=16) were interventional, as per the eligibility criteria of the SLR. Of these, the majority (n=13) were non-RCTs. The SLR identified only one randomised controlled trial (RCT), the CABINET trial, that provides clinical evidence for cabozantinib monotherapy for the treatment of advanced neuroendocrine tumours that have progressed after systemic treatment.^{2, 13}

Full details of the SLR methodology used to identify the clinical evidence relevant to cabozantinib in this submission, including the search and population, intervention, comparator, outcome (PICO) strategy, preferred reporting items for systematic reviews and meta-analyses (PRISMA)

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flow diagram, list of included studies, and list of excluded studies at full-text review, is provided in Appendix B.

2.2 List of relevant clinical effectiveness evidence

CABINET was the only trial identified by the SLR that provides clinical evidence on the efficacy and safety of cabozantinib as a treatment in the patient population of relevance for this submission. A summary of the CABINET trial is presented in Table 6.

Table 6: Clinical effectiveness evidence

Study	CABINET (NCT03375320; Alliance A021602)
Study design	Phase III, US-based, multicentre, randomised, double-blind, placebo-controlled study
Population	Adults with pNETs or epNETs whose disease has progressed after prior systemic therapy
Intervention(s)	Cabozantinib (60 mg once daily orally every 28 days)
Comparator(s)	Placebo (60 mg once daily orally every 28 days)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Reported outcomes specified in the decision problem^a	• Progression-free survival (PFS) • Overall survival (OS) • Objective response rate (ORR) • Adverse effects associated with treatment • Health-related quality of life (HRQoL)
All other reported outcomes	• Duration of response (DOR) • Disease control rate (DCR) • Concordance between the investigator and BIRC response assessments

^a Outcomes marked in bold are included in the economic model.

Abbreviations: BIRC: blinded independent review committee; DCR: disease control rate; DOR: duration of response; epNET: extra-pancreatic neuroendocrine tumour; HRQoL: health-related quality of life; mg: milligram; ORR: objective response rate; OS overall survival; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour.

Sources: ClinicalTrials.gov (NCT03375320);⁸⁷ Chan et al. 2024.¹³

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Trial design

The Phase III CABINET trial (Alliance A021602; NCT03375320) was a US-based, multicentre, randomised, double-blind, placebo-controlled study that evaluated the efficacy, safety and tolerability of cabozantinib in patients with progressive pNETs or epNETs. The epNET primary tumour sites were further classified into two pre-specified subgroups: midgut GI/unknown and non-midgut GI/lung/other.¹³

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Patients were also required to have progressed disease after a prior systemic therapy, which included the following treatments:

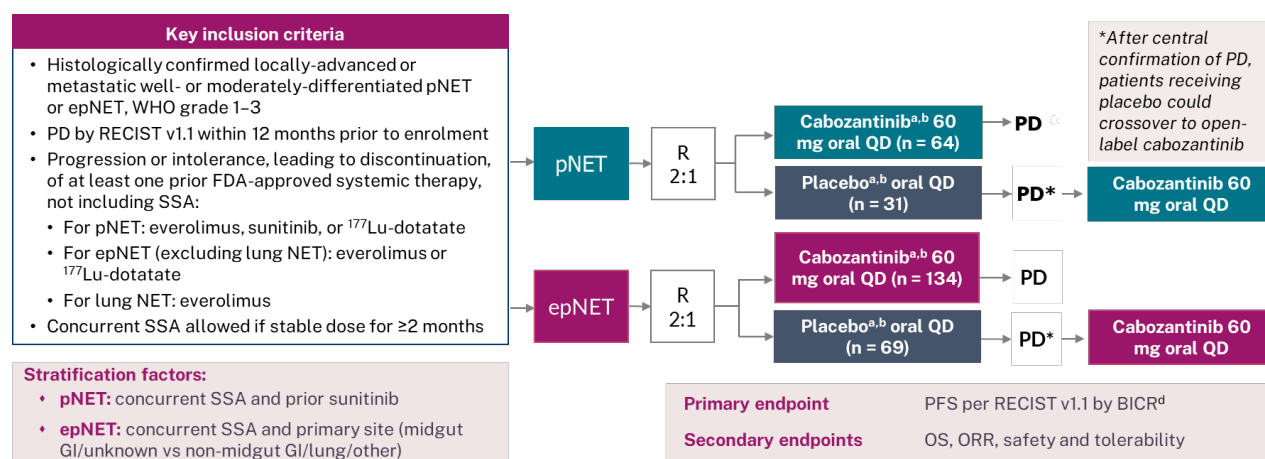
- pNET: everolimus, sunitinib, or PRRT
- epNET (excluding lung NET): everolimus or PRRT
 - Lung NET: everolimus

Prior treatment with SSAs alone was not sufficient to meet the definition of previous systemic treatment.

Patient enrolment was facilitated using the web-based Oncology Patient Enrollment Network (OPEN) registration system and an Interactive Web Response System (IWRS) randomisation assignment. Patients were randomly assigned to receive cabozantinib (60 mg once daily) or placebo (60 mg once daily) in a 2:1 ratio. Randomisation was performed using the permuted-blocks method with a block size of six. Randomisation in the pNET cohort was stratified according to concurrent SSA use (yes or no) and receipt of prior sunitinib therapy (yes or no). Randomisation in the epNET cohort was stratified according to primary tumour site (midgut GI/unknown versus non-midgut GI/lung/other) and concurrent SSA use (yes or no).

A schematic of the CABINET study design is provided in Figure 5.

Figure 5: Overview of CABINET study design



^a Interruptions and dose reductions for cabozantinib (40 mg, then 20 mg) and placebo were specified for adverse event management. ^b Blinded treatment continued until PD, unacceptable toxicity or withdrawal of consent. ^c If investigator assessments of PD were confirmed by blinded real-time central review, patients were unblinded to treatment assignment. ^d Patients were evaluated every 12 weeks by radiographic imaging for tumour response and progression.

Abbreviations: BIRC: blinded independent review committee; epNET: extra-pancreatic neuroendocrine tumour; GI: gastrointestinal; ¹⁷⁷Lu-dotatate: ¹⁷⁷Lutetium-dotatate; mg: milligram; NET: neuroendocrine tumour; ORR: objective response rate; OS: overall survival; PD: progressed disease; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour; QD: once daily; R: randomised; RECIST: Response Evaluation Criteria in Solid Tumours; SSA: somatostatin analogue; WHO: World Health Organization.

Sources: ClinicalTrials.gov (NCT03375320);⁸⁷ Chan et al. 2024 ;¹³ Ipsen Data on File, 2024 (CABINET CSR).²

Follow-up visits

Patients were evaluated at baseline and every 12 weeks (±1 week) for tumour response and progression (as determined by Response Evaluation Criteria in Solid Tumours [RECIST] 1.1) following the start of study treatment, by radiographic imaging. Post-treatment assessments

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continued every 12 weeks until progression or the start of new anticancer therapy and every six months up to eight years after randomisation or death, whichever came first.⁸⁸

As described in Section 2.4, given compelling efficacy in terms of progression-free survival (PFS) observed during the interim analyses of both cohorts, patient recruitment was terminated early and the study unblinded to allow crossover for patients in the placebo arm (i.e. to allow them to receive open-label cabozantinib treatment).^{2, 13} For patients who crossed over, the baseline was re-established and tumour assessments were restarted (every 12 weeks). If radiographic disease progression was not confirmed by blinded real-time central review, patients continued with blinded study treatment and underwent study treatment assessments in accordance with the protocol.⁸⁸

Adverse events (AEs) were reported each 28-day cycle (Day 1 of each 28-day cycle and Day 15 [± 3 days] of Cycles 1 and 2) from baseline up to 30 days after the patient's last treatment date. AEs occurring more than 30 days after treatment discontinuation were recorded only if they were possibly, probably, or definitely related to study treatment.^{88,2}

Within the CABINET trial, a sub study (A021602-HO1) was conducted to assess if cabozantinib will improve quality of life and decrease disease-related symptoms as compared to placebo. Participation in the HRQoL sub-study was optional and patients who participated completed the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30), EORTC QLQ-GI.NET21 and Patient Global Impression of Change (PGIC) at baseline and every 12 weeks (± 1 week) until disease progression or the start of a new anticancer therapy.⁸⁸

2.3.2 Trial methodology

The CABINET trial methodology is summarised in Table 7 and outcomes measures and definitions are summarised in Table 8.

Table 7: Summary of trial methodology

Trial name	CABINET (NCT03375320)
Location	CABINET was conducted across 62 study centres in the US
Trial design	The CABINET trial was a, US-based, Phase III, multicentre, double-blind, randomised controlled trial that assessed the efficacy and safety of cabozantinib versus placebo for patients with progressive pNETs or epNETs, whose disease had progressed after prior systemic therapy
Eligibility criteria for participants	Patients were deemed eligible for inclusion in the CABINET trial if they met the following eligibility criteria: • Well or moderately differentiated pNETs or epNETs • Locally advanced/unresectable or metastatic disease • WHO tumour grades of 1 to 3 • Any primary tumour site • Evidence of disease progression within 12 months prior to study registration, as assessed by RECIST 1.1 criteria • ECOG status 0 to 2 • Disease progression or unacceptable side-effect profile leading to discontinuation after at least one systemic therapy (excluding SSAs). Prior lines of therapy included the following: ○ pNET: everolimus, sunitinib, or PRRT

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	○ GI NET: everolimus or PRRT ○ Lung NET: everolimus • Both functional and non-functional tumours were allowed • Patients were allowed concurrent use of SSAs provided the dose was stable for at least two months prior to enrolment The full eligibility criteria for the CABINET trial are presented in Appendix J.
Intervention	Cabozantinib (60 mg once daily)
Comparator	Placebo (60 mg once daily)
Method of study drug administration	Cabozantinib was administered orally
Permitted and disallowed concomitant medication	Patients were allowed to receive concurrent use of SSAs provided the dose was stable for at least two months prior to enrolment. Patients were also allowed to receive low dose aspirin (≤ 81 mg per day) and anticoagulation with therapeutic doses of LMWH, provided the dose was stable for at least 6 weeks prior to registration
Primary outcome(s)	The primary endpoint of the CABINET trial was PFS, as assessed by BIRC (defined in Table 8)
Secondary endpoints	Secondary and safety outcomes of the CABINET trial included: • OS • ORR • Safety and tolerability Secondary endpoints are defined in Table 8
Exploratory endpoints (relevant to the submission)	Exploratory outcome variables include: • DOR • DCR • Concordance between the investigator and BIRC response assessments • HRQoL
Pre-planned subgroup analyses	Subgroup analyses of the key CABINET trial endpoints were performed to assess consistency of PFS results. The following subgroups were of primary interest, based on predicted prognostic factors and baseline stratification: • Age (<65 years, ≥ 65 years) • Sex • Race (white, other) • ECOG performance status • Number of prior systemic therapies (1, 2, ≥ 3) • Receipt of prior everolimus • Receipt of prior PPRT • Tumour grade • Histologic differentiation • Histological type • Stratification factors for the pNET cohort: ○ Concurrent SSA use ○ Prior sunitinib therapy • Stratification factors for the epNET cohort: ○ Concurrent SSA use ○ Primary site (midgut/unknown versus non-midgut/lung/other)

Duration of study and follow-up	Data from the primary DCO (24th August 2023) represent a median duration of follow-up of: • pNET cohort: 23.2 months and 25.2 months in the cabozantinib and placebo groups, respectively • epNET cohort: 23.3 months and 23.0 months in the cabozantinib and placebo groups, respectively

Abbreviations: BIRC: blinded independent review committee; CSR: clinical study report; DCO: data cutoff; DCR: disease control rate; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; epNET: extrapancreatic neuroendocrine tumour; GI: gastrointestinal; HRQoL: health-related quality of life; LMWH: low molecular weight heparin; NET: neuroendocrine tumour; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour; PRRT: peptide receptor radionuclide therapy; RECIST: Response Evaluation Criteria in Solid Tumours; SSA: somatostatin analogue; WHO: World Health Organisation

Source: Ipsen Data on File, 2024 (CABINET CSR).²

Table 8: Outcome measures and definitions

Outcome	Definition
PFS	Defined as the time from randomisation to the first radiographic documentation of disease progression, per RECIST 1.1 determined by BIRC, or death from any cause. RECIST 1.1 criteria included:⁸⁹ • CR: disappearance of all target lesions, pathological lymph nodes must have reduction in short axis to <10mm • PR: At least 30% decrease in sum of diameters of target lesions, using baseline sum of diameters as reference • PD: At least a 20% increase in the sum of diameters of target lesions, where smallest sum on study is used as reference. The sum must also demonstrate an absolute increase of 5 mm • SD: Neither sufficient increase or decrease to qualify for PR or PD, using smallest sum on study for reference
OS	The time from randomisation to death from any cause
ORR	Defined as the proportion of patients with best overall response of either confirmed CR or PR as assessed per RECIST 1.1 (see above)
DOR	Defined as the time of a documented CR or PR to the time of documented radiographic progression, per RECIST 1.1 (see above)
DCR	Defined as the proportion of patients with a best overall response of CR, PR, or SD, per RECIST 1.1 (see above)
HRQoL	Adjusted mean change from baseline in global QoL score from the EORTC QLQ-C30 global health status/QoL scores: a questionnaire that assesses the quality of life, global health status, HRQoL, functioning domains and common cancer symptoms of patient. Adjusted mean change from baseline in PCIG: a questionnaire that assesses a patient's overall perception of improvement or change in their condition over time
Safety and tolerability	Analyses including AEs, SAEs, discontinuation of investigational product due to AE(s), deaths, laboratory data, and vital signs

Abbreviations: AE: adverse event; BIRC: blinded independent review committee; CR: complete response; DCR: disease control rate; CSR: clinical study report; DOR: duration of response; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HRQoL: health-related quality of life; ORR: objective response rate; OS: overall survival; PCIG: Patient's Clinical Impression of Global; PD: progressive disease; PFS: progression-free survival; PR: partial response; QoL: quality of life; RECIST: Response Evaluation Criteria in Solid Tumours; SAE: serious adverse event; SD: stable disease.

Source: Ipsen Data on File, 2024 (CABINET CSR),² Ipsen Data on File, 2024 (CABINET Protocol),⁸⁸ Ipsen Data on File, 2024 (Descriptive Analysis of Questionnaire Responses in the CABINET QoL Substudy),⁹⁰ Schwartz, 2016.⁸⁹

2.3.3 Baseline characteristics

Demographic characteristics

Baseline demographics were generally well balanced between treatment arms in both cohorts, as shown in Table 9.^{2, 13}

For the pNET cohort, the median age was 60 years in the cabozantinib arm and 64 years in the placebo arm.¹³ The majority of patients in both treatment arms (cabozantinib arm: 63%; placebo arm: 52%) were <65 years of age. In total, 55% of patients in both treatment arms received SSA concurrently; 27% of patients in the cabozantinib arm and 29% of patients in the placebo arm had received prior sunitinib therapy.^{2, 13}

In both arms of the epNET cohort, the median age was 66 years, and the majority of patients (55%) were ≥65 years of age. In total, 69% of patients in the cabozantinib arm and 70% of patients in the placebo arm received SSA concurrently; 55% in both treatment arms had midgut/unknown as the primary tumour site.^{2, 13}

UK clinical experts highlighted that cabozantinib would be used in UK clinical practice in line with the CABINET trial population, which informs the anticipated marketing authorisation of cabozantinib and the proposed treatment pathway (see Section 1.3.4).¹²

Table 9: Key demographic and baseline characteristics (pNET cohort and epNET cohort; ITT population)

Characteristic	pNET cohort		epNET cohort	
	Cabozantinib (n=64)	Placebo (n=31)	Cabozantinib (n=134)	Placebo (n=69)
Age (years)				
Median (range)	59.5 (29–79)	64.0 (39–79)	66.0 (28–86)	66.0 (30–82)
Male	37 (58%)	18 (58%)	60 (45%)	38 (55%)
Female	27 (42%)	13 (42%)	74 (55%)	31 (45%)
Race, n (%)				
White	54 (84%)	25 (81%)	115 (86%)	55 (80%)
Black or African American	3 (4.7%)	3 (9.7%)	9 (6.7%)	7 (10%)
Asian	4 (6.3%)	0	3 (2.2%)	1 (1.4%)
American Indian or Alaska Native	1 (1.6%)	0	0	0
Native Hawaiian or Other Pacific Islander	1 (1.6%)	0	0	0
Not reported	0	2 (6.5%)	2 (1.5%)	4 (5.8%)
Unknown	0	1 (3.2%)	5 (3.7%)	2 (2.9%)
Multiple	1 (1.6%)	0	0	0
Ethnicity, n (%)				
Hispanic or Latino	2 (3.1%)	2 (6.5%)	8 (6.0%)	9 (13%)
Not Hispanic or Latino	61 (95%)	26 (84%)	125 (93%)	56 (81%)
Not reported	1 (1.6%)	2 (6.5%)	0	3 (4.3%)

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Unknown	0	1 (3.2%)	1 (0.7%)	1 (1.4%)
ECOG performance status (as reported on the OPEN registration system)				
0	35 (55%)	15 (48%)	49 (37%)	32 (46%)
1	28 (44%)	16 (52%)	84 (63%)	36 (52%)
2	1 (1.6%)	0	1 (0.7%)	1 (1.4%)

Abbreviations: ECOG: Eastern Cooperative Oncology Group; epNET: extra-pancreatic neuroendocrine tumour; ITT: intent-to-treat; OPEN: Oncology Patient Enrollment Network; pNET: pancreatic neuroendocrine tumour.

Sources: Ipsen Data on File, 2024 (CABINET CSR; pNET: Table 30; epNET: Table 13).²

Disease and treatment characteristics

Patients enrolled in the CABINET study were required to have advanced or metastatic pNETs or epNETs that had progressed after at least one prior systemic therapy. Prior treatment with SSAs alone was not sufficient to meet the definition of previous systemic treatment. Baseline disease status was similar between treatment arms for each cohort and was consistent with the study entry criteria (Table 10).²

There was a long time from diagnosis to randomisation in both the pNET cohort and epNET cohort of the CABINET trial. This is unsurprising given patients had received, and progressed on, multiple prior systemic therapies prior to enrolment in the trial. For the pNET cohort, the median time from diagnosis to randomisation was 71.3 months for the cabozantinib arm and 73.6 months for the placebo arm.² For the epNET cohort, the median time from diagnosis to randomisation was 64.7 months for the cabozantinib arm and 75.9 months for the placebo arm.

There were some differences in cohort allocation and stratification between the OPEN registration system used for cohort allocation and stratification and electronic data capture (EDC). As a result, seven patients with a diagnosis of pNET were misallocated during enrolment to the epNET cohort. Three patients with a diagnosis of epNET were misallocated during enrolment to the pNET cohort. A post-hoc analysis to adjust for misallocation of patients to the pNET and epNET cohort was also performed to correct for misallocations. However, given only small numbers of patients were misallocated, and misallocation was balanced across treatment arms, sensitivity analysis using disease allocation and stratification factors per EDC was consistent with the primary analysis. The results based on OPEN (the intention-to-treat [ITT] population) form the key evidence base for this submission as this post-hoc adjustment breaks randomisation. Results for the sensitivity analysis are presented in Appendix J.

The CABINET population is heavily pre-treated, with a mean number of prior systemic therapies ranging between 1.8 and 2.7, largely including PRRT (around 60% in all populations) and everolimus (between 64% and 80%).² Generally, UK clinical experts stated that cabozantinib would likely be used in clinical practice in line with the CABINET trial population, which informs the anticipated marketing authorisation.¹² This aligns with the high unmet need in the population addressed in this submission who have limited treatment options other than BSC, once they have progressed on prior lines of systemic therapy. Further details on prior systemic treatments are presented in Table 10.

Table 10: Cancer history and baseline disease status (pNET cohort and epNET cohort; ITT population)

	pNET cohort		epNET cohort	
	Cabozantinib (n=64)	Placebo (n=31)	Cabozantinib (n=134)	Placebo (n=69)
Tumour type, n (%)				
pNET ^a	62 (97%)	30 (97%)	4 (3.0%)	3 (4.3%)
epNET ^b	2 (3.1%)	1 (3.2%)	130 (97%)	66 (96%)
Histologic type:				
Carcinoid tumour	1 (1.6%)	1 (3.2%)	85 (63%)	54 (78%)
Atypical carcinoid tumour	0	0	26 (19%)	11 (16%)
Not specified ^c	1 (1.6%)	0	19 (14%)	1 (1.4%)
Time from initial diagnosis of the primary tumour to randomisation (months)^d				
Mean (SD)	85.7 (48.38)	86.1 (53.85)	89.7 (77.15)	90.5 (63.40)
Median (Range)	71.3 (18–214)	73.6 (18–230)	64.7 (9–489)	75.9 (14–340)
Primary tumour site, n (%)				
Pancreas	62 (97%)	30 (97%)	4 (3.0%) ^a	3 (4.3%) ^a
Lung	0	0	27 (20%)	12 (17%)
Stomach	1 (1.6%) ^b	0	3 (2.2%)	2 (2.9%)
Small bowel (including duodenum, jejunum, ileum)	1 (1.6%) ^b	0	37 (28%)	29 (42%)
Appendix	0	0	1 (0.7%)	0
Caecum	0	1 (3.2%) ^b	3 (2.2%)	0
Non-caecum colon	0	0	2 (1.5%)	0
Rectum	0	0	5 (3.7%)	6 (8.7%)
Thymus	0	0	6 (4.5%)	4 (5.8%)
Unknown	0	0	22 (16%) ^e	2 (2.9%) ^e
Other	0	0	24 (18%) ^f	11 (16%) ^f
Functional (hormone secretion) status, n (%)				
Functional tumour	11 (17%)	5 (16%)	41 (31%)	25 (36%)
Non-functional tumour	48 (75%)	22 (71%)	75 (56%)	34 (49%)
Unknown	5 (7.8%)	4 (13%)	18 (13%)	10 (14%)
Tumour grade, n (%)				
G1	14 (22%)	7 (23%)	37 (28%)	15 (22%)
G2	39 (61%)	19 (61%)	86 (64%)	48 (70%)
G3	8 (13%)	3 (9.7%)	8 (6.0%)	5 (7.2%)
Unknown ^a	3 (4.7%)	2 (6.5%)	3 (2.2%)	1 (1.4%)
Histologic differentiation, n (%)				
Well differentiated	59 (92%)	30 (97%)	118 (88%)	61 (88%)
Moderately differentiated	4 (6.3%)	0	6 (4.5%)	5 (7.2%)
Poorly differentiated	0	0	0	0
Not specified	1 (1.6%)	1 (3.2%)	10 (7.5%)	3 (4.3%)
Extent of disease, n (%)				

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Locally advanced	1 (1.6%)	2 (6.5%)	0	0
Metastatic	63 (98%)	29 (94%)	134 (100%)	69 (100%)
Number of prior systemic anticancer regimens^a				
Prior SSA use, n (%)	63 (98%)	30 (97%)	124 (93%)	64 (93%)
Mean (SD)	2.7 (1.54)	2.6 (1.74)	1.9 (1.04)	1.8 (1.07)
Median (Range)	3.0 (1–8)	2.0 (1–7)	2.0 (1–5)	2.0 (1–6)
≥3	33 (52%)	12 (39%)	35 (26%)	15 (22%)
Types of prior systemic anti-cancer regimens (excluding SSAs)^h				
Everolimus, n (%)	51 (80%)	25 (81%)	96 (72%)	44 (64%)
PRRT, n (%)	38 (59%)	18 (58%)	81 (60%)	41 (59%)
Anti-VEGFR TKI	19 (30%)	8 (26%)	7 (5.2%)	6 (8.7%)
Sunitinib	18 (28%)	7 (23%)	4 (3.0%)	1 (1.4%)
Other anti-VEGFR TKI	1 (1.6%)	1 (3.2%)	3 (2.2%)	5 (7.2%)
Cytotoxic chemotherapy regimens	44 (69%)	18 (58%)	51 (38%)	23 (33%)
Other	6 (9.4%)	3 (9.7%)	10 (7.5%)	2 (2.9%)

^a Seven patients with a diagnosis of pNET were misallocated during enrolment to the epNET cohort. ^b Three patients with a diagnosis of epNET were misallocated during enrolment to the pNET cohort. ^c Eligible patients with pNETs and epNETs were required to meet only ONE of the following criteria: 1) well- or moderately differentiated NET; 2) low- or intermediate-grade NET; or 3) carcinoid or atypical carcinoid tumour. ^d Time from initial diagnosis of the primary tumour to randomisation was only measured in 67 of the 69 patients in the placebo arm of the epNET cohort. ^e Exact primary tumour location could not be identified but a diagnosis of epNET was made. ^f Other includes mesenteric, ampullary, hindgut, biliary tract, larynx, pre-sacral, kidney and ethmoid sinus; ^g A regimen was defined as a unique systemic anticancer therapy, excluding SSAs. ^h More than one category may be self-reported by the patient.

Abbreviations: epNET: extra-pancreatic neuroendocrine tumour; G: Grade; ITT: intent-to-treat; OPEN: Oncology Patient Enrolment Network; pNET: pancreatic neuroendocrine tumour; PRRT: peptide receptor radionuclide therapy; SD: standard deviation; SSA: somatostatin analogue; TKI: tyrosine kinase inhibitor; VEGFR: vascular endothelial growth factor receptor.

Sources: Ipsen Data on File, 2024 (CABINET CSR; pNET: Tables 31–33; epNET: Tables 14–16).²

2.3.4 Participant flow

pNET cohort

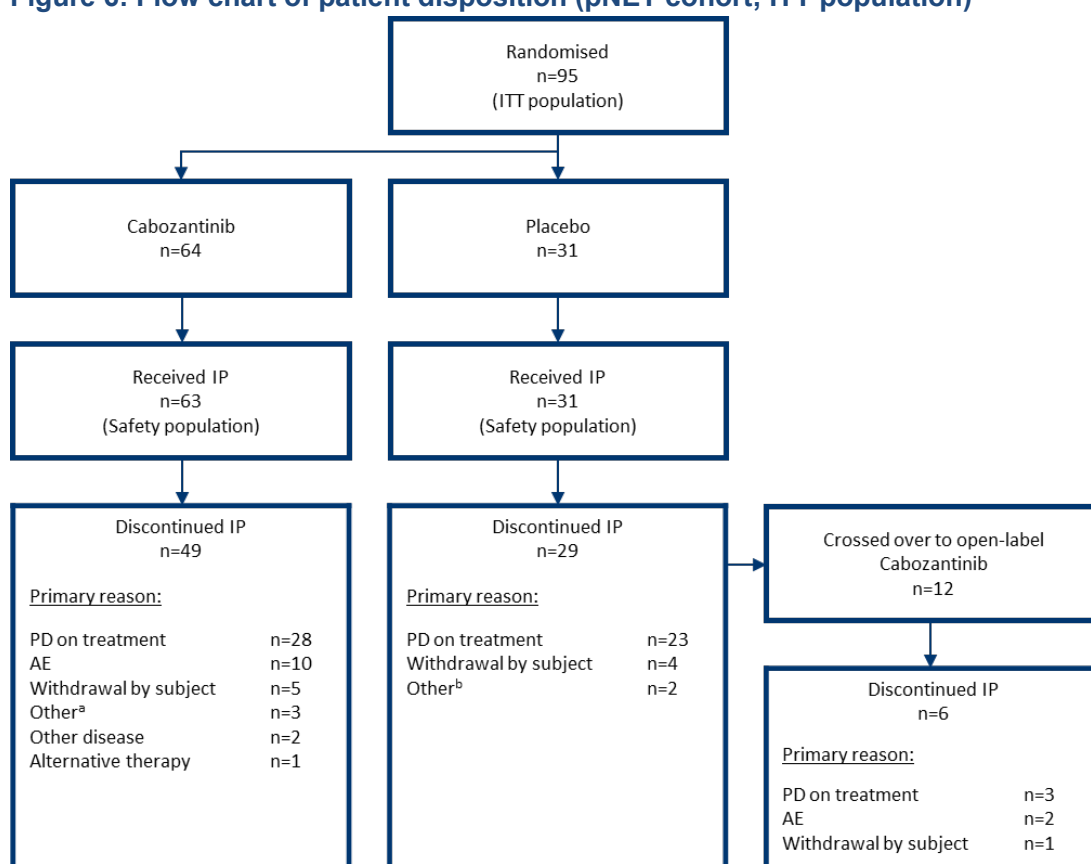
Patient disposition in the pNET cohort is summarised in Figure 6. A total of 95 patients with pNETs were randomised (cabozantinib arm: 64; placebo arm: 31). One patient in the cabozantinib arm withdrew from the study prior to receiving study treatment.¹ At the 24th August 2023 data cut-off (DCO):

- Study treatment had been discontinued by 49 patients (77%) in the cabozantinib arm and 29 patients (94%) in the placebo arm, primarily due to disease progression (cabozantinib arm: 44%; placebo arm: 74%) and AEs, side effects or complications (cabozantinib arm: 16%; placebo arm: 0%).²
- A total of 12 patients (41%) from the placebo arm crossed-over to open-label cabozantinib treatment following real-time centrally confirmed disease progression and discontinuation of investigational product (IP).²

- A total of 14 patients in the cabozantinib arm and 2 patients in the placebo arm were still receiving blinded study treatment, and 6 patients who had previously crossed over from the placebo arm were receiving open-label cabozantinib.²
- The median follow-up times were 23.2 months in the cabozantinib arm and 25.2 months in the placebo arm.²

In the pNET cohort, 3 patients (cabozantinib arm: 2; placebo arm: 1) had a diagnosis of epNET and were misallocated to the pNET cohort.²

Figure 6: Flow chart of patient disposition (pNET cohort; ITT population)



DCO 24th August 2023. ^a In the CABOMETYX® arm, 'other' included the following: clinical progression (1 patient), physician discretion (1 patient), and treatment hold for >28 days (1 patient). ^b In the placebo arm, 'other' included the following: treatment hold for >28 days (1 patient) and palliative care (1 patient).

Abbreviations: AE: adverse event; DCO: data cut-off; IP: investigational product; ITT: intent-to-treat; PD: progressive disease; pNET: pancreatic neuroendocrine tumour.

Source: Ipsen Data on File, 2024 (CABINET CSR; Figure 10).²

epNET cohort

Patient disposition in the epNET cohort is summarised in Figure 7. A total of 203 patients with epNETs were randomised (cabozantinib arm: 134; placebo arm: 69). Two patients in each treatment arm withdrew from the study prior to receiving any study treatment.¹³ At the 24th August 2023 DCO:

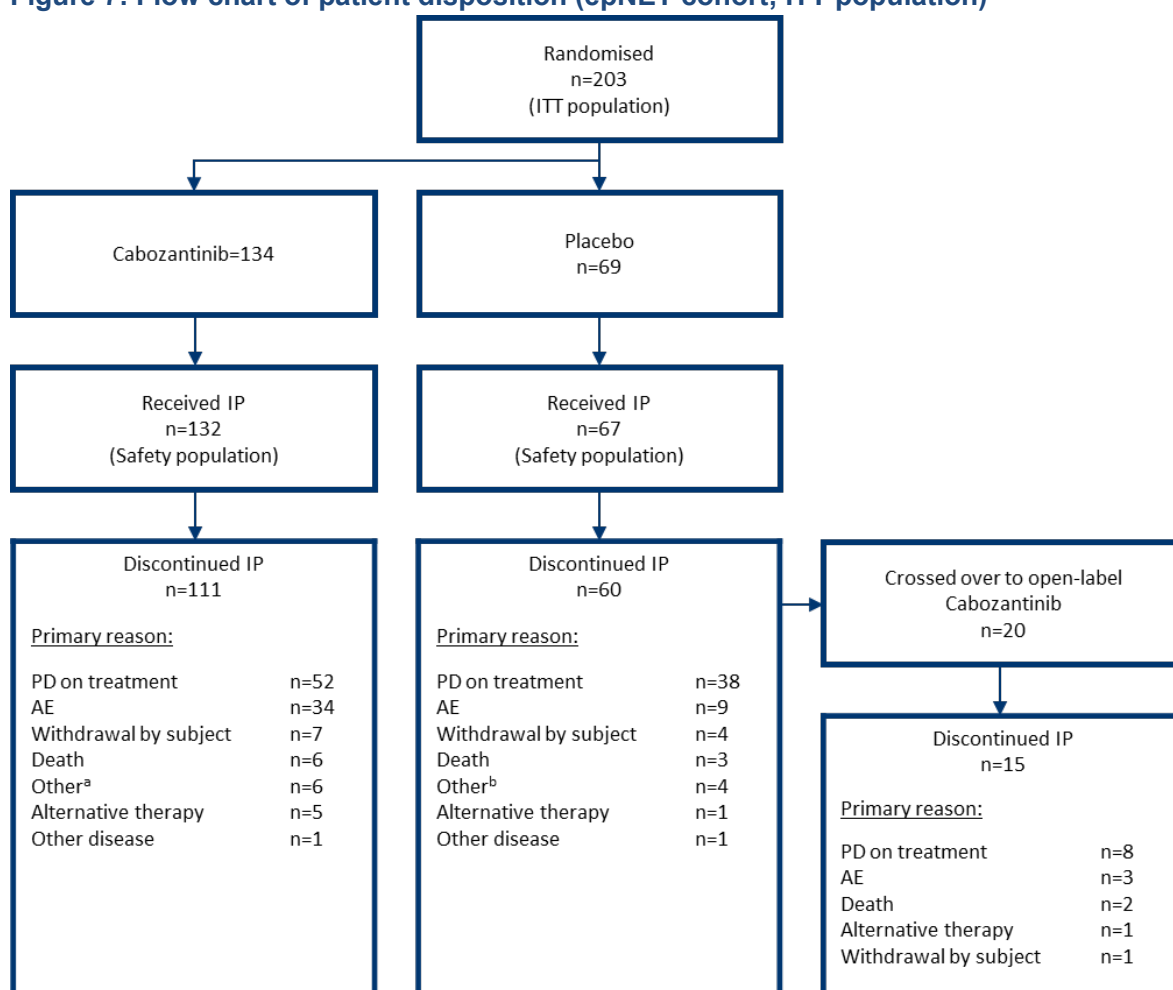
- Study treatment had been discontinued by 111 patients (83%) in the cabozantinib arm and 60 patients (87%) in the placebo arm, primarily due to disease progression (cabozantinib arm: 39%; placebo arm: 55%) or occurrence of an AE (cabozantinib arm: 25%; placebo arm: 13%).²

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- A total of 20 patients (29%) from the placebo arm crossed-over to open-label cabozantinib treatment following real-time centrally confirmed disease progression and discontinuation of IP.²
- Blinded study treatment was being received by 21 patients in the cabozantinib arm and 7 patients in the placebo arm. Five patients who had previously crossed over from the placebo arm were receiving open-label cabozantinib.²
- The median follow-up times were 23.3 months in the cabozantinib arm and 23.0 months in the placebo arm.²

In the epNET cohort, 7 patients (4 randomised to the cabozantinib arm and 3 randomised to the placebo arm) had a diagnosis of pNET and were misallocated to the epNET cohort.²

Figure 7: Flow chart of patient disposition (epNET cohort; ITT population)



DCO 24th August 2023. ^a In the cabozantinib arm, 'other' included the following: clinical progression (2 patients), worsening of non-target lesion (1 patient), loss of consciousness (1 patient), poor performance status (1 patient), and non-compliance (1 patient). ^b In the placebo arm, 'other' included the following: clinical progression (3 patients) and increase in tumour lesion size (liver nodule) (1 patient).

Abbreviations: AE: adverse event; CSR: clinical study report; epNET: extra-pancreatic neuroendocrine tumour; IP: investigational product; ITT: intent-to-treat; PD: progressive disease.

Source: Ipsen Data on File, 2024 (CABINET CSR; Figure 2).²

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Data cuts

Initially, three analyses were planned for the CABINET trial. Two interim analyses for PFS futility were pre-planned for both disease cohorts when 33% and 66% of the projected number of events had occurred. A final efficacy analysis was also planned for when 100% of the projected number of events had occurred (149 PFS events for the pNET cohort, and 164 PFS events for the epNET cohort).

However, on 28th July 2023, the Data and Safety Monitoring Board (DSMB) reviewed the interim analyses for PFS for the pNET and epNET cohorts. Based on compelling efficacy in terms of PFS by investigator and blinded independent review committee (BIRC) observed during the interim analyses of both cohorts, the DSMB voted unanimously to recommend termination of patient recruitment and unblinding of the study to enable potential crossover for patients on the placebo treatment arms (i.e. to allow them to receive open-label cabozantinib treatment).^{2, 13}

Following the DSMB recommendation, enrolment into the study was stopped on 7th August 2023. Unblinding of trial group assignments and crossover of placebo-treated patients to open-label cabozantinib occurred on 24th August 2023. The final efficacy analysis (i.e. when 100% of the projected events had occurred) originally planned will no longer be conducted and therefore the 24th August 2023 represents the DCO for the final analyses of PFS, objective response rate (ORR) and safety which is presented in this submission.^{2, 13} A prespecified analysis of OS was conducted with the primary analysis of PFS.²

Available analyses

All results presented throughout this submission are aligned to the clinical study report (CSR). Results from the CABINET trial are also available in the Chan *et al.*, 2024 manuscript.¹³ However, the results from the CSR are presented in this submission as, unlike the results reported in Chan *et al.*, 2024, the censoring rules applied in the analysis included in the CSR are aligned with EMA guidelines.¹³ Therefore, there may be small differences in data between these two sources. In all cases, the CSR is considered the primary data source.

As discussed in Section 2.3.3 a post-hoc analysis to adjust for misallocation of patients to the pNET and epNET cohort was also performed to correct for misallocations. However, the results in the CSR are preferred as this post-hoc adjustment breaks randomisation. This reallocation analysis is presented in Appendix J as supportive evidence and demonstrates similar results.

In summary, the data presented henceforth represent the 24th August 2023 DCO generated following the recommendation of early termination of the CABINET trial, as reported in the CSR.

Study populations and statistical methods

The definitions used for the study populations in the trial are presented in Table 11. A summary of the statistical analysis methods used in the trial are presented in Table 12.

Table 11: Trial populations used for the analysis of outcomes in CABINET

Analysis Set	Definition	Outcomes analysed
ITT population (pNET n=95; epNET n=203)	All randomised patients within each cohort (pNET and epNET). The ITT populations were used to analyse patient baseline characteristics, disease characteristics, and efficacy endpoints. Patients were grouped based on their assigned treatment at randomisation	Efficacy
Safety population (pNET n=94; epNET n=199)	All patients who received at least one dose of any study medication. The safety population was used for exposure and safety analyses, and patients were grouped based on the actual treatments that they received	Safety
HRQoL population (pNET n=83; epNET n=171)^a	All QoL data to be analysed were collected as IPD from CABINET as part of the protocol-specified QoL sub study (A021602-HO1)	HRQoL

^a 83 participants in the pNET cohort and 171 participants in the epNET cohort had at least one EORTC QLQ-C30 response during the course of the sub study

Abbreviations: CSR: clinical study report; epNET: extra pancreatic neuroendocrine tumour; HRQoL: health-related quality of life; EORTC: European Organisation for Research and Treatment of Cancer; IPD: individual patient data; ITT: intention-to-treat; pNET: pancreatic neuroendocrine tumour; QLQ: quality of life questionnaire core 30; QoL: quality of life.

Source: Ipsen Data on File, 2024 (CABINET CSR);² Ipsen Data on File, 2024 (Descriptive Analysis of Questionnaire Responses in the CABINET QoL Substudy).⁹⁰

Table 12: Statistical methods for the primary analysis

Hypothetical objective	The study was designed to test the hypothesis that cabozantinib tablets (60 mg once daily) have superior efficacy and acceptable tolerability compared with placebo in patients with advanced NETs that have progressed after systemic treatment (excluding SSAs)
Statistical analysis	- The primary statistical analysis of the efficacy of cabozantinib included all randomised patients and compared the treatment groups on the basis of randomised treatment, regardless of the treatment actually received (ITT). When assessing safety and tolerability, summaries were produced based on the Safety Population. This included all patients who received at least one dose of randomised treatment (cabozantinib or placebo) Primary endpoint: PFS - For PFS, a type 1 error spend of two-sided 0.002 (i.e. one-sided 0.001) had been pre-specified for each protocol-defined futility analysis and a two-sided spend of 0.046 (i.e. one-sided 0.023) had been pre-specified for the primary analysis of PFS per RECIST 1.1 by BIRC (primary endpoint) within each disease cohort, using the stratification factors at randomisation. As the DSMB recommended early unblinding of the study at the trial interim analyses, the PFS analysis was compared between the treatment arms at the two-sided significance level of 0.002 (i.e. one-sided significance level of 0.001). The HR for PFS was estimated using a stratified Cox proportional hazards model, and the 95% CI for the HR was provided² - For the primary endpoint analysis, participants were censored per FDA guidance - Only adequate tumour assessments with an overall response of CR, PR, SD (Non-CR/Non-PD), or PD obtained from RECIST by BIRC were considered in the determination of progression/censoring dates - Patients who received a subsequent non-protocol anticancer therapy (NPACT) after randomisation and before experiencing an event were censored at the date of the last adequate tumour assessment on or prior to the date of initiation of subsequent NPACT. - Patients who did not have a PFS event were censored for PFS at the last adequate tumour assessment date prior to initiation of the new subsequent NPACT, including crossover therapy - For the primary calculation of PFS duration, patients with PD or death following two or more consecutive missing tumour assessments were censored at the date of the last adequate tumour assessment prior to the missing scans. PFS analyses were initially censored according to Alliance-specified rules (which ignored missing scans); however, censoring rules were updated to follow FDA-recommended censoring rules in the SAP addendum Key secondary endpoints - Per the FDA guidance for survival analysis, a nominal alpha was spent for each of the descriptive analyses conducted prior to the analysis of OS (secondary endpoint). OS at the analysis was compared between treatment arms using the stratified log-rank test at a two-sided significance level of 0.046 (i.e. one-sided significance level of 0.023). A hierarchical approach was used to control for family-wise type-I error rate for the analysis of OS² - As OS data were immature at the DCO date of 24th August 2023 and had not reached the prespecified number of events required for the analysis, a nominal alpha of two-sided significance level 0.002 (i.e. one-sided significance level of 0.001) was used to compare the two treatment arms. Median OS was estimated for both treatment arms using the KM method, along with 95% CIs and landmark OS values. For the analysis of OS, the duration of OS was calculated from randomisation to the date of death or the last known alive date,

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	with all deaths prior to the DCO date counted as events ²
Sample size, power calculation	The CABINET trial planned to enrol approximately 185 patients in the pNET cohort and 210 patients in the epNET cohort, to provide the trial with 90% power to detect a HR of 0.583 between the two treatment arms^{2, 13}
Data management, patient withdrawals	- Patients could discontinue study treatment or withdraw consent to participate in the study at any time. If constraints of this protocol were detrimental to the patient's health and/or the patient no longer wished to continue protocol therapy, then study treatment was discontinued, the reason for discontinuation was documented, and the patient was followed (if the patient agreed) for response and survival until death or 8 years after registration (randomisation) - In general, other than for partial dates, missing data was not imputed and was treated as missing. The algorithms for imputation of partial dates varied depending upon the parameter (see Appendix A of SAP included in reference pack alongside this submission) HRQoL - Patients were censored from QoL analyses upon disease progression. The booklet submitted closest to and at most 6 weeks before or after each pre-defined timepoint was selected after booklets without any non-missing items were excluded. - QLQ-C30 and QLQ-GINET.21 domain scores were calculated if at least half of the items from the scale were non-missing, assuming that missing items had values equal to the mean of non-missing items.^a A QLQ-C30 summary score was only computed if all domain scores were non-missing - Descriptive summary statistics (mean, 95% CI) were plotted separately for pNET and epNET patients, at Weeks 0, 12, 24, 36, 48 and 60, for QLQ-C30 and PGIC global scores as well as QLQ-C30 and QLQ-GINET21 domain scores^b - No method was identified to calculate an overall summary score for QLQ-GINET21 and therefore this is not presented. CIs were not calculated at timepoints where fewer than two patients were included in either arm. CIs were truncated at the minimum or maximum possible score for the given questionnaire (0 and 100 for EORTC questionnaires and 1 and 7 for PGIC) if required; in this case, CIs are represented by a dotted line
Multiplicity	No adjustments were made for multiple analyses of PFS and OS, as the only formal testing for this analysis is PFS, and the analysis of OS was not formally tested. The planned methodology for the analysis of OS used a hierarchical approach to control for family-wise type-I error rate, with OS formally tested only if the primary efficacy endpoint, PFS, is statistically significantly different between the 2 treatment arms within each cohort. As it has been demonstrated, PFS was statistically significant; therefore, OS was formally tested based on this prespecified plan

^a For GINET21, items with "N/A" responses were disregarded in the calculation of missing and non-missing items; however, no treatment scale score was calculated if "N/A" was selected for "Have you had side-effects from your treatment?" and "Have you had a problem from repeated injections?" ^b Confidence intervals were computed as 1.96 times the standard error either side of the mean.

Abbreviations: BIRC: blinded independent review committee; CI: confidence interval; CSR: clinical study report; DCO: data cut-off; HR: hazard ratio; FDA: Food and Drug Administration; ITT: intention-to-treat; KM: Kaplan-Meier; mg: milligram; NPACT: non-protocol anticancer therapy; OS: overall survival; PFS: progression-free survival; PGIC: Patient Global Impression of Change; RECIST: Response Evaluation Criteria in Solid Tumours; SAP: statistical analysis plan; SD: stable disease; SSA: somatostatin analogue; QoL: quality of life; QLQ-C30: Quality Of Life Questionnaire Core 30; QLQ-GINET.21: Quality of Life Questionnaire-Gastrointestinal Neuroendocrine Tumors 21.

Source: Ipsen Data on File, 2024 (CABINET CSR),² Ipsen Data on File, 2024 (CABINET SAP)⁹¹ Ipsen Data on File, 2024 (Descriptive Analysis of Questionnaire Responses in the CABINET QoL Substudy).⁹⁰

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2.5 Critical appraisal of the relevant clinical effectiveness evidence

Full details of the SLR, including methods and results of the quality assessment can be found in Appendix B. A summary of the quality assessments conducted based on the revised Cochrane risk-of-bias tool (RoB2) for the CABINET trial is presented in Table 13, which demonstrates CABINET to be a high quality trial at low risk of bias.

Table 13: Assessment of quality for CABINET, assessed by the RoB2 tool

Criteria	Response	Notes
Randomisation process	Low risk	All of the three quality assessment questions for the randomisation process domain were considered low risk. Despite not being able to confirm a complete lack of bias given crossover from placebo to cabozantinib impacting OS data, the risk overall was still low. There were some differences in cohort allocation and stratification between the OPEN registration system used for cohort allocation and stratification and EDC. As a result, seven patients with a diagnosis of pNET were misallocated during enrolment to the epNET cohort. However, misallocation was balanced across treatment arms, and the resulting risk of bias is considered low. Given only small numbers of patients were misallocated, and misallocation was balanced across treatment arms, sensitivity analysis using disease allocation and stratification factors per EDC was consistent with the primary analysis.
Effect of assignment to intervention	Low risk	ITT was used for all primary analyses, which are not subject to bias due to crossover (patients were eligible to crossover from placebo to open-label cabozantinib on progression, and thus PFS endpoints are not subject to bias). Whilst crossover from placebo to open-label cabozantinib may introduce bias in results for OS (a secondary endpoint), appropriate analyses were explored to adjust for the impact of crossover. Further details on the adjustments explored are outlined in Appendix L. Therefore, this was considered low risk overall.
Missing outcome data	Low risk	ITT was used for all primary analyses, and thus there is low risk of missing outcome data.
Measurement of outcome	Low risk	No information to suggest outcomes were measured differently, methods equally applied to both treatments.
Selection of the reported results	Low risk	The reported result corresponds to the intended outcome measurement.
Overall risk of bias	Low risk	

Abbreviations: EDC: electronic data capture; ITT: intention-to-treat; OPEN: Oncology Patient Enrollment Network; OS: overall survival; PFS: progression-free survival. RoB2: revised Cochrane risk-of-bias tool.

2.6 Clinical effectiveness results of the relevant studies

As discussed in Section 2.4, all results presented throughout this submission are aligned to the CSR, which is considered the primary evidence source for the CABINET trial. The post-hoc

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analysis adjusting for misallocation of patients to the pNET and epNET cohort is presented in Appendix J as supportive evidence and demonstrates similar results.

The CABINET trial met its primary objective, demonstrating superior efficacy in terms of PFS for patients with both pNETs and epNETs receiving cabozantinib versus placebo. Statistical and clinically meaningful benefits were also demonstrated amongst the secondary efficacy endpoints, as shown in Table 14.

Table 14: Summary of CABINET efficacy endpoint results

Outcome Measure	pNET		epNET	
	Cabozantinib (n=64)	Placebo (n=31)	Cabozantinib (n=134)	Placebo (n=69)
PFS				
Number of events, n (%)	32 (50)	25 (81)	71 (53)	40 (58)
Median PFS (months)	13.83	4.47	8.48	3.98
HR (95% CI)	0.23 (0.12, 0.42)		0.38 (0.25, 0.58)	
Stratified 2-sided p-value	<0.0001		<0.0001	
OS				
Number of events, n (%)	21 (33)	11 (35)	60 (45)	37 (54)
Median OS	40.08	31.11	21.95	19.71
HR (95% CI)	0.95 (0.45, 2.00)		0.86 (0.56, 1.31)	
Log-rank test: p-valued	0.8852		0.4871	
ORR				
Number of CR, n (%)	0	0	0	0
Number of PR, n (%)	12 (19)	0	7 (5.2)	0
Confirmed ORR (95% CI)	19 (10.1, 30.5)		5.2 (2.1, 10.5)	

Abbreviations: CI: confidence interval; CR: complete response; epNET: extrapancreatic neuroendocrine tumour; HR: hazard ratio; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour; PR: partial response.

Source: Ipsen Data on File, 2024 (CABINET CSR; pNET: Tables 35, 38 and 40; epNET: Tables 18, 21 and 23).²

2.6.1 Primary endpoint: progression-free survival

PFS was selected as the primary endpoint in the CABINET trial and has been validated and accepted as an endpoint for other treatments in patients with progressive NETs.² PFS is the National Cancer Institute (NCI)-recommended endpoint for Phase III studies for well-differentiated NETs.⁸⁶ The NET Task Force of the NCI GI Steering Committee also recommend PFS as a feasible and relevant primary endpoint for Phase III studies in NETs where there is likely to be a delay in progression.^{74, 86} Prolonged PFS is a clinically relevant endpoint as it delays the reduction in HRQoL associated with progression or relapse. Therefore, PFS has been selected as the primary endpoint of multiple key clinical trials in advanced NETs, irrespective of NETs setting.^{76, 92-94}

Furthermore, the use of PFS as a surrogate endpoint for overall survival (OS) has been validated in surrogacy analysis in this disease area. In observational cohorts of patients with metastatic NETs treated with single-agent SSAs or everolimus, longer PFS was found to be associated with improved OS.⁷⁶

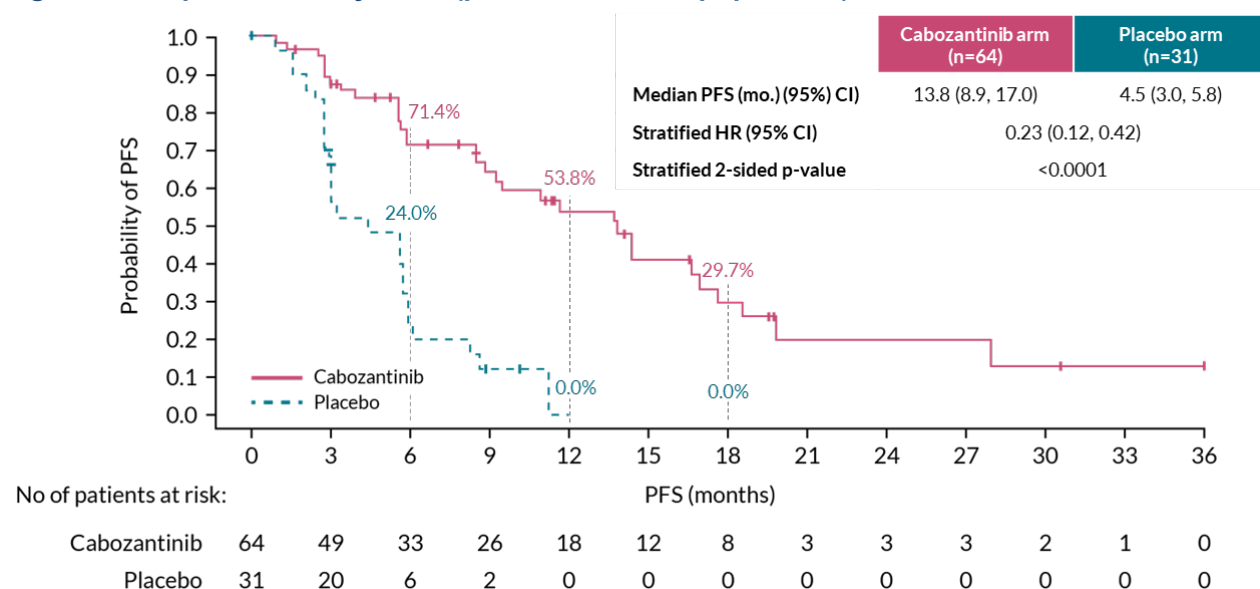
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pNET cohort

The risk of disease progression or death was 77% lower and the median PFS was ~9.4 months longer for patients receiving cabozantinib compared with placebo (median PFS: 13.83 months versus 4.47 months; hazard ratio [HR]: 0.23; 95% confidence interval [CI]: 0.12, 0.42; stratified 2-sided $p < 0.0001$); this improvement was statistically significant and considered clinically meaningful.² PFS events had occurred for 50% of patients ($n=32$; median follow-up 23.2 months) in the cabozantinib arm and for 81% of patients ($n=25$; median follow-up 25.2 months) in the placebo arm by the DCO of 24th August 2023. Sensitivity analysis for PFS using investigator assessments were consistent with results as assessed by BIRC (see Tables 20 and 37 in the CABINET CSR included in the reference pack and Appendix J for further details).

At 12 months, 53.8% of patients in the cabozantinib group and 0.0% of patients in the placebo group were alive and progression-free, as assessed by BIRC (Figure 8). The separation between the cabozantinib curve and placebo curve was maintained at landmarks of 6, 12 and 18 months.

Figure 8: KM plot of PFS by BIRC (pNET cohort; ITT population)



DCO: 24th August 2023. A bold pink or blue dash indicates a censored observation in the cabozantinib or placebo arm, respectively. The grey dotted lines and associated percentages for each treatment arm indicate the KM landmark estimates of percent of patients event-free at 6, 12 or 18 months. Stratification factors for pNET: 1. Concurrent SSA Use (Yes, No) and 2. Prior sunitinib therapy (Yes, No). Stratification was per OPEN criteria.

Abbreviations: BIRC: blinded independent review committee; CI: confidence interval; DCO: data cut-off; HR: hazard ratio; ITT: intent-to-treat; KM: Kaplan-Meier; LR: log-rank test; pNET: pancreatic neuroendocrine tumour; OPEN: Oncology Patient Enrollment Network.

Source: Ipsen Data on File, 2024 (CABINET CSR; Figure 11).²

epNET cohort

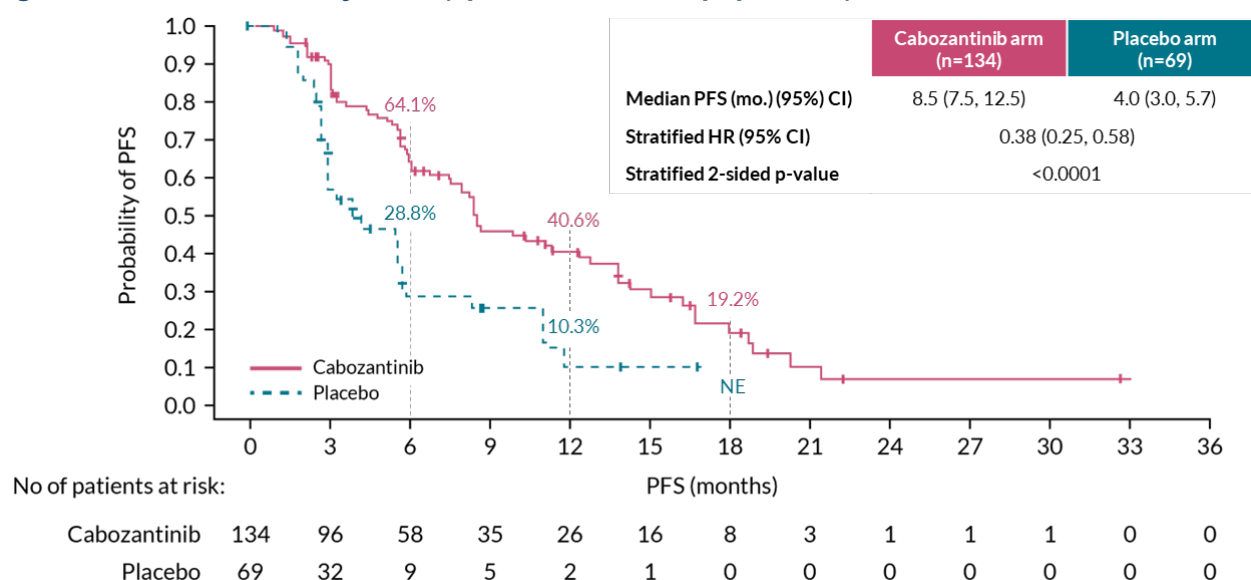
The risk of disease progression or death was 62% lower compared to placebo and the median PFS was 4.5 months longer with cabozantinib than with placebo (median PFS: 8.48 months versus 3.98 months; HR: 0.38; 95% CI: 0.25, 0.58; stratified 2-sided $p < 0.0001$); this improvement was statistically significant and considered clinically meaningful. PFS events occurred for 53% of patients ($n=71$; median follow-up: 23.3 months) in the cabozantinib arm and for 58% of patients ($n=40$; median follow-up: 23.0 months) in the placebo arm by the DCO of 24th August 2023.²

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Sensitivity analysis for PFS using investigator assessments were consistent with results as assessed by BIRC (see CSR included in the reference pack for further details).

At 12 months, 40.6% of patients in the cabozantinib group and 10.3% of patients in the placebo group were alive and progression-free, as assessed by BIRC (Figure 9). The separation between the cabozantinib curve and placebo curve was maintained at landmarks of 6, 12 and 18 months.

Figure 9: KM Plot of PFS by BIRC (epNET cohort; ITT population)



DCO: 24th August 2023. A bold pink or blue dash (– or |) indicates a censored observation. The grey dotted lines and associated percentages indicate the KM landmark estimates of percent of patients event-free at 6, 12 or 18 months. Stratification factors for epNET: 1. Concurrent SSA Use (Yes, No) and 2. Primary Site (Midgut/Unknown versus Non-midgut GI/Lung/Other). Stratification was per OPEN criteria.

Abbreviations: BIRC: blinded independent review committee; CI: confidence interval; DCO: data cut-off; epNET: extra-pancreatic neuroendocrine tumour; HR: hazard ratio; ITT: intent-to-treat; KM: Kaplan-Meier; LR: log-rank test; OPEN: Oncology Patient Enrollment Network.

Source: Ipsen Data on File, 2024 (CABINET CSR; Figure 3).²

2.6.2 Secondary endpoint: overall survival

Interpretation of OS data is limited due to the crossover design of the CABINET trial, and the immaturity of OS data at the time of clinical trial termination. In total, 34% of patients (n=32) in the pNET cohort and 48% of patients (n=97) in the epNET cohort had died across the cabozantinib and placebo arms. OS results were also confounded by 39% of patients with pNETs in the placebo arm (n=12) and 29% of patients with epNETs in the placebo arm (n=20) crossing over to open-label cabozantinib treatment after progression.²

Despite potential confounding due to crossover, a numerical benefit in OS was observed for cabozantinib versus placebo in the pNET cohort and epNET cohort. In both cohorts, OS HRs were <1, favouring the cabozantinib arm over the placebo arm.²

pNET cohort

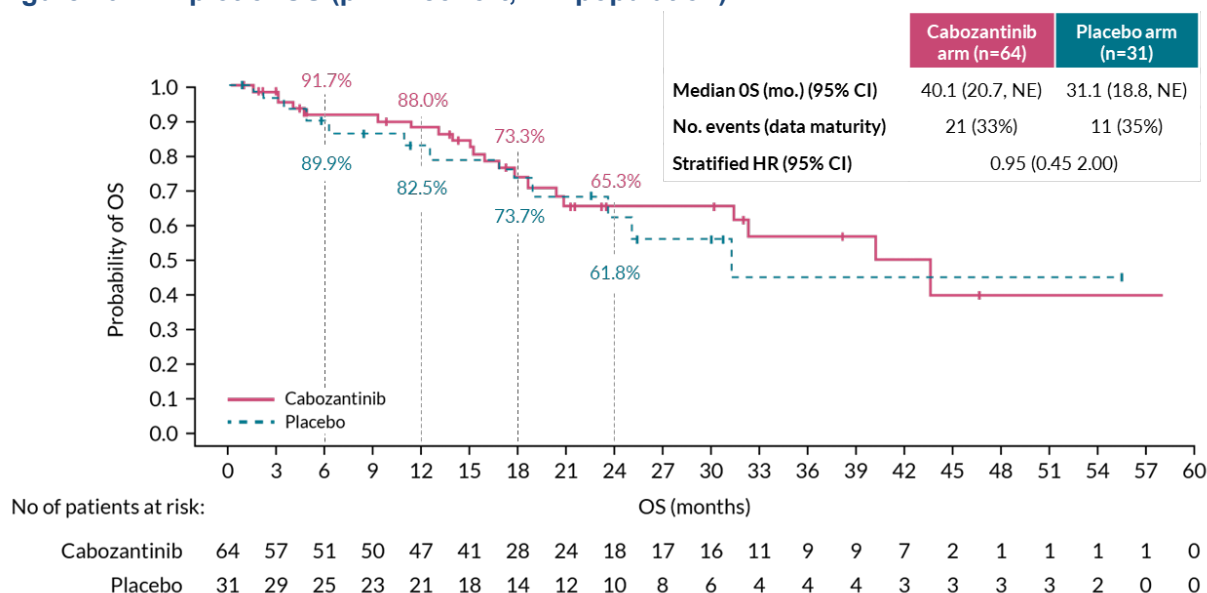
In the pNET cohort, 33% of patients (n=21) in the cabozantinib arm and 35% of patients (n=11) in the placebo arm had died at the time of DCO of 24th August 2023. A total of 39% of patients in the placebo arm (n=12) crossed over to receive cabozantinib; these patients were not censored

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at the time of crossover and were analysed under the arm to which they were randomised (i.e. placebo) for OS under ITT principles.²

The KM estimates of median OS were 40.08 months in the cabozantinib arm and 31.11 months in the placebo arm (stratified HR: 0.95; 95% CI: 0.45, 2.00; p=0.8852). KM estimates showed that, at most time-points, the proportion of patients estimated to be alive was greater in the cabozantinib arm compared with the placebo arm (Figure 10).²

Figure 10: KM plot of OS (pNET cohort; ITT population)



DCO: 24th August 2023. A bold pink or blue dash indicates a censored observation in the cabozantinib or placebo arm, respectively. The grey dotted lines and associated percentages for each treatment arm indicate the KM landmark estimates of percent of patients event-free at 6, 12 or 18 months. Stratification factors for pNET: 1. Concurrent SSA Use (Yes, No) and 2. Prior sunitinib therapy (Yes, No). Stratification was per OPEN criteria.

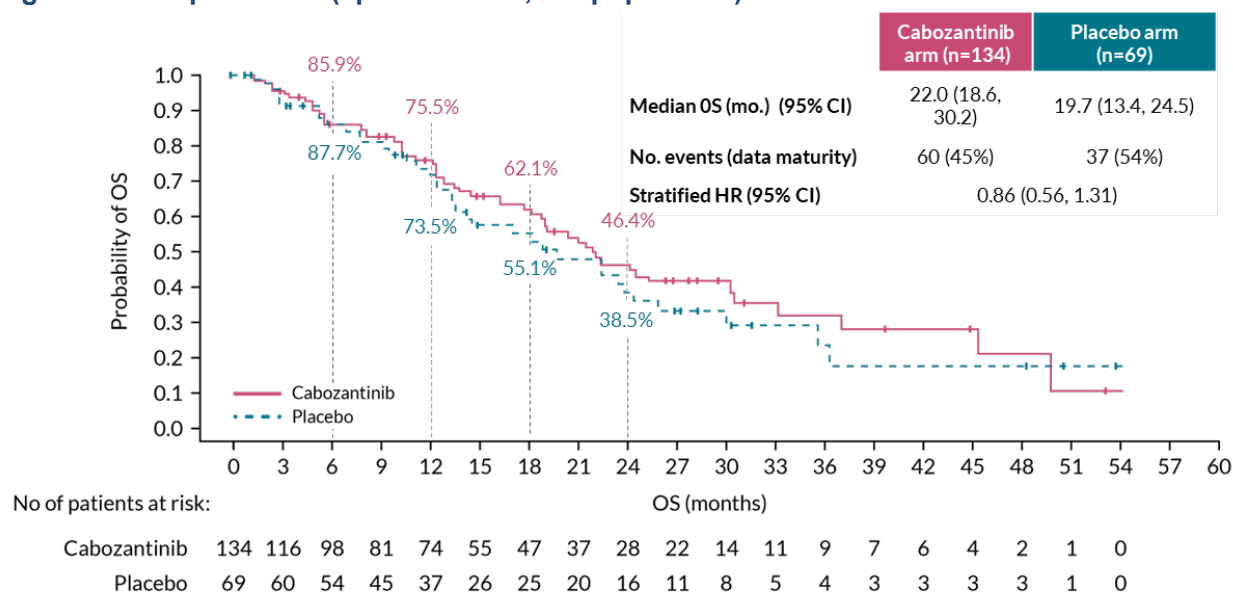
Abbreviations: CI: confidence interval; DCO: data cut-off; HR: hazard ratio; ITT: intent-to-treat; LR: log-rank test; OPEN: Oncology Patient Enrollment Network; OS: overall survival; pNET: pancreatic neuroendocrine tumour.

Source: Ipsen Data on File, 2024 (CABINET CSR; Figure 13).²

epNET cohort

In the epNET cohort, 45% of patients (n=60) in the cabozantinib arm and 54% of patients (n=37) in the placebo arm had died at the time of DCO of 24th August 2023. In the placebo arm, 29% of patients (n=20) crossed over to receive cabozantinib; these patients were not censored at the time of crossover and were analysed under the arm to which they were randomised (i.e. placebo) for OS under ITT principles.² The KM estimates of median OS were 21.95 months in the cabozantinib arm and 19.71 months in the placebo arm (HR: 0.86; 95% CI: 0.56, 1.31; p=0.4871). KM estimates showed that, at most time-points, the proportion of patients estimated to be alive was greater in the cabozantinib arm than the placebo arm (Figure 11).²

Figure 11: KM plot of OS (epNET cohort; ITT population)



DCO: 24th August 2023. A bold pink or blue dash indicates a censored observation in the cabozantinib or placebo arm, respectively. The grey dotted lines and associated percentages for each treatment arm indicate the KM landmark estimates of percent of patients event-free at 6, 12 or 18 months. Stratification factors for epNET: 1. Concurrent Somatostatin Analogue Use (Yes, No) and 2. Primary Site [Midgut/Unknown versus Non-midgut GI/Lung/Other]. Stratification was per OPEN criteria.

Abbreviations: CI: confidence interval; DCO: data cut-off; epNET: extra-pancreatic neuroendocrine tumour; HR: hazard ratio; ITT: intent-to-treat; KM: Kaplan-Meier; LR: log-rank test; OPEN: Oncology Patient Enrollment Network; OS: overall survival.

Source: Ipsen Data on File, 2024 (CABINET CSR; Figure 5).²

OS analyses adjusted for crossover

The impact of subsequent therapies is discussed in greater detail in Section 2.7. Despite a numerical OS benefit being observed, to determine the true impact of cabozantinib on overall survival, a post-hoc inverse-probability-of-censoring weighting (IPCW) analysis was used to adjust for crossover. HRs were reduced following adjustment in both the pNET and epNET cohorts, demonstrating a reduced hazard of death with cabozantinib. IPCW was deemed the more suitable method to adjust for crossover than the pre-specified Rank Preserving Structural Failure Time Model (RPSFTM). IPCW could account for prognostic factors in the estimation of weights and treatment effects and adjust the ITT HRs close to 1 more robustly than RPSFTM.⁹⁵ Details of the methodology of the IPCW analysis are presented in Appendix J and the results from this analysis are provided in Section 3.3.4.

2.6.3 Secondary endpoint: objective response rate

BIRC-assessed ORR was defined as the proportion of patients with best overall response of complete response (absence of detectable cancer) or partial response (greater than 30% reduction in size of tumour) and therefore is a clinically relevant endpoint as it directly measures the size of the tumour. Improvements in ORR indicate the tumour is responding to treatment which can translate to reduced symptoms for patients and improve physical functioning.⁸⁹

pNET cohort

In the pNET cohort, 19% of patients (n=12) in the cabozantinib arm had a confirmed PR and no patients had a confirmed CR, giving a confirmed ORR of 19% (95% CI: 10.1%, 30.5%). In

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comparison, no patients in the placebo arm had either a CR or PR, giving an ORR of 0% (95% CI: 0%, 11.2%) (Figure 12). These data yielded a confirmed ORR treatment difference of 18.8% (95% CI: 9.2%, 28.3%; with a p-value from the stratified Cochran–Mantel–Haenszel [CMH] test of 0.0115) (Table 15).²

The median time from randomisation to confirmed objective response was 5.78 months (range: 2.8–8.7) in the cabozantinib arm (n=12).² The best percentage change in BIRC-assessed tumour target lesion size from baseline is shown in Figure 12. The proportion of patients in the cabozantinib arm who had a post-baseline reduction in tumour target lesion size was higher than that observed in the placebo arm (80% versus 24%).²

epNET cohort

In the epNET cohort, 5.2% of patients (n=7) in the cabozantinib arm had a confirmed PR and no patients had a confirmed CR, giving a confirmed ORR of 5.2% (95% CI: 2.1%, 10.5%). In comparison, no patients in the placebo arm had either a CR or PR, giving an ORR of 0% (95% CI: 0%, 5.2%). These data yielded a confirmed ORR difference of 5.2% (95% CI: 1.5%, 9.0%; with a p-value from the stratified CMH test of 0.0524) (Table 15).²

The median time from randomisation to confirmed objective response was 5.5 months (range: 2.8–8.4 months) in the cabozantinib arm (n=7).²

The best percentage change in BIRC-assessed tumour target lesion size from baseline is shown in Figure 13. The proportion of patients in the cabozantinib arm who had a post-baseline reduction in tumour size was higher than that observed in the placebo arm (68% versus 30%).²

Table 15: ORR by BIRC (ITT population)

	pNET cohort		epNET cohort	
	Cabozantinib (n=64)	Placebo (n=31)	Cabozantinib (n=134)	Placebo (n=69)
Patients with measurable disease at baseline	64 (100%)	31 (100%)	133 (99%)	69 (100%)
Patients with baseline and at least one post-baseline sum of diameters	56 (88%)	29 (94%)	111 (83%)	63 (91%)
Patients with only non-target lesion at baseline	0	0	1 (0.7%)	0
Confirmed BOR^a				
Confirmed CR	0	0	0	0
Confirmed PR	12 (19%)	0	7 (5.2%)	0
Stable disease	39 (61%)	17 (55%)	87 (65%)	37 (54%)
PD	5 (7.8%)	12 (39%)	15 (11%)	24 (35%)
Unable to evaluate	0	0	0	1 (1.4%)
Missing	8 (13%)	2 (6.5%)	25 (19%)	7 (10%)
No qualifying post-baseline assessments on or before PFS censoring or event date ^b	8 (13%)	2 (6.5%)	23 (17%)	6 (8.7%)
SD or non-CR/non-PD not meeting minimum criteria (>42 days) from randomisation	0	0	2 (1.5%)	1 (1.4%)

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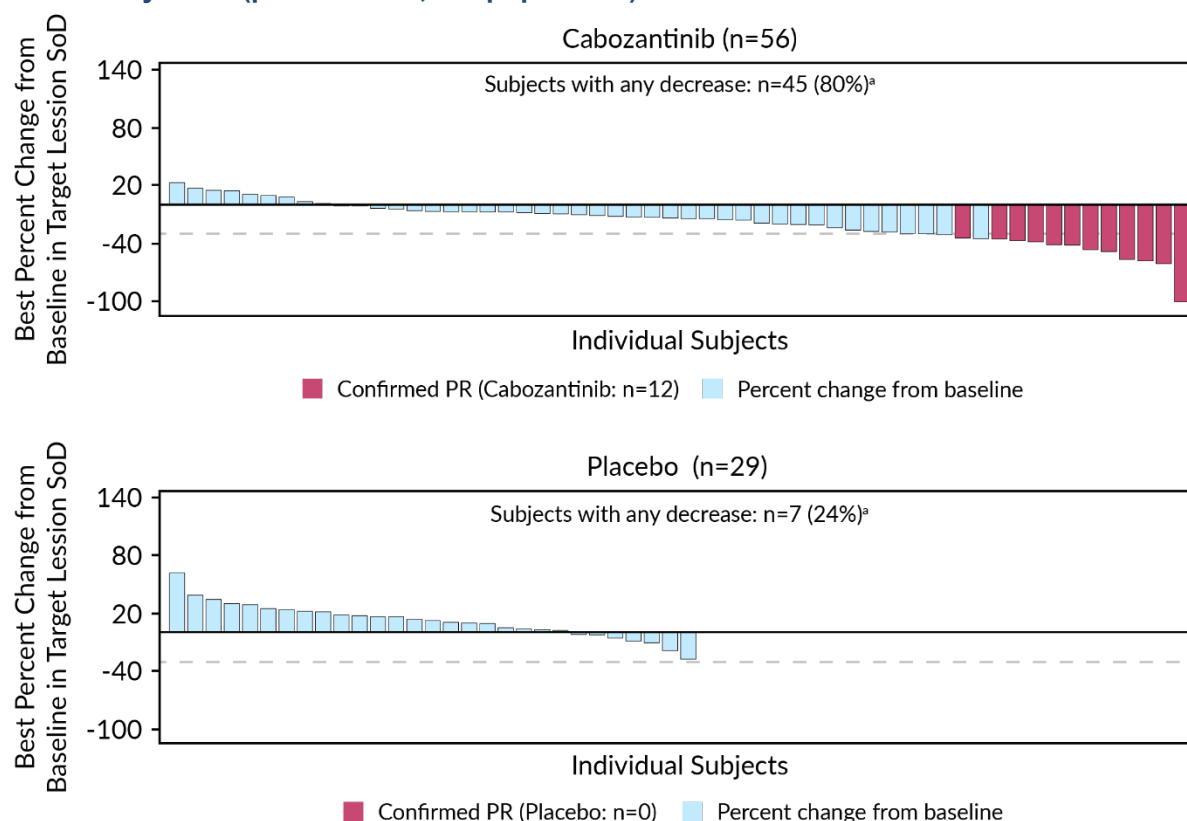
Confirmed ORR, n (%)^c	12 (19%)	0 (0.0%)	7 (5.2%)	0 (0.0%)
95% CI	(10.1%, 30.5%)	(0.0%, 11.2%)	(2.1%, 10.5%)	(0.0%, 5.2%)
Confirmed ORR treatment difference (95% CI) ^d	18.8% (9.2%, 28.3%)		5.2% (1.5%, 9.0%)	
p-value from stratified CMH test	0.0115		0.0524	

DCO: 24th August 2023. ^a Confirmed best overall response is derived based on RECIST 1.1. Only responses per the first radiographic documentation of disease progression, per RECIST 1.1 determined by BIRC are considered. The protocol did not define a minimal interval between the initial response scan and confirmatory scan; for calculation purposes, a minimum of 28 days was used. ^b No qualifying post-baseline assessments on or before PFS censoring or event date included the following: In the cabozantinib arm: AE (2 patients), other (death) (2 patients), withdrawal (2 patients), no study treatment given (1 patient), and first scheduled imaging time-point after the clinical cutoff date (1 patient). In the placebo arm: other (death) (1 patient) and withdrawal (1 patient). ^c Confirmed ORR is defined as proportion of patients with best overall response of confirmed CR or confirmed PR. The 95% CIs are calculated using Clopper Pearson's methods. ^d Using asymptotic confidence limits based on large number theorem.

Abbreviations: AE: adverse event; BIRC: blinded independent review committee; BOR: best overall response; CI: confidence interval; CMH: Cochran–Mantel–Haenszel; CR: complete response; DCO: data cut-off; ITT: intent-to-treat; ORR: objective response rate; PD: progressive disease; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour; PR: partial response.

Source: Ipsen Data on File, 2024 (CABINET CSR; pNET: Table 40; epNET: Table 23).²

Figure 12: Waterfall plot of best percentage change in tumour target lesion size from baseline by BIRC (pNET cohort; ITT population)

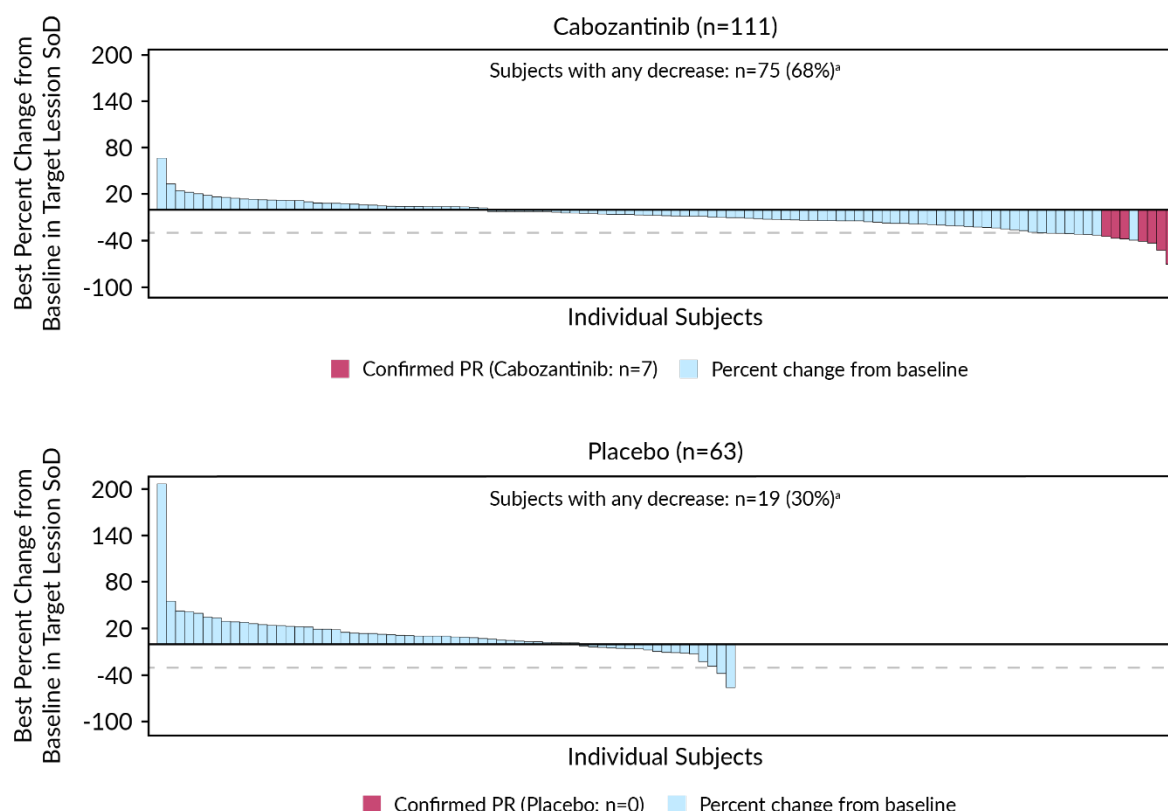


DCO: 24th August 2023. The plot shows patients with at least one baseline and postbaseline assessment.

Abbreviations: BIRC: blinded independent review committee;; DCO: data cut-off; ITT: intent-to-treat; pNET: pancreatic neuroendocrine tumour; PR: partial response; SoD: sum of diameters.

Source: Ipsen Data on File, 2024 (CABINET CSR; Figure 14).²

Figure 13: Waterfall plot of best percentage change in tumour target lesion size from baseline by BIRC (epNET cohort; ITT population)



DCO: 24th August 2023. ^a The plot shows patients with at least one baseline and postbaseline assessment.

Abbreviations: BIRC: blinded independent review committee; DCO: data cut-off; epNET: extra-pancreatic neuroendocrine tumour; ITT: intent-to-treat; SoD: sum of diameters.

Source: Ipsen Data on File, 2024 (CABINET CSR; Figure 6).²

Additional endpoint: duration of response

In the pNET cohort, of the 12 patients in the cabozantinib arm who had a BIRC-assessed best overall response (BOR) of PR, 5 had subsequent documented disease progression and 1 died. For these patients, the KM estimate of the median duration of response (DOR), per BIRC, was 11.2 months (95% CI: 5.8, not evaluable [NE]) suggesting durability of response to cabozantinib treatment, and the 3-, 6-, and 12-month event-free rates were 100%, 89%, and 32%, respectively.² Similarly, in the epNET cohort, of the 7 patients in the cabozantinib arm who had a BIRC-assessed BOR of PR, 4 had subsequent documented disease progression, and 1 died. For these patients, the KM estimate of the median DOR, per BIRC, was 8.26 months (95% CI: 4.47, NE), and the 3-, 6-, and 12-month event-free rates were 100%, 50%, and 25%, respectively.²

In both the pNET cohort and epNET cohort, no patients in the placebo arm had either a CR or PR as BOR; as such, KM estimates of DOR were not evaluable.²

Additional endpoint: disease control rate

In the pNET cohort, the BIRC-assessed disease control rate (DCR) (the proportion of patients with a BOR of CR, PR, or SD) was 80% (95% CI: 68%, 89%) in the cabozantinib arm and 55% (95% CI: 36%, 73%) in the placebo arm. The difference in DCR between treatment arms was 24.8% (95% CI: 5%, 45%).²

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Similarly, in the epNET cohort, the BIRC-assessed DCR was 70% (95% CI: 62%, 78%) in the cabozantinib arm and 54% (95% CI: 41%, 66%) in the placebo arm. The difference in DCR between treatment arms was 16.5% (95% CI: 2%, 31%).²

Accordingly, a reduced proportion of patients had a BOR of progressive disease for cabozantinib versus placebo, in both cohorts of the trial. As per Section 1.3.5, a key treatment goal in NETs is to extend PFS and avoid the associated reduction in HRQoL on progression

2.6.4 Additional endpoint: health-related quality of life

Three HRQoL questionnaires were used to capture patient reported outcomes (PROs) at baseline and scheduled assessments (every 12 weeks [± 1 week] until progression or start of new anticancer therapy) in CABINET: the EORTC QLQ-C30, QLQ-GINET21 and the Patients' Global Impression of Change (PGIC).

- The EORTC QLQ-C30 is an internationally validated and widely used measure designed to assess the HRQoL of cancer patients participating in clinical trials.⁹⁶ The 30-item measure considers the global health status, and the physical, role, emotional, cognitive, and social functioning of patients, as well as common cancer symptoms experienced by patients. A higher overall QLQ-C30 summary score indicates better HRQoL (range: 0 – 100).⁹⁶
- The QLQ-GINET21 is an internationally validated measure designed to assess the HRQoL of patients with GEP NETs participating in clinical trials. The 21-item measure considers disease-specific QoL issues important to patients with NETs and supplements the QLQ-C30, with higher scores suggesting a greater HRQoL.⁹⁷
- PGIC is a validated and widely used single-item measure designed to evaluate patients' overall perception of change in their condition since beginning treatment. The measure uses a 7-point scale ranging from "very much improved" to "very much worse," allowing patients to rate their impression of change in symptoms, daily activities, and overall quality of life. A lower PGIC score indicates greater perceived improvement in the patient's condition (range: 1–7).⁹⁸

HRQoL data from the 24th August 2023 DCO for EORTC QLQ-C30 (overall summary scores) are presented below. Descriptive summary statistics were plotted separately for pNET and epNET patients, at Weeks 0, 12, 24, 36, 48 and 60, for QLQ-C30. Additional data by HRQoL domain and from the QLQ-GINET21 questionnaires are available in the CABINET Protocol (Appendix I) included in the reference pack alongside this submission.

EORTC QLQ-C30

A summary of the EORTC QLQ-C30 summary scores and global health domain scores for patients in the cabozantinib and placebo arms at different timepoints in the CABINET trial are presented in Figure 14 and Figure 15, for the pNET and epNET cohorts, respectively. In general, the EORTC QLQ-C30 overall and global health domain scores for patients treated with cabozantinib were similar to that of patients treated with placebo in both the pNET and epNET cohorts, based on the final DCO. The CIs between the cabozantinib and placebo arms generally overlapped as time progressed, with no clear trend in favour of either treatment.

In both cohorts, patients treated with cabozantinib retained similar EORTC QLQ-C30 overall and global health domain scores compared to baseline as the study progressed. Towards the end of the study (i.e. Week 36 onwards), the global health domain scores were higher for cabozantinib compared with placebo in the pNET cohort but the inverse was true in the epNET cohort. These

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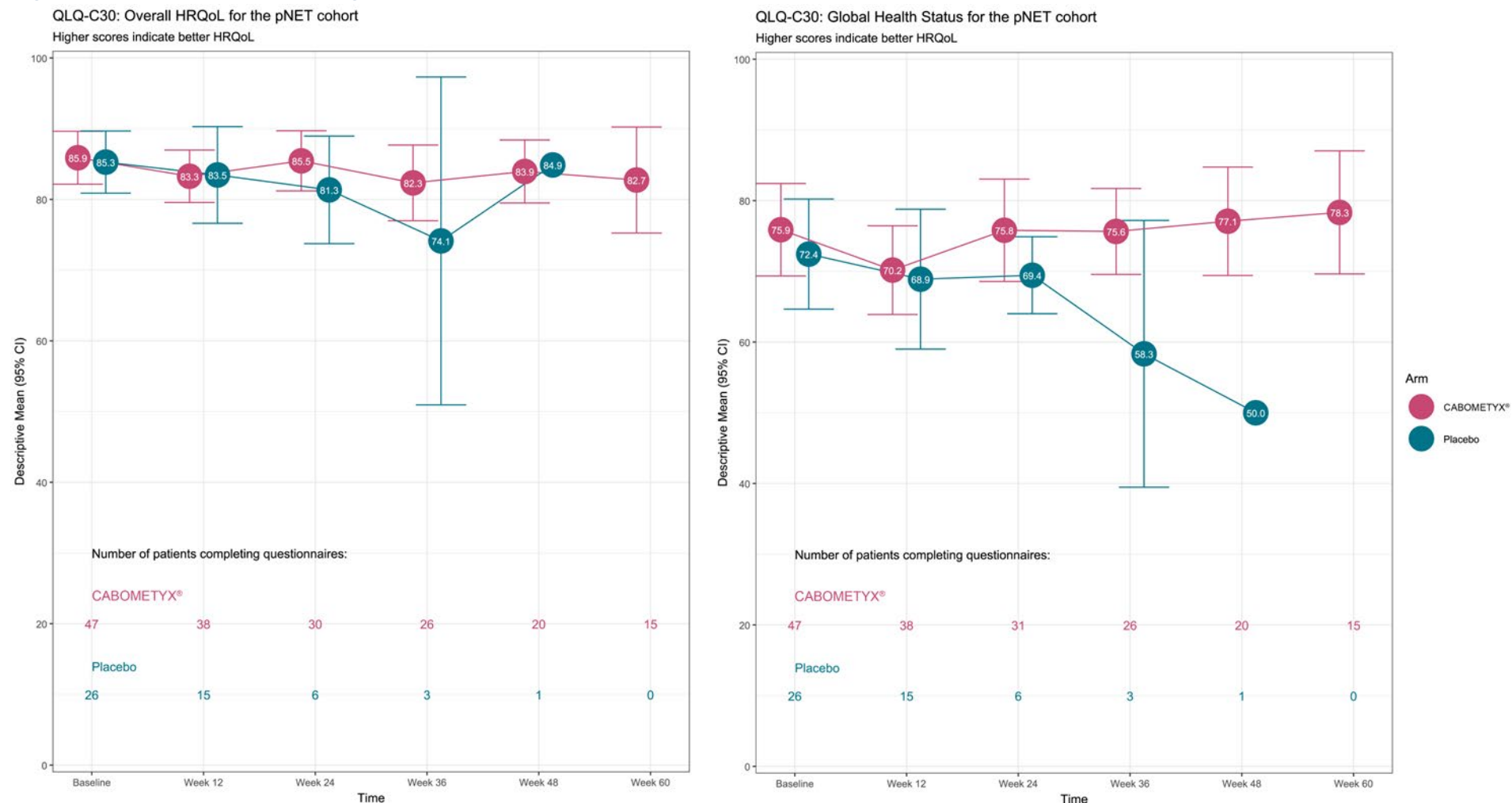
differences are likely due to the limited patient numbers assessed in the placebo arm of both cohorts and these results from Week 36 onwards should be interpreted with caution. Generally, these PRO results demonstrate that cabozantinib, compared to placebo, does not compromise patient HRQoL throughout the course of treatment in both the pNET and epNET cohorts.

QLQ-GINET 21 and PGIC

The results from the QLQ-GINET21 and PGIC questionnaires are consistent with the QLQ-C30 overall and global health domain scores and demonstrated HRQoL for patients treated with cabozantinib was similar to that of patients treated with placebo in both the pNET and epNET cohorts, based on the final DCO.

A summary of the QLQ-GINET 21 and PGIC scores for patients in the cabozantinib and placebo arms at different timepoints are presented in Appendix J.

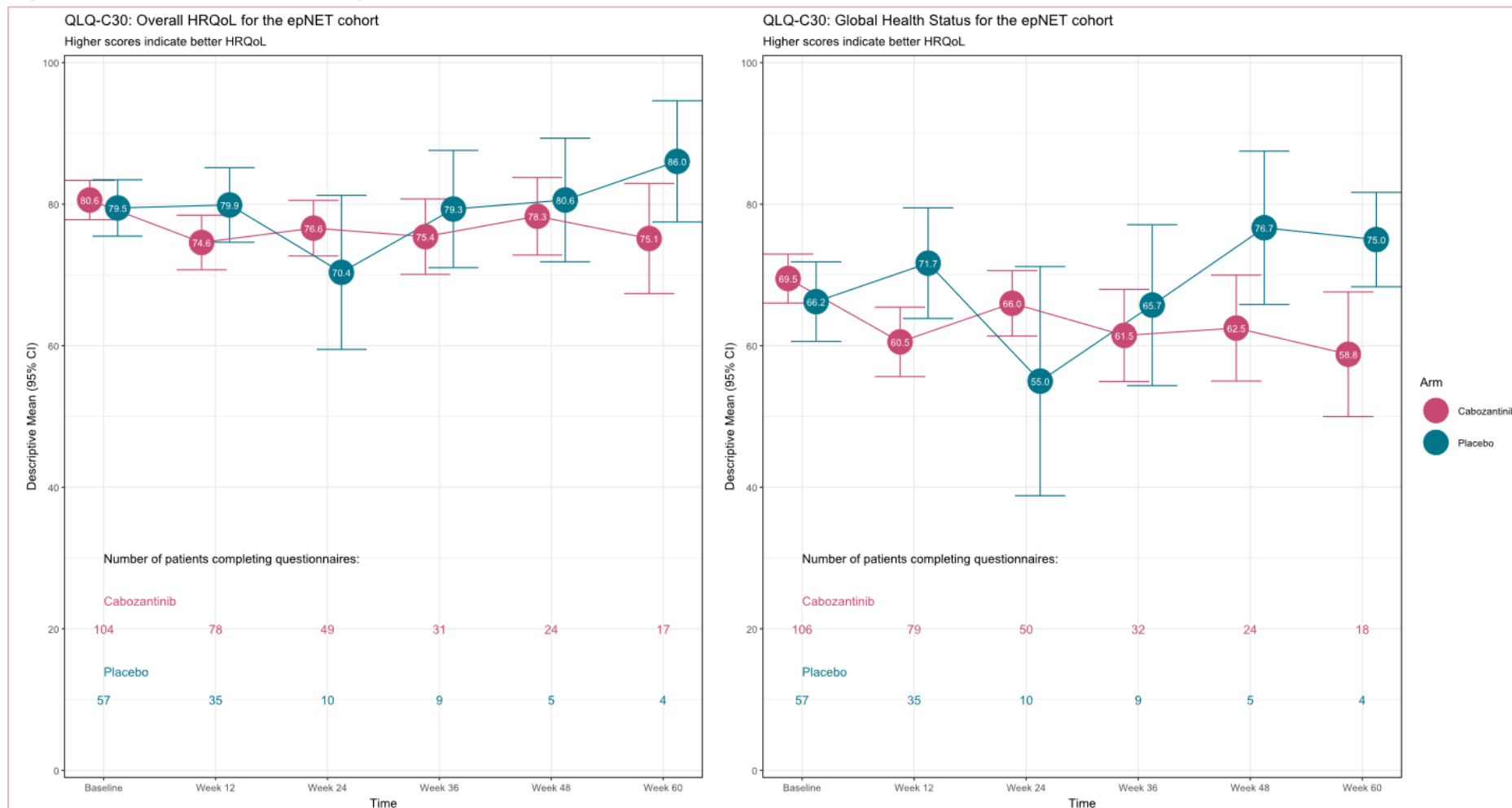
Figure 14: QLQ-C30 overall and global health status scores (pNET cohort; HRQoL population)



Abbreviations: CI: confidence interval; HRQoL: health-related quality of life; pNET: pancreatic neuroendocrine tumour.
Source: Ipsen Data on File, 2024 (Descriptive Analysis of Questionnaire Responses in the CABINET QoL Substudy).⁹⁰

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Figure 15: QLQ-C30 overall and global health status scores (epNET cohort; HRQoL population)



Abbreviations: CI: confidence interval; HRQoL: health-related quality of life; PGIC: patients' global impression of change; pNETs: pancreatic neuroendocrine tumours.
Source: Ipsen Data on File, 2024 (Descriptive Analysis of Questionnaire Responses in the CABINET QoL Substudy).⁹⁰

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2.7 Subsequent treatments used in the relevant studies

Patients in CABINET were permitted to receive non-protocol anticancer therapies (NPACTs), referred to hereafter as subsequent treatment, in both arms, and crossover cabozantinib in the placebo arm. Subsequent treatments included systemic therapies as well as locoregional liver directed therapy and external beam radiation. Subsequent treatment was permitted following discontinuation of study drugs.^{2, 13}

In the cabozantinib arm, subsequent treatments were received by 25 (39%) and 45 (34%) patients in the pNET and epNET cohorts respectively.² This was predominantly cytotoxic chemotherapy and PRRT as outlined in Table 16.² The median time from randomisation to initiation of subsequent treatment was 8.3 months in the pNET cohort and 8.9 months in the epNET cohort.²

In the placebo arm, 18 (58%) and 40 (58%) of patients initiated systemic NPACT or crossed over to cabozantinib in the pNET and epNET cohorts respectively. Subsequent treatments received in the placebo arm were predominantly anti-VEGFR TKIs in the pNET cohort and cytotoxic chemotherapy in the epNET cohort (Table 16).² Similar proportions of subsequent treatments received were observed between arms in the epNET cohort. The median time from randomisation to crossover or initiation of subsequent treatment was 8.1 months in the pNET cohort and 5.0 months in the epNET cohort.²

The substantial proportion of patients receiving subsequent treatment in both arms, as well as crossover to cabozantinib, makes it challenging to assess the effect of cabozantinib in improving OS compared to placebo. Notably, patients in the placebo arm were permitted to crossover to cabozantinib upon progression.^{2, 13} Consequently, a considerable proportion of patients in the placebo arm received crossover cabozantinib (12 [39%] in the pNET cohort and 20 [29.0%] in the epNET cohort), which is likely to be further confound the OS results.²

The CABINET trial did not collect data on the time to progression on subsequent treatment (PFS2) or the time spent on each subsequent therapy. These were not pre-specified outcomes in the protocol and would have required active long-term follow-up.²

Table 16: Summary of the subsequent treatments received in CABINET (pNET cohort)

	pNET cohort		epNET cohort	
	Cabozantinib (N=64)	Placebo (N=31)	Cabozantinib (N=134)	Placebo (N=69)
Proportion of patients receiving subsequent treatment	25 (39%)	18 (58%)	50 (37%)	40 (58%)
Cabozantinib (crossover)	N/A	12 (39%)	N/A	20 (29.0%)
PRRT	8 (13%)	2 (6.5%)	15 (11%)	3 (4.3%)
Everolimus	2 (3.1%)	0	4 (3.0%)	3 (4.3%)
Anti-VEGFR TKI	5 (7.8%)	3 (9.7%)	7 (5.2%)	4 (5.8%)
Cytotoxic chemotherapy regimens	15 (23%)	0	21 (16%)	8 (12%)
Other anticancer therapies	4 (6.3%)	1 (3.2%)	9 (6.7%)	3 (4.3%)

Percentages are expressed as a proportion of the total pNET or epNET cohorts.

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Abbreviations: ITT: intention-to-treat; NPACT: non-protocol anticancer therapy; pNET: pancreatic neuroendocrine tumour; PRRT: peptide receptor radionuclide therapy; SD: standard deviation; VEGFR TKI: vascular endothelial growth factor receptor tyrosine kinase inhibitor.
Source: Ipsen Data on File, 2024 (CABINET CSR; Table 39 and Table 22).²

2.8 Subgroup analysis

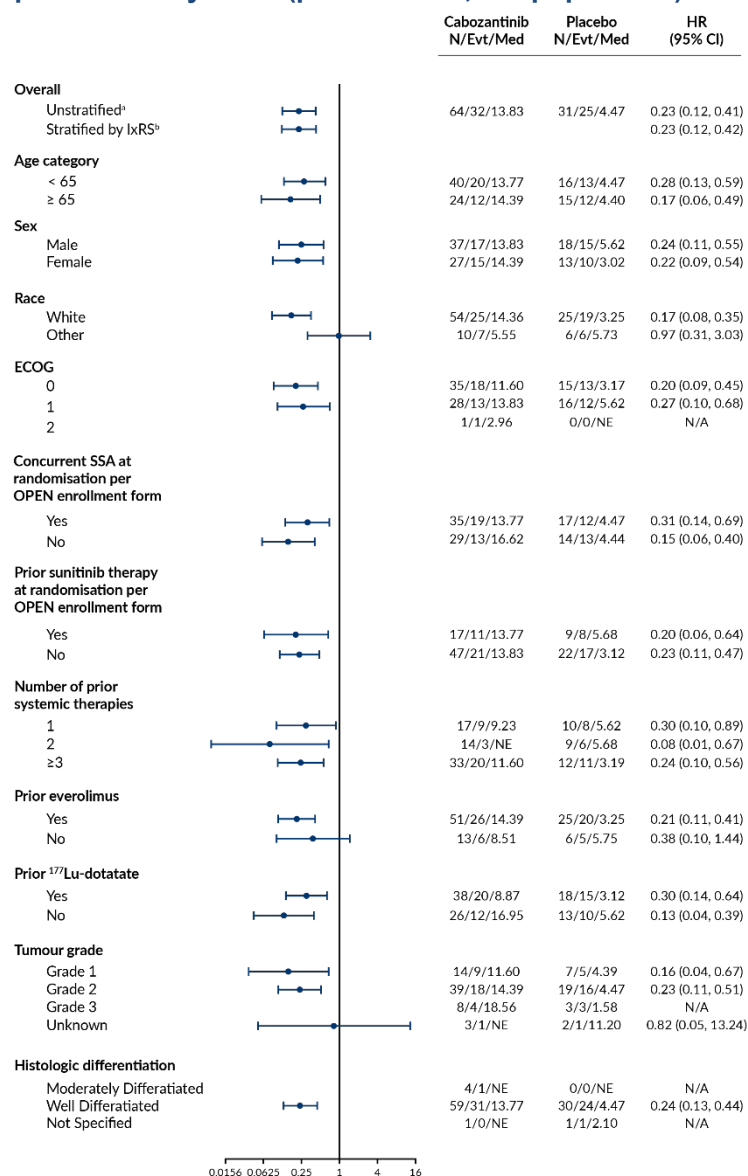
Subgroup analyses were prespecified for the primary endpoint (PFS, as assessed by BIRC) to determine how the treatment effect varied across different key subgroups. Notably, however, these subgroup analyses were not powered to show differences between cabozantinib and placebo. The results of these subgroup analyses should therefore be interpreted with caution.

All subgroup analyses presented below for the pNET cohort and overall epNET cohort were prespecified. Additionally, a post-hoc analysis of the epNET cohort was conducted to determine PFS by primary tumour site (GI NETs, lung [including thymic] NETs and other/unknown NETs), and is presented in Appendix C. Randomisation was not stratified according to this classification of subgroups by primary tumour type (instead, randomisation was stratified by midgut GI/unknown versus non-midgut GI/lung/other); results of these subgroup analyses should therefore be interpreted with caution due to potential imbalances in patient characteristics across treatment arms and associated confounding.

Key subgroup analyses of the BIRC-assessed analyses of are displayed in Forest plots for the pNET cohort and epNET cohorts in Figure 16 and Figure 17, respectively.² Overall, a consistent PFS benefit for cabozantinib over placebo was observed across all key subgroups of both the pNET and epNET cohorts, indicating that the efficacy of cabozantinib was generally consistent across the relevant subpopulations enrolled in the CABINET trial. All HRs were <1 across subgroups, favouring the cabozantinib arm. For the majority of subgroups, the upper bound of the 95% CI was also <1.² In the few subgroups where a significant benefit was not observed, the lack of statistical significance can be attributed to the small patient numbers in these subgroups and therefore a limited number of events. These categories were race (other) and Grade 3 tumours in both cohorts, prior everolimus in the pNET cohort and 3 or more prior lines of therapy, Eastern Cooperative Oncology Group (ECOG) 0, histology (not specified) or primary tumour site (non-midgut) in the epNET cohort.

Treatment benefits were observed irrespective of age, sex, performance status and number of prior therapies, demonstrating the potential for cabozantinib to provide an effective treatment option in an all-comer NETs population.

Figure 16: Forest plot of PFS by BIRC (pNET cohort; ITT population)

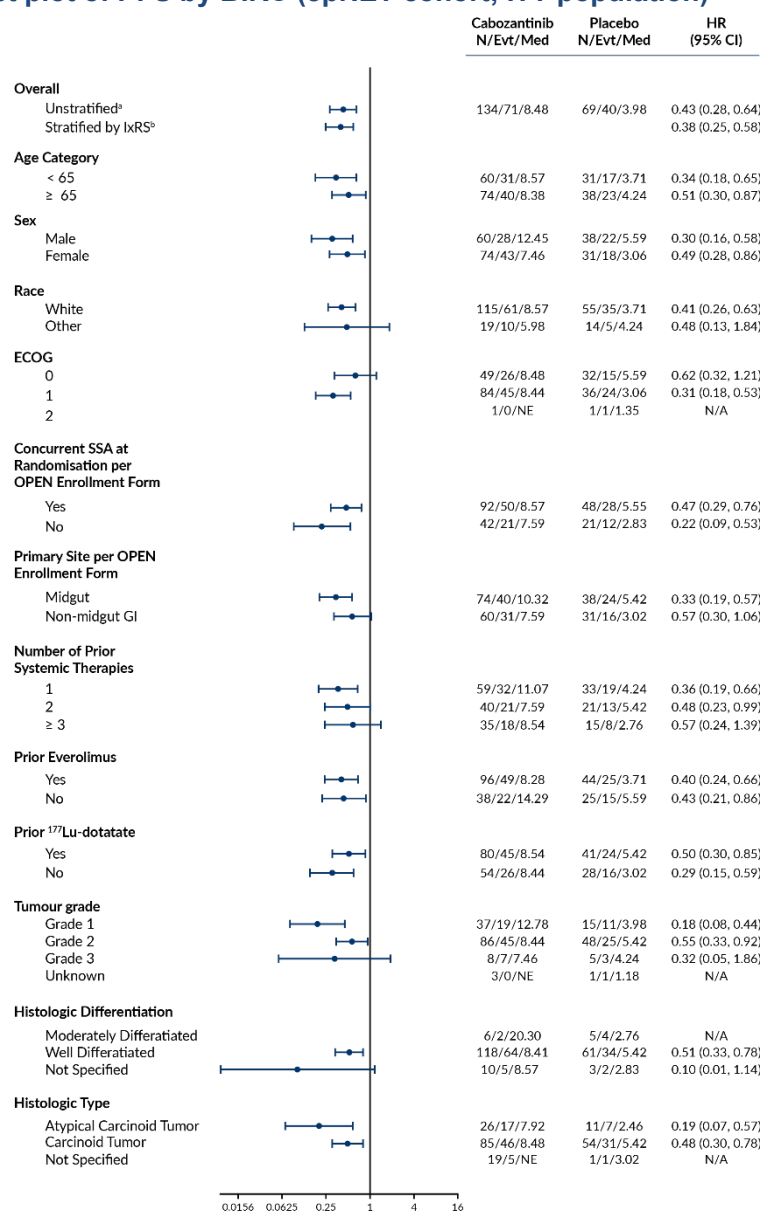


DCO: 24th August 2023. ^a HR and 95% CI estimates from the unstratified Cox proportional hazards model are presented for both subgroups. ^b Stratification factors are as follows: (1) concurrent SSA use (yes, no) and (2) prior sunitinib therapy (yes, no).

Abbreviations: BIRC: blinded independent review committee; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; Evt: number of patients with events; HR: hazard ratio; ITT: intent-to-treat; IxRS: interactive voice/web response system (ie, the OPEN registration system); Med: median; N: number of patients; NA: not applicable; NE: not estimable; OPEN: Oncology Patient Enrolment Network; pNET: pancreatic neuroendocrine tumour

Source: Ipsen Data on File, 2024 (CABINET CSR; Figure 16).²

Figure 17: Forest plot of PFS by BIRC (epNET cohort; ITT population)



DCO: 24th August 2023. ^a HR and 95% CI estimates from the unstratified Cox proportional hazards model are presented for both subgroups. ^b Stratification factors are as follows: (1) concurrent SSA use (yes, no) and (2) primary site (midgut/unknown versus non-midgut GI/lung/other).

Abbreviations: BIRC: blinded independent review committee; CI: confidence interval; DCO: data cut-off; ECOG: Eastern Cooperative Oncology Group; Evt: number of patients with events; GI: gastrointestinal; HR: hazard ratio; ITT: intent-to-treat; IxRS: interactive voice/web response system (i.e. the OPEN registration system); Med: median; N: number of patients; NA: not applicable; OPEN: Oncology Patient Enrolment Network; SSA: somatostatin analogue.

Source: Ipsen Data on File, 2024 (CABINET CSR; Figure 8).²

2.9 Meta-analysis

As only one trial evaluating the efficacy and safety of cabozantinib in the relevant patient population and indication was identified, a meta-analysis was not necessary.

2.10 Indirect and mixed treatment comparisons

As noted in Section 1.1, BSC is considered the most appropriate comparator in this appraisal. Cabozantinib is anticipated to be used in UK clinical practice in line with the population enrolled in the CABINET trial, which informed the anticipated marketing authorisation for cabozantinib in this indication, which reflects a heavily pre-treated population with the highest unmet need for new treatment options. After progression on SSAs, the treatment pathway is highly individualised, with systemic treatments restricted to subgroups based on specific patient characteristics. Chemotherapy regimens are not commonly used in Grade 1 and 2, well-differentiated tumours given high treatment burden and a lack of robust efficacy data. For many patients who have progressed on subsequent systemic therapy, the only remaining treatment option is BSC. Unlike other systemic treatments, the marketing authorisation for cabozantinib is not restricted by tumour subtype, SSTR status, functional status or grade. Accordingly, clinical experts experienced in the treatment of NETs consulted for this submission confirmed that the appropriate comparator for cabozantinib on the basis of its marketing authorisation and the CABINET trial is BSC.¹²

The CABINET trial provides direct efficacy and safety evidence for cabozantinib versus placebo (representing concomitant SSA usage only), which can be considered a proxy for BSC. As such, indirect or mixed treatment comparisons are not required.

Furthermore, no relevant RCTs investigating other systemic therapy were identified in the SLR (with the exception of two small studies based in China investigating surufatinib versus everolimus or sunitinib); RCTs investigating other systemic treatments used in UK clinical practice were excluded on the basis that less than 70% of patients had received a relevant prior line of therapy, and thus the enrolled population could not be considered comparable to CABINET. Further details of these studies are available in Appendix B.

2.11 Adverse reactions

2.11.1 Treatment exposure and dose modifications

In the pNET cohort, 63 patients in the cabozantinib arm and 31 patients in the placebo arm received at least one dose of study treatment. In the epNET cohort, 132 patients in the cabozantinib arm and 67 patients in the placebo arm received at least one dose of study treatment. These patients were included in the respective safety populations.²

Among patients in the pNET cohort, the median duration of exposure was 8.28 months in the cabozantinib arm and 2.86 months in the placebo arm. The median average daily dose of cabozantinib was 41.36 mg, and the median dose intensity was 68.93%. Dose reductions were reported for 68% and 19% of patients in the cabozantinib and placebo treatment arms, respectively; dose holds were reported for 86% and 48% of patients, respectively.²

Among patients in the epNET cohort, the median duration of exposure was 5.37 months in the cabozantinib arm and 2.79 months in the placebo arm. The median average daily dose of cabozantinib was 42.86 mg, and the median dose intensity was 71.43%. Dose reductions were reported for 66% and 10% of patients in the cabozantinib and placebo treatment arms, respectively; dose holds were reported for 83% and 48% of patients, respectively.²

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For further details on treatment exposure and dose modifications, please refer to the CABINET CSR (Section 12.1).²

2.11.2 Overview of AEs

An overview of AEs in both the pNET cohort and epNET cohort is presented in Table 17. In both cohorts, compared with the placebo arm, the cabozantinib arm had a higher proportion of patients with AEs considered related to study treatment, serious AEs (SAEs), Grade 3/4 AEs, and AEs leading to dose modification or reduction. In the pNET cohort, no Grade 5 AEs were reported although a single death did occur in a cabozantinib-treated patient due to tumour but was not entered in EDC. In the epNET cohort, Grade 5 AEs were similar between treatment arms.²

In addition, among the 32 total crossover patients (randomised to placebo and crossed over to open-label cabozantinib after disease progression) across the pNET and epNET cohorts, safety results were consistent with those from patients who received cabozantinib only.

Overall, there were no new safety findings from this study for cabozantinib compared to studies of cabozantinib in other indications.²

Table 17: Overview of AEs (pNET and epNET cohorts; safety population)

	pNET cohort		epNET cohort	
	Cabozantinib (n=63)	Placebo (n=31)	Cabozantinib (n=132)	Placebo (n=67)
AE	63 (100%)	31 (100%)	132 (100%)	67 (100%)
Related AE	62 (98%)	26 (84%)	130 (98%)	56 (84%)
SAE	29 (46%)	7 (23%)	58 (44%)	27 (40%)
Related SAE	23 (37%)	2 (6.5%)	38 (29%)	14 (21%)
Worst Grade 3 or 4 AE	46 (73%)	14 (45%)	89 (67%)	26 (39%)
Worst Grade 3 or 4 Related AE	41 (65%)	7 (23%)	78 (59%)	18 (27%)
Worst Grade 4 AE	7 (11%)	0	9 (6.8%)	1 (1.5%)
Worst Grade 4 Related AE	6 (9.5%)	0	8 (6.1%)	1 (1.5%)
Worst Grade 5 AE	0 ^a	0	9 (6.8%)	5 (7.5%)
Worst Grade 5 Related AE	0	0	4 (3.0%)	1 (1.5%)
AE leading to dose reduction	31 (49%)	5 (16%)	50 (38%)	5 (7.5%)
AE leading to dose hold	52 (83%)	13 (42%)	106 (80%)	25 (37%)
AE leading to dose modification (reduction or hold)	56 (89%)	16 (52%)	113 (86%)	28 (42%)
AE leading to treatment discontinuation	12 (19%)	3 (9.7%)	36 (27%)	13 (19%)
Related AE leading to treatment discontinuation	9 (14%)	1 (3.2%)	34 (26%)	9 (13%)

DCO: 24th August 2023. Patients counted only once within each category but may be counted in multiple categories. ^a A single death occurred due to tumour (per the patient status CRF) during the safety reporting window but was not entered as a Grade 5 AE.

Abbreviations: AE: adverse events; CRF: Case report form; DCO: data cut-off; epNET: extra-pancreatic neuroendocrine tumour; ETM: event to monitor; pNET: pancreatic neuroendocrine tumour; SAE: serious adverse event.

Source: Ipsen Data on File, 2024 (CABINET CSR; Table 46).²

2.11.3 Incidence of AEs

AEs of any grade

In the pNET cohort, the most frequently reported any-grade AEs (>50% of patients) of any cause were fatigue (79% in the cabozantinib arm versus 61% in the placebo arm), elevated aspartate aminotransferase (AST; 76% versus 48%), elevated alanine aminotransferase (ALT; 73% versus 39%), diarrhoea (63% versus 23%), and hypertension (63% versus 48%) (Table 18).²

In the epNET cohort, the most frequently reported any-grade AEs (>50% of patients) of any cause were fatigue (72% in the cabozantinib arm versus 58% in the placebo arm), elevated aspartate aminotransferase (AST) (70% versus 22%), diarrhoea (65% versus 42%), hypertension (64% versus 40%), elevated alanine aminotransferase (ALT) (63% versus 22%), and platelet count reduction (52% versus 12%) (Table 18).²

Table 18: Summary of frequent any-grade AEs of any cause (≥20% in either treatment arm; pNET cohort and epNET cohort; safety population)

Preferred Terms	pNET cohort		epNET cohort	
	Cabozantinib (n=63)	Placebo (n=31)	Cabozantinib (n=132)	Placebo (n=67)
Patients with at least 1 AE, n (%)	63 (100%)	31 (100%)	132 (100%)	67 (100%)
Fatigue	50 (79%)	19 (61%)	95 (72%)	39 (58%)
AST increased	48 (76%)	15 (48%)	93 (70%)	15 (22%)
Diarrhoea	40 (63%)	7 (23%)	86 (65%)	28 (42%)
Hypertension	40 (63%)	15 (48%)	84 (64%)	27 (40%)
ALT increased	46 (73%)	12 (39%)	83 (63%)	15 (22%)
Platelet count decreased	21 (33%)	6 (19%)	68 (52%)	8 (12%)
Nausea	24 (38%)	10 (32%)	52 (39%)	14 (21%)
Stomatitis^a	30 (48%)	3 (9.7%)	51 (39%)	8 (12%)
WBC count decreased	-	-	49 (37%)	3 (4.5%)
Neutrophil count decreased	14 (22%)	2 (6.5%)	45 (34%)	4 (6.0%)
PPE syndrome	27 (43%)	4 (13%)	45 (34%)	4 (6.0%)
Decreased Appetite	15 (24%)	6 (19%)	44 (33%)	10 (15%)
Dysgeusia	18 (29%)	2 (6.5%)	43 (33%)	2 (3.0%)
Hypothyroidism	-	-	41 (31%)	2 (3.0%)
Anaemia	16 (25%)	10 (32%)	39 (30%)	13 (19%)
Blood alkaline phosphatase increased	13 (21%)	7 (23%)	38 (29%)	21 (31%)
Hyperglycaemia	21 (33%)	13 (42%)	36 (27%)	23 (34%)
Lymphocyte count decreased	14 (22%)	5 (16%)	36 (27%)	11 (16%)

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Weight decreased	-	-	36 (27%)	5 (7.5%)
Abdominal pain	14 (22%)	5 (16%)	34 (26%)	27 (40%)
Blood creatinine increased	-	-	31 (23%)	8 (12%)
Hypophosphatemia	16 (25%)	2 (6.5%)	-	-
Vomiting	16 (25%)	5 (16%)	-	-
Dizziness	15 (24%)	1 (3.2%)	-	-
Blood thyroid stimulating hormone increased	13 (21%)	0	-	-

Preferred terms in **bold** font are solicited events.

DCO: 24th August 2023. MedDRA 26.1 used for coding. Dash signified that the AE was not reported in at least 20% of patients in either treatment arm of the relevant cohort ^a Equivalent to solicited term "mucositis oral" which was coded to stomatitis.

Abbreviations: AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DCO: data cut-off; epNET: extra-pancreatic neuroendocrine tumour; pNET: pancreatic neuroendocrine tumour; PPE: palmar-plantar erythrodysesthesia; WBC: white blood count.

Source: Ipsen Data on File, 2024 (CABINET CSR; Tables 47 and 48).²

Treatment-related AEs

In the pNET cohort, AEs were considered by the investigator as related to study drug for 98% of patients in the cabozantinib arm and 84% of patients in the placebo arm. The most frequently reported TRAEs (>50% of patients in either treatment arm) were fatigue (75% versus 39%), elevated ALT (63% versus 26%), elevated AST (63% versus 26%), diarrhoea (59% versus 9.7%), and hypertension (54% versus 23%).²

In the epNET cohort, AEs were considered by the investigator as related to study drug for 98% of patients in the cabozantinib arm and 84% of patients in the placebo arm. The most frequently reported treatment-related AEs (TRAEs; >50% of patients in either treatment arm) were elevated aspartate aminotransferase (AST; 65% versus 18%), fatigue (61% versus 43%), elevated alanine aminotransferase (ALT; 58% versus 15%), diarrhoea (55% versus 30%), and hypertension (52% versus 21%).²

For both cohorts, the most frequently reported any-cause AEs presented in Table 18 above (in **bold**) were all solicited events; these consisted of certain AEs that were considered 'expected' per protocol. Solicited events included: elevated ALT/AST, diarrhoea, fatigue, hyperglycaemia, hypertension, hypothyroidism, mucositis oral, neutrophil count decreased, palmar-plantar erythrodysesthesia (PPE) syndrome, platelet count decreased, and rash maculo-papular.² Patients were specifically requested to report the frequency of these 15 solicited events at each visit.

Solicited events had a higher-than-expected frequency in both the cabozantinib and placebo arms. However, the study included patients with functional NETs who are known to have significant symptom burden. Therefore, rates of AEs in the cabozantinib arm should be viewed in the context of the increased event rates on the placebo arm (9.7% of patients discontinued treatment).² Additionally, the need to specifically report these AEs at each visit may have contributed to their higher-than-expected frequency of reporting.

For further details on frequently reported AEs, please refer to the CABINET CSR (Section 12.2).²

Grade 3/4 AEs

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In the pNET cohort, Grade 3/4 AEs of any cause were reported for 73% of patients in the cabozantinib arm and 45% of patients in the placebo arm (Table 19). The most frequently reported Grade 3/4 AEs were hypertension (22% versus 13%), fatigue (14% versus 6.5%), and PPE syndrome (9.5% versus 0%) (Table 16).²

In the epNET cohort, Grade 3/4 AE of any cause were reported for 67% of patients in the cabozantinib arm and 39% of patients in the placebo arm. The most frequently reported Grade 3/4 AEs were hypertension (26% versus 6.0%), fatigue (14% versus 9.0%), and diarrhoea (11% versus 4.5%) (Table 19).²

The most common Grade 3/4 AEs of any cause were broadly consistent with the known cabozantinib tolerability profile.² For further details on the severity of AEs, please refer to the CABINET CSR (Section 12.2.3.2).²

Table 19: Summary of Grade 3/4 AEs of any cause reported for >4% of patients in either treatment arm (pNET cohort and epNET cohort; safety population)

Preferred Term	pNET cohort		epNET cohort	
	Cabozantinib (n=63)	Placebo (n=31)	Cabozantinib (n=132)	Placebo (n=67)
Patients with at least one Grade 3/4 AE, n (%)	46 (73%)	14 (45%)	89 (67%)	26 (39%)
Hypertension	14 (22%)	4 (13%)	34 (26%)	4 (6.0%)
Fatigue	9 (14%)	2 (6.5%)	19 (14%)	6 (9.0%)
Diarrhoea	4 (6.3%)	0	14 (11%)	3 (4.5%)
PPE syndrome	6 (9.5%)	0	-	-
Lymphocyte count decreased	5 (7.9%)	0	12 (9.1%)	1 (1.5%)
Abdominal pain	-	-	11 (8.3%)	4 (6.0%)
Nausea	5 (7.9%)	1 (3.2%)	-	-
Embolism	4 (6.3%)	0	-	-
Stomatitis^a	4 (6.3%)	0	-	-
Vomiting	4 (6.3%)	0	-	-
Blood alkaline phosphatase increased	-	-	6 (4.5%)	4 (6.0%)
Blood bilirubin increased	3 (4.8%)	1 (3.2%)	3 (2.3%)	4 (6.0%)
Blood pressure increased	3 (4.8%)	0	-	-
Hypoxia	3 (4.8%)	0	-	-
Pain	3 (4.8%)	0	-	-
Pulmonary embolism	3 (4.8%)	0	-	-
Sepsis	3 (4.8%)	0	-	-
Dyspnoea	-	-	6 (4.5%)	3 (4.5%)
Weight decreased	-	-	6 (4.5%)	0
Syncope	-	-	5 (3.8%)	5 (7.5%)

Preferred terms in **bold** font are solicited events.

DCO: 24th August 2023. At each level of patient summarisation, a patient is counted once for the most severe event if the patient reported one or more events. MedDRA 26.1 was used for coding. ^a Equivalent to solicited term "mucositis oral" which was coded to stomatitis.

Abbreviations: AE: adverse event; AST: aspartate aminotransferase; DCO: data cut-off; epNET: extra-pancreatic neuroendocrine tumour; pNET: pancreatic neuroendocrine tumour; PPE: palmar-plantar erythrodysesthesia.

Source: Ipsen Data on File, 2024 (CABINET CSR; Table 51 and Table 52).²

SAEs

In the pNET cohort (safety population), SAEs of any cause were reported for 46% of patients in the cabozantinib arm and 23% of patients in the placebo arm. Frequently reported SAEs were vomiting (6.3% versus 0%), embolism, hypoxia, nausea, sepsis (each reported for 4.8% of patients in the cabozantinib arm and no patients in the placebo arm) and small intestinal obstruction (1.6% versus 9.7%). SAEs that occurred within 30 days of the last dose of study treatment were considered related to study treatment for 37% of patients in the cabozantinib arm and 6.5% of patients in the placebo arm. Within this time frame, vomiting (6.3% versus 0%) was the most frequently reported treatment-related SAE. No treatment-related SAEs were reported >30 days after the last dose of study treatment.²

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In the epNET cohort (safety population), SAEs of any cause were reported for 44% of patients in the cabozantinib arm and 40% of patients in the placebo arm. Hypertension (6.1% versus 1.5%), abdominal pain (5.3% versus 6.0%), diarrhoea (3.0% versus 4.5%) and vomiting (3.0% in both arms) were the most frequently reported SAEs. SAEs that occurred within 30 days of the last dose of study treatment were considered related to study treatment for 29% of patients in the cabozantinib arm and 21% of patients in the placebo arm. Within this time frame, hypertension (6.1% versus 0%) was the most frequently reported treatment-related SAE. No treatment-related SAEs were reported >30 days after the last dose of study treatment.²

For further details on other SAEs, please refer to the CABINET CSR (see Section 12.3.4.4).²

2.11.4 Treatment discontinuation due to AEs

In the pNET cohort, study treatment was discontinued due to an AE of any cause for 19% of patients in the cabozantinib arm and 9.7% of patients in the placebo arm. AEs that led to treatment discontinuation were considered by the investigator as related to treatment for 14% of patients in the cabozantinib arm and 3.2% of patients in the placebo arm.²

In the epNET cohort, study treatment was discontinued due to an AE of any cause for 27% of patients in the cabozantinib arm and 19% of patients in the placebo arm. AEs that led to treatment discontinuation were considered by the investigator as related to treatment for 26% of patients in the cabozantinib arm and 13% of patients in the placebo arm.²

Although the frequency of treatment discontinuation was higher in patients receiving cabozantinib, there was a notable frequency of TRAEs and treatment discontinuation due to investigator-assessed treatment-related AEs in the placebo arm, indicating that the study included a highly symptomatic NET population and that blinding was effective.²

For further details on treatment discontinuation due to AEs, please refer to the CABINET CSR (Section 12.3.4.4).²

2.11.5 Deaths

In the pNET cohort (safety population), 21 patients (33%) in the cabozantinib arm and 8 patients (26%) in the placebo arm had died by the DCO of 24th August 2023, as outlined in Table 20. In the epNET cohort, 58 patients (44%) in the cabozantinib arm and 27 patients (40%) in the placebo arm had died. Most deaths were attributed to progressive disease and most occurred >30 days after the last dose of study drug by the DCO.²

Table 20: Summary of Deaths and Primary Reasons for Death (pNET and epNET; safety population)

Preferred term	pNET cohort		epNET cohort	
	Cabozantinib (n=63)	Placebo (n=31)	Cabozantinib (n=132)	Placebo (n=67)
Total number of deaths	21 (33%)	8 (26%)	58 (44%)	27 (40%)
Primary reason for death				
Tumour (progressive disease)	15 (24%)	5 (16%)	35 (27%)	14 (21%)
Drug-related	0	0	0	0
Unknown	5 (7.9%)	2 (6.5%)	14 (11%)	8 (12%)

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Other	1 (1.6%)	1 (3.2%)	9 (6.8%)	5 (7.5%)

DCO: 24th August 2023.

Abbreviations: DCO: data cut-off; epNET: extra-pancreatic neuroendocrine tumour; pNET: pancreatic neuroendocrine tumour.

Source: Ipsen Data on File, 2024 (CABINET CSR; Table 53).²

2.12 Ongoing studies

Currently, the CABINET trial is the only trial of cabozantinib monotherapy in advanced neuroendocrine tumours that have progressed after prior systemic therapy. There are no ongoing trials in this indication that would provide additional data for cabozantinib within the timeframe of this appraisal.

2.13 Interpretation of clinical effectiveness and safety evidence

Clinical efficacy for cabozantinib in patients with pNETs and epNETs

The clinical efficacy and safety evidence for cabozantinib in advanced pNETs and epNETs that have progressed after prior systemic therapy is derived from the CABINET trial. The CABINET trial was the first Phase III trial to investigate the efficacy of cabozantinib in patients with advanced NETs, and enrolled patients regardless of primary tumour site, functional status, concurrent SSA use or prior therapies received.

Due to overwhelming efficacy in the interim analysis of PFS in the pNET and epNET cohorts of CABINET, the trial was terminated early. At the DCO of 24th August 2023, a statistically significant and clinically meaningful increase in median PFS was demonstrated in patients treated with cabozantinib compared to those treated with placebo, in both the pNET cohort (13.83 versus 4.47 months; HR: 0.23; 95% CI: 0.12, 0.42) and epNET cohort (8.48 months versus 3.98 months; HR: 0.38; 95% CI: 0.25, 0.58). This represents a 77% and 62% decrease in the risk of disease progression or death in the pNET and epNET cohorts, respectively.^{2, 13} KM curves revealed that the PFS benefit was achieved early and maintained consistently over time in both pNET and epNET cohorts at landmarks of 3, 6, 12, 18 and 24 months. A consistent PFS benefit for cabozantinib over placebo was observed across key subgroups in CABINET, demonstrating the efficacy of cabozantinib in an all-comer NET population.

Although CABINET was not powered to test for statistical significance in OS, a numerical benefit was observed in cabozantinib versus placebo in both pNET and epNET cohorts (OS HRs <1). Due to the crossover trial design of CABINET and the high rate of subsequent therapy usage in both trial arms, OS was likely confounded (crossover and subsequent therapy usage could cause a potential inflation of OS in the placebo arm). PFS should be considered a more appropriate measure of clinical benefit than OS in NET clinical trials and has been validated as a surrogate endpoint in this disease area.⁷⁶

Furthermore, treatment with cabozantinib was associated with an ORR benefit of 18.8% (95% CI: 9.2%, 28.3%) in the pNET cohort (a significant improvement) and 5.2% in the epNET cohort (tending towards improvement), compared to patients treated with placebo with a ORR of 0%.²

The efficacy benefits of cabozantinib were achieved without compromising patient HRQoL, with similar EORTC QLQ-C30 overall and global health domain scores observed between cabozantinib and placebo arms in both the pNET and epNET cohorts. As patients with

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progressive NETs often experience worsening HRQoL, with longer follow-up, the PFS benefit associated with cabozantinib would be expected to delay deterioration of HRQoL.³⁶

Safety evidence for cabozantinib in patients with pNETs and epNETs

The CABINET safety results showed that cabozantinib is associated with a predictable and manageable safety profile with no notable safety findings across trial patients in both the pNET cohort and epNET cohort. Although there was a substantial proportion of Grade 3/4 AEs in patients who were treated with cabozantinib (73% in the pNET cohort and 67% in the epNET cohort), these high rates should be viewed in the context of the high rates of Grade 3/4 AEs observed in patients treated with placebo (45% in the pNET cohort and 39% in the epNET cohort). This suggests that the overall patient population enrolled in the CABINET trial was a highly symptomatic patient population. This is not unexpected as the cohort included patients with functional NETs who have a significant symptom burden. Additionally, hypertension, fatigue, diarrhoea and PPE syndrome were the most frequently reported AEs. These represent solicited AEs which were required to be reported at each patient visit, therefore potentially increasing the frequency.

Internal validity

The clinical evidence base presented as part of the submission has been derived from an SLR that was conducted according to the principles of systematic reviewing published in the Cochrane handbook. The clinical SLR identified the pivotal clinical trial, CABINET, as the primary evidence source for cabozantinib and placebo in the population of interest. The results of the quality assessment of CABINET demonstrated that it is a methodologically robust and well-reported trial. The Phase III CABINET study of cabozantinib is a large (particularly in the context of a relatively rare disease), multicentre trial designed and adequately powered to demonstrate that cabozantinib provides superior improvements in PFS compared to placebo.

External validity

Population

The CABINET trial and its results are relevant to the decision problem outlined in the NICE scope, specifically the population of interest, which is adult patients with pNETs or epNETs whose disease had progressed after prior systemic therapy. The patient population was broad, which is reflected in the anticipated marketing authorisation, including patients irrespective of SSTR status, functional status and grade.² UK Clinical experts highlighted that cabozantinib would be expected to be used in UK clinical practice in line with the CABINET trial population, which informs the anticipated marketing authorisation of cabozantinib.⁷⁹

Intervention

Cabozantinib was administered in CABINET in line with how it would be used in UK clinical practice in the population covered by the marketing authorisation.

Comparator

CABINET evaluated the efficacy and safety of cabozantinib compared to placebo, which represented concomitant SSA usage only, and can be considered a proxy for BSC. As discussed in Section 1.1, BSC is the appropriate comparator in this appraisal. Cabozantinib is anticipated to be used in UK clinical practice in line with the population enrolled in the CABINET trial, which

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informed the anticipated marketing authorisation for cabozantinib in this indication, which reflects a heavily pre-treated population with the highest unmet need for new treatment options. After progression on SSAs, the treatment pathway is highly individualised, with systemic treatments restricted to subgroups based on specific patient characteristics. Chemotherapy regimens are not commonly used in Grade 1 and 2, well-differentiated tumours given high treatment burden and a lack of robust efficacy data. For many patients who have progressed on subsequent systemic therapy, the only remaining treatment option is BSC. Unlike other systemic treatments, the marketing authorisation for cabozantinib is not restricted by tumour subtype, SSTR status, functional status or grade. Accordingly, clinical experts experienced in the treatment of NETs consulted by the Company confirmed that the appropriate comparator for cabozantinib on the basis of its marketing authorisation and the CABINET trial is BSC.¹²

Outcomes

A range of endpoints were evaluated in CABINET, including those outlined in the NICE scope, that are relevant to patients and clinicians. Where relevant, outcomes were assessed by BIRC, which is generally considered to be more robust than investigator assessment. The primary endpoint of PFS is an established and NCI-recommended endpoint to measure clinical benefit in Phase III studies for well-differentiated NETs. A longer PFS is both associated with a delay in the reduction of HRQoL and has also been validated as a surrogate endpoint for OS. CABINET was powered to test for significance for PFS but not OS, ORR or HRQoL.

Study design

Due to the differences in biology and potential responsiveness to treatment, the CABINET trial was designed with two cohorts (pNET and epNETs) to independently test the efficacy and safety of cabozantinib in these populations. Although the crossover design may impact the OS results, this was considered a suitable approach from an ethical perspective given the comparator arm did not include an investigational therapy, and appropriate analyses were explored to adjust for the impact of crossover. Further details on the adjustments explored are outlined in Appendix L.

Conclusions

In summary, cabozantinib demonstrated a statistically significant and clinically meaningful improvement in PFS, a numerically higher OS and an improvement in ORR when compared with placebo. A consistent PFS benefit for cabozantinib over placebo was observed across key subgroups of both the pNET and epNET cohorts, demonstrating the potential for cabozantinib to provide an effective treatment option in an all-comer NETs population. Cabozantinib was associated with a predictable and manageable safety profile in the context of a highly symptomatic patient population. This is particularly important given the associated toxicity of alternative treatment options at later lines in this heavily pre-treated population, such as chemotherapy; given the associated toxicity, chemotherapy is not widely used in this patient population in UK practice (limited to patients with high disease burden or grade 3 tumours).

For many patients who have progressed on at least one prior systemic therapy (not including SSAs), the only remaining treatment option is BSC. Cabozantinib addresses a clear unmet need for an additional effective treatment option for patients with pNETs or epNETs, regardless of primary tumour site, tumour grade, SSTR expression status or functional status in patients who have progressed on prior systemic therapy.

3 Cost effectiveness

Summary of the cost-effectiveness analysis

- A *de novo* cost-effectiveness model was developed to assess the cost-effectiveness of cabozantinib versus BSC in adult patients with advanced pNET or epNET who experienced treatment failure or disease progression following treatment with a prior systemic therapy, except SSAs
- The patient population was informed by data from the efficacy population (N=298) of the CABINET trial
- The model adopted a cohort-based partitioned survival model (PSM) approach, in line with prior NICE appraisals in NETs (TA539 and TA449).^{3, 4} It comprised three mutually exclusive health states: progression-free (PF), progressed disease (PD) and death. Patients were redistributed among the three health states at each model cycle; the length of one cycle was equal to four weeks (28 days)
- Parametric survival functions were fitted to CABINET trial data to extrapolate progression-free survival (PFS) and overall survival (OS). NICE TSD14 guidance was followed to determine the most appropriate extrapolations, including seeking expert clinical opinion for clinical plausibility of long-term survival predictions⁹⁹
- Costs included in the model were drug acquisition, administration, treatment-related adverse events (TRAEs), concomitant therapy (CCT), subsequent treatment, resource use and end of life costs. Utility inputs were derived from CABINET trial data for the PF health state and using a relative decrement from Swinburn *et al.* (2012) applied to the CABINET PF values for PD³⁵

Base-case deterministic results

- Cabozantinib was found to be associated with higher costs but also higher life years gained and higher QALYs than BSC
- In the base case analysis, cabozantinib at PAS price resulted in a deterministic ICER of £24,815 for pNETs and £12,849 for epNETs with a 1.2x severity modifier applied (£15,419 for epNETs without a severity modifier) versus BSC; these ICERs are below the cost-effectiveness threshold of £30,000 per QALY for the pNET group, and well below the threshold of £20,000 in the epNET group
- This yielded an incremental net health benefit (INHB) at a willingness to pay threshold of £30,000 per QALY of 0.14 and 0.49 with severity modifier applied (0.34 without a severity modifier) in pNETs and epNETs, respectively

Sensitivity and scenario analyses

- ICER estimates obtained from the probabilistic sensitivity analysis (PSA) to take account of combined uncertainty in the model were similar to the base case deterministic ICERs. In the PSA, cabozantinib was found to have a ■■■% and ■■■% (with a 1.2x severity modifier applied) probability of cost-effectiveness versus BSC in pNET and epNET groups, respectively, at a WTP threshold of £30,000 per QALY.
- Of parameters explored in the deterministic sensitivity analysis (DSA), the IPCW-adjusted OS HR was found to be the most influential parameters on the ICERs versus BSC.
- Scenario analyses were conducted to explore the impact of alternative discount rates, utility values, parametric models for cabozantinib OS, PFS and TTD, independent modelling of PFS and TTD for BSC, administration and subsequent treatment costs, and resource use. In all of the scenario analyses conducted, the ICERs for cabozantinib at PAS price (with the x1.2 severity modifier applied in the epNET cohort) were found to be below a cost-effectiveness threshold of £30,000 per QALY in the pNET group, and well below the threshold of £20,000 in the epNET group

Conclusion

- The cost-effectiveness analysis illustrates that cabozantinib represents a cost-effective use of NHS resource versus BSC, which would address a key unmet in this population that have few treatment options after progression on prior systemic therapies

3.1 Published cost-effectiveness studies

A systematic literature review (SLR) was conducted in May 2024 and updated in January 2025 which aimed to identify all relevant economic evaluations, utilities studies and cost and resource use studies conducted in adult patients with advanced pNET or epNET who experienced treatment failure or disease progression following treatment with a prior systemic therapy. Previous systemic treatments were defined as everolimus, sunitinib, ¹⁷⁷Lu-dotatate, CAPTEM, STZ/5-FU, FOLFOX and IFN- α .

Due to the limited evidence identified, for the utilities studies and cost and resource use studies, the SLR scope was expanded to include studies where at least one patient had been pre-treated with a prior systemic therapy. For economic evaluations, the scope was further expanded to include any economic evaluation in NETs published in key markets (including England) within the last 10 years. Full details of the economic SLR search strategy, study selection process and results are reported in Appendix E.

Across both the original SLR and SLR update, a total of 13 publications reporting on six unique economic evaluations were identified by the SLR. Of the six economic evaluations, three were classified by the authors as cost effectiveness-analyses,^{80, 100, 101} and three as cost-utility analyses.¹⁰²⁻¹⁰⁴ The majority of economic evaluations (N=4) reported a partition survival model structure,^{80, 100, 101, 103} of which Mujica-Mota 2018 specified a semi-Markov model.¹⁰¹ The remaining two studies reported a Markov model structure.^{102, 104}

An overview of these six studies is presented in Table 21. No studies evaluating the cost-effectiveness of cabozantinib were identified.

Table 21: Summary list of published cost-effectiveness studies

Study characteristics			Economic outcomes			Model features		
Study name	Disease characteristics (functional status; grade [net type]) ^a	Intervention and comparator	Total costs (£)	Total benefits	ICER (costs [£] per QALY gained)	Cost year; discount	Model structure	Health states
Glover 2021 ⁸⁰	NR; NR	¹⁷⁷ Lu-dotatate ^b	113,103	QALYs: 5.11	21,827	2017/2018; 3.5% for costs and benefits	Model: partitioned survival TH: 20 years CL: NR Perspective: NHS/PSS	PFS; PPS; death
		Everolimus	72,497	QALYs: 3.25	NA			
		¹⁷⁷ Lu-dotatate ^b	117,915	QALYs: 5.87	15,768			
		Sunitinib	81,350	QALYs: 3.55	NA			
		¹⁷⁷ Lu-dotatate ^b	111,289	QALYs: 4.49	28,038			
		SoC 1 (high dose octreotide LAR) ^b	60,326	QALYs: 3.12	NA			
		¹⁷⁷ Lu-dotatate ^b	118,525	QALYs: 5.64	22,146			
		SoC 2 (high dose octreotide LAR) ^c	53,033	QALYs: 2.96	NA			
Mujica-Mota 2018 ¹⁰¹	NR; low or intermediate grade	Everolimus (analysed as an intervention and comparator)	Pre-progression: 27,559 Post-progression: 15,087 Total: 42,646	LYs: Pre-progression: 1.28 Post-progression: 3.41 Total: 4.69	Total (vs BSC): 45,493	2016; 3.5% for costs and benefits (no PAS discount)	Model: semi-Markov partitioned survival TH: 40 years CL: 28 days Perspective: NHS/PSS	Pre-progression; post-progression; death
	Mixed; NR	Sunitinib	Pre-progression: 24,566 Post-progression: 18,627 Total: 43,192	LYs: Pre-progression: 1.60 Post-progression: 4.79 Total: 6.39	Total (vs everolimus): 745 Total (vs BSC): 20,717			
	NR; NR	BSC (intervention not specified)	Pre-progression: 2,712 Post-progression: 13,049	LYs: Pre-progression: 0.57 Post-progression: 2.89 Total: 3.46	NA			

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Study characteristics			Economic outcomes			Model features			
Study name	Disease characteristics (functional status; grade [net type]) ^a	Intervention and comparator	Total costs (£)	Total benefits	ICER (costs [£] per QALY gained)	Cost year; discount	Model structure	Health states	
			Total: 15,761						
	NR; NR	Everolimus	36,933	QALYs: 2.73 LYs: 4.18	NR	2015; 3.5% for costs (no PAS discount)	Model: semi-Markov partitioned survival TH: 20 years CL: 1 month Perspective: NHS/PSS	SD; PD; death	
		Sunitinib	38,569	QALYs: 2.71 LYs: 4.18	NA				
		Sunitinib	36,247		NR	2015; 3.5% for costs (PAS discount; first cycle of sunitinib free)			
		177Lu-dotatate	NR		NR	NA		NR; 3.5% for costs and benefits	PFS; PPS; death
		Everolimus				9,847			
		Sunitinib				-68,916f			
SMC 2018 ¹⁰³	NR; NR	¹⁷⁷ Lu-dotatate	NR	NR	NA	NR; NR	Model: partitioned survival TH: 20 years CL: NR Perspective: NHS Scotland	PFS; PPS; death	
		Everolimus			26,103				
		Sunitinib			17,487				
		BSC 1 (octreotide LAR) ^e			25,068				
		BSC 2 (octreotide LAR) ^e			26,964				
SMC 2023 ¹⁰⁴	NR; NR	Belzutifan	NR	NR	68,375	NR; simple discount (not elaborated)	Model: Markov TH: Lifetime (59 years based on assumed starting age of 41) CL: NR Perspective: NHS Scotland	Pre-surgery; surgery; event-free after surgery; metastatic disease; death	
		SoC (immediate surgery or active surveillance)	NR	NR	NA				

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Study characteristics			Economic outcomes			Model features		
Study name	Disease characteristics (functional status; grade [net type]) ^a	Intervention and comparator	Total costs (£)	Total benefits	ICER (costs [£] per QALY gained)	Cost year; discount	Model structure	Health states
Smith-Palmer 2021 ¹⁰⁰	NR; NR	¹⁷⁷ Lu-dotatate	117,922 ^d	QALYs: 4.78 ^d	25,068	NR; 3.5% for costs	Model: partitioned survival TH: 20 years CL: 4 weeks Perspective: NHS Scotland	PFS; PPS; death
		BSC (60 mg octreotide LAR)	52,470	QALYs: 2.16	NA			
		¹⁷⁷ Lu-dotatate	113,423 ^d	QALYs: 4.88 ^d	16,390			
		Sunitinib	81,303	QALYs: 2.92	NA			
		¹⁷⁷ Lu-dotatate	108,445 ^d	QALYs: 4.12 ^d	26,103			
		Everolimus	70,974	QALYs: 2.69	NA			
Glover 2021 ⁸⁰	NR; NR (GI NETs)	¹⁷⁷ Lu-dotatate	100,584	QALYs: 4.17	24,145	2017/2018; 3.5% for costs and benefits	Model: partitioned survival TH: 20 years CL: NR Perspective: NHS/PSS	PFS; PPS; death
		Everolimus	74,687	QALYs: 3.10	NA			
		¹⁷⁷ Lu-dotatate	100,073	QALYs: 4.17	26,528			
		SoC (high dose octreotide LAR)	67,454	QALYs: 2.94	NA			
Mujica-Mota 2018 ¹⁰¹	Non-functioning; NR (GI midgut and lung NETs)	Everolimus	Pre-progression: 30,513 Post-progression: 16,882 Total: 47,334	QALYs: Pre-progression: 1.04 Post-progression: 2.70 Total: 3.74 LYs: Pre-progression: 1.42 Post-progression: 4.79 Total: 6.21	44,557	2016; 3.5% for costs and benefits	Model: semi-Markov partitioned survival TH: 40 years CL: 28 days Perspective: NHS/PSS	Pre-progression; post-progression; death
		BSC (intervention not specified)	Pre-progression: 2,450 Post-progression: 14,076 Total: 16,526	QALYs: Pre-progression: 0.65 Post-progression: 2.39 Total: 3.05 LYs: Pre-progression: 0.83	NA			

Study characteristics			Economic outcomes			Model features		
Study name	Disease characteristics (functional status; grade [net type]) ^a	Intervention and comparator	Total costs (£)	Total benefits	ICER (costs [£] per QALY gained)	Cost year; discount	Model structure	Health states
				Post-progression: 3.99 Total: 4.82				
	Non-functioning; NR (GI midgut NETs)	Everolimus	Pre-progression: 38,215 Post-progression: 17,627 Total: 55,842	QALYs: Pre-progression: 1.49 Post-progression: 2.88 Total: 4.37 LYs: Pre-progression: 2.08 Post-progression: 5.42 Total: 7.5	199,233			
		BSC (intervention not specified)	Pre-progression: 4,194 Post-progression: 16,925 Total: 21,119	QALYs: Pre-progression: 1.10 Post-progression: 3.09 Total: 4.19 LYs: Pre-progression: 1.44 Post-progression: 5.62 Total: 7.05	NA			
	NR; NR (lung NETs)	Everolimus	49,168	QALYs: 3.18 LYs: 5.12	31,016	NR; 3.5% for costs	Model: semi-Markov partitioned survival TH: 40 years CL: 4 weeks Perspective: NHS/PSS	NR
		BSC (intervention not specified)	12,249	QALYs: 1.99 LYs: 2.96	NA			
	NR; NR (GI midgut NETs)	Everolimus	52,018	QALYs: 3.57 LYs: 5.75	78,330			
		BSC (intervention not specified)	16,628	QALYs: 3.11 LYs: 4.9	NA			
		177Lu-dotatate	83,667	QALYs: 4.19	NA			

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Study characteristics			Economic outcomes			Model features		
Study name	Disease characteristics (functional status; grade [net type]) ^a	Intervention and comparator	Total costs (£)	Total benefits	ICER (costs [£] per QALY gained)	Cost year; discount	Model structure	Health states
				LYs: 6.66				
		Everolimus	52,018	QALYs: 3.57 LYs: 5.75	50,499			
		BSC (intervention not specified)	16,628	QALYs: 3.11 LYs: 4.9	62,158			
	Non-functioning; NR (GI midgut and lung NETs)	Everolimus	59,720	QALYs: 4.29 LYs: 5.79	43,642	2015; 3.5% for costs	Model: semi-Markov partitioned survival TH: 30 years CL: 1 month Perspective: NHS/PSS	SD; PD; death
		BSC (intervention not specified)	25,817	QALYs: 3.51 LYs: 4.78	NA			
	NR; NR (GI midgut NETs)	177Lu-dotatate	NR	NR	19,816	NR; 3.5% for costs and benefits	Model: semi-Markov partitioned survival TH: 20 years CL: 1 month Perspective: NHS/PSS	PFS; PPS; death
		Everolimus (intervention not specified)			NA			
SMC 2017 ¹⁰²	Non-functioning; Grade 1/2 (GI and lung NETs)	Everolimus	NR	NR	26,241	NR; simple discount (not elaborated)	Model: Markov TH: 30 years CL: 1 month Perspective: NHS Scotland	SD; PD; death
		BSC (mixed ⁹)			NA			
SMC 2018 ¹⁰³	NR; NR (GI NETs)	¹⁷⁷ Lu-dotatate	NR	NR	26,830	NR; NR	Model: partitioned survival	PFS; PPS; death

Study characteristics			Economic outcomes			Model features		
Study name	Disease characteristics (functional status; grade [net type]) ^a	Intervention and comparator	Total costs (£)	Total benefits	ICER (costs [£] per QALY gained)	Cost year; discount	Model structure	Health states
		BSC (LAR octreotide LAR)			NA		TH: 20 years CL: NR Perspective: NHS Scotland	
Smith-Palmer 2021 ¹⁰⁰	NR; NR (GI NETs)	177Lu-dotatate + 30 mg octreotide	84,990	QALYs: 3.25	26,830	NR; 3.5% for costs	Model: partitioned survival TH: 20 years CL: 4 weeks Perspective: NHS Scotland	PFS; PPS; death
		BSC (60 mg octreotide LAR)	49,289	QALYs: 1.92	NA			

N represented the number of studies that reported economic outcomes. Cost and cost-effectiveness data has been rounded to integers; benefits have been presented to two decimal places. ^a Functional status, grade and Ki-67 index were prespecified at the start of extraction as disease characteristics of interest. Notably, none of the included studies reported Ki-67 index. As such, this has not been presented in the table. For epNET data, specific NET types have been specified, where reported. ^b ¹⁷⁷Lu-dotatate data were based on a MAIC between the Dutch cohort of ERASMUS and RADIANT-3 (for comparison with everolimus and SOC 1) or NCT00428597 (for comparison with sunitinib and SOC 2). ^c SoC 1 and SoC 2 data were derived from RADIANT-4 and NCT00428597 respectively. ^d ¹⁷⁷Lu-dotatate data were based on a MAIC between the Dutch cohort of ERASMUS and A6181111 (assuming equivalence between octreotide and BSC; for comparison with BSC), A6181111 (for comparison with sunitinib) or RADIANT-3 (for comparison with everolimus). ^e BSC data were based on a MAIC between the Dutch cohort of ERASMUS and a sunitinib study (not elaborated) for BSC 1 or an everolimus study (not elaborated) for BSC 2. ^f ¹⁷⁷Lu-dotatate was less expensive and more effective than the comparator (sunitinib), saving costs while improving outcomes, as such the ICER is negative. ^g BSC was comprised of several treatments including analgesics, other pain medication, somatostatin analogues and external beam radiation therapy.

Abbreviations: BSC: best supportive care; CL: cycle length; epNET: extra-pancreatic neuroendocrine tumour; GI: gastrointestinal; HR: hazard ratio; HRQoL: health-related quality-of-life; LAR: long-acting release; LYs: life-years; NA: not applicable; NETs: neuroendocrine tumours; NHS/PSS: National Health Service/Personal Social Services; NR: not reported; OS: overall survival; PAS: patient access scheme; PD: progressed disease; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour; PPS: post-progression survival; QALYs: quality-adjusted life years; SD: stable disease; SoC: standard of care; TH: time horizon.

3.2 **Economic analysis**

The economic SLR found no economic evaluations investigating cabozantinib versus BSC in [REDACTED]

[REDACTED]. Therefore, a *de novo* cost-effectiveness analysis has been conducted to assess the cost-effectiveness of cabozantinib versus BSC within its marketing authorisation for this indication. The cost-effectiveness model employed for this economic analysis was built in Microsoft Excel®.

In line with the NICE reference case, the analysis was conducted from the perspective of the NHS and Personal Social Services (PSS) over a lifetime time horizon (equivalent to approximately 40 years) with the discount rate set to 3.5% for both costs and benefits.¹⁰⁵

The economic evaluation was performed then line with the NICE reference case:

- Health outcomes were measured both in terms of life years gained (LYGs) and quality-adjusted life years (QALYs) gained
- The primary outcome measure for the economic evaluation was the incremental cost-effectiveness ratio (ICER; cost per QALY gained) as well as the incremental net health benefit (INHB; net health gain less the increased cost) when cabozantinib was compared with BSC.
- Clinical effectiveness for cabozantinib and BSC was measured through PFS and OS outcomes (see Section 3.3)

Costs and health-related utilities were allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle. In line with the NICE reference case, only direct health care costs were considered in the model, including treatment acquisition costs, administration costs, concomitant therapy (CCT), subsequent treatment, monitoring and resource use, AE management and terminal care costs (see Section 3.5).

3.2.1 **Patient population**

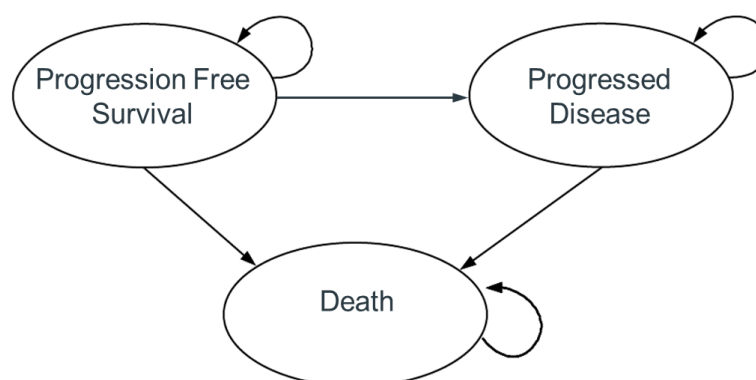
The economic analysis considered [REDACTED]. This population is aligned with the anticipated marketing authorisation for cabozantinib in this indication and the patient population enrolled in the CABINET trial (N=298), which provides the clinical evidence for cabozantinib and BSC in this population. In England, for many patients who have progressed on at least one prior systemic therapy, there are no effective treatment options remaining other than BSC; cabozantinib could therefore provide a substantial clinical benefit for these patients.

3.2.2 **Model structure**

The cost-effectiveness model (CEM) was developed in Microsoft Excel® and adopted a partitioned-survival model (PSM) structure in line with the prior NICE appraisals in NETs for ¹⁷⁷Lu-dotatate, everolimus and sunitinib for treating unresectable or metastatic neuroendocrine tumours (TA539 and TA449).^{3, 4} Figure 18 provides a schematic of the model structure, with arrows representing the transitions that a patient can make within one model cycle within or to different health states.

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Figure 18: Schematic of the PSM structure



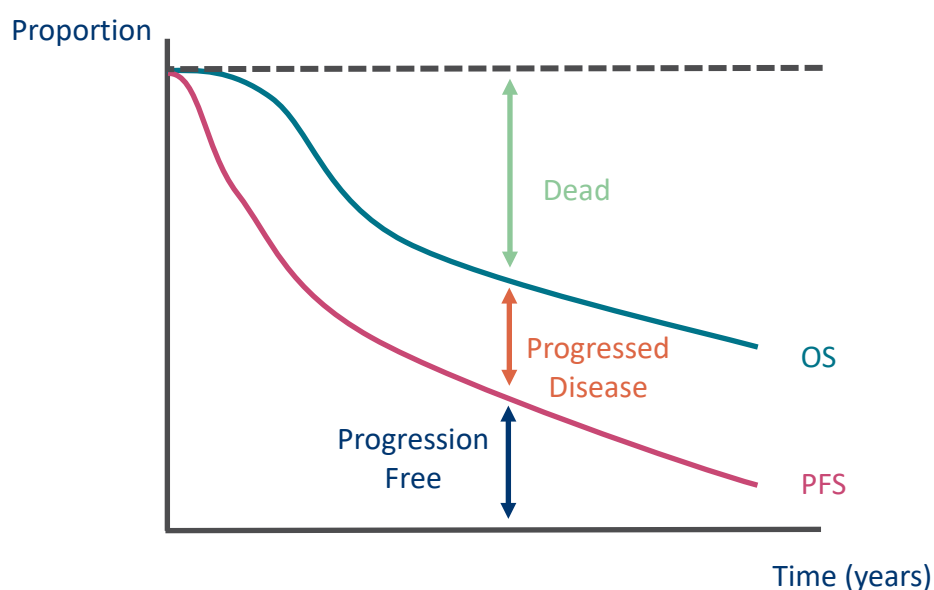
Abbreviations: PSM: partitioned survival model

As outlined in Figure 18, the structure of the PSM comprised of three health-states that were determined by the cumulative survival probabilities of PFS and OS data from CABINET as follows:

- **Progression-free (PF):** All patients enter the model in this health state with their disease in a stable or responding state and not actively progressing. In this health state, patients receive either cabozantinib or BSC and will incur costs associated with treatment acquisition, administration, concomitant therapy, adverse event (AE) management and resource use. Patients remain in this health state until disease progression upon which they will move either into the progressed disease (PD) state. The proportion of patients in this health state was calculated using PFS data
- **Progressed Disease:** Patients who have met the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria for disease progression will move from PFS and remain in this health state until death. Here patients are assumed to incur costs for subsequent treatment and resource use. The proportion of patients within this health state is calculated using the difference between PFS and OS
- **Death:** Patients move into this absorptive health state from either PFS or PD and remain here for the rest of the modelled time horizon. Patients no longer incur costs, life years or utilities. The proportion of patients in this health state is calculated using OS data (one minus the proportion of patients alive)

A graphical depiction of the health states used in the PSM is presented in Figure 19.

Figure 19: Schematic of the PSM health states



The data in the figure are fictitious and used for illustrative purposes only. The proportion of patients in the PD state is calculated as the proportion of patients alive (based on the OS estimates) minus proportion of patients progression-free (based on the PFS estimates); this is shown in the figure with the orange text.

Abbreviations: OS: overall survival; PD: progressed disease; PF: progression-free; PFS: progression-free survival; PSM: partitioned survival model

Patients were redistributed among the three health states in each model cycle; the length of which was 28 days (four weeks) to align with the treatment cycles of cabozantinib and BSC (concomitant SSA). PFS was bounded by OS to avoid logical inconsistencies, OS was constrained by the age and gender matched general population survival to ensure plausibility of the results, and TTD curves were bounded by PFS given it is reasonable to assume that treatment would not occur beyond progression. Treatment acquisition, treatment administration, costs of managing AEs (PF only), and CCT were all costed based on time on treatment (ToT).

Rationale for the selected model structure

The PSM structure was deemed the most appropriate model structure to inform the cost-effectiveness of cabozantinib versus BSC for several reasons.

A PSM allows for intuitive inclusion of PFS and OS data which are the key outcomes in oncology indications and key endpoints recorded in the CABINET trial. Modelling OS and PFS based on study-observed events facilitates the replication of within-trial data and means the model accurately reflects disease progression and the observed survival profile of patients treated with cabozantinib and BSC. The PSM structure also allows uncertainty in survival extrapolations to be explored.

A PSM approach was selected over a state transition model (STM), such as a Markov model. While the STM approach has certain advantages, such as the ability to include additional health states to capture the disease in more detail, or to allow for more complex modelling of subsequent treatments, this level of detail was deemed unnecessary for this submission, given the population of relevance is a highly pre-treated population. Furthermore, there are likely to be an insufficient number of clinical events occurring in the CABINET trial to reliably inform transition probabilities. By using a PSM, a range of survival estimates could be generated and validated by Company evidence submission template for cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment

clinicians to generate clinically plausible estimates of long-term survival, and the change in event rates over time anticipated with cabozantinib could be more easily explored. One potential limitation of the PSM structure includes the lack of an explicit link between PFS and OS, as each outcome is modelled independently. This could lead to incongruent relationships of PFS and OS (e.g. the PFS and OS curves crossing). However, in this model the curves produce plausible estimates and PFS is capped by OS to prevent any logical inconsistencies.

In addition, the PSM model structure and the included disease states are expected to reflect unresectable or metastatic NETs, as it is a progressive disease that, in advanced stages, typically leads to death. The PSM approach also aligns with TA449 and TA539, the previous NICE appraisals in unresectable or metastatic NETs, in which the use of a PSM was accepted by the NICE committee.^{4, 106} As such, a PSM model was considered the most appropriate model structure for this submission. The model structure also does not allow for patients to improve their health state, which reflects the progressive nature of the condition.

Features of the cost-effective analysis

There are no prior NICE appraisals in the indication of interest for this submission. For completeness, the features of economic evaluations submitted in prior appraisals in NETs (TA449 and TA539) are provided in Table 22 below.^{3, 4}

Table 22: Features of the economic analysis in previous evaluations in unresectable or metastatic NETs

Factor	Previous evaluation		Current evaluation	
	TA449 Everolimus and sunitinib	TA539 ¹⁷⁷ Lu-dotatate	Chosen values	Justification
Date of publication	June 2017	August 2018	N/A	N/A
Relevant comparator for this appraisal?	No	No	N/A	N/A
Model structure	Partitioned survival model		Partitioned survival model	Allows for intuitive incorporation of PFS and OS data, which are the key outcomes in cancer indications and key outcomes collected in the CABINET trial, and aligned with the prior appraisals.
Time horizon	Lifetime (40 years)		Lifetime (40 years)	The base case utilises a lifetime horizon value, equivalent to approximately 40 years, calculated using 100 years minus the average starting age of patients in the model. Sufficient to capture any differences in costs or outcomes between the technologies being compared
Cycle length	4 weeks		4 weeks	Appropriate to capture the incidence of modelled events and associated outcomes. This also aligns with the treatment cycles of both cabozantinib and BSC (SSAs) and is consistent with prior appraisals
Half cycle correction	A half-cycle correction is applied		A half-cycle correction is applied	The approach is aligned with the prior appraisals.

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Treatment waning effect	Not reported	Not included	OS data from the CABINET trial are already relatively mature, and thus any waning of treatment effect following discontinuation of cabozantinib is already captured within the OS data informing the survival extrapolations in the model. Furthermore, survival extrapolations were selected accounting for clinical expectations of long-term survival following treatment with cabozantinib and BSC. Treatment effect waning has not been considered in the model as is in line with the prior appraisals.
Source of utilities^a	All interventions were assumed to have similar HRQoL due to being offered at the same point in the treatment pathway pNETs (pre and post-progression): A6181111 GI and lung NETs: Pre-progression: • Everolimus + BSC: unpublished treatment-specific values from RADIANT-4 IPD • PRRT: ERASMUS Post-progression: • All interventions: pooled analysis of RADIANT-4	PFS: derived from CABINET data PD: A relative decrement applied to CABINET PF utility values calculated from Swinburn <i>et al.</i> (2012)³⁵	Utility values derived from CABINET for PD were deemed clinically implausible due to being higher than those in PF (for pNETs). These were also deemed unreliable due to a limited number of observations informing this state. Therefore, a relative decrement calculated from Swinburn <i>et al.</i> (2012) was applied to the CABINET PF utility values.³⁵ The model also included other potentially relevant utility values in scenarios for the PD health state. These included using utility values directly from Swinburn <i>et al.</i> (2012) as well as direct values and a relative decrement from the ERASMUS trial.^{35, 107} Applying a relative decrement was deemed to more closely reflect the clinical trial population than using direct utility values, and the resultant base case values from Swinburn <i>et al.</i> (2012) were deemed clinically plausible during UK clinician feedback.^{35, 107}
Resource use	• Health-state rather than treatment specific values included • Included resource use types included multiple subsets of: physician visits, procedures and tests as well as hospitalisations	• Health-state rather than treatment specific values • Resource use types include: CT scans, hospitalisation, other imaging, lab tests and visits. No subsets of these	The resource use values included were based on a publication identified in the healthcare resource use (HCRU) SLR (Casciano <i>et al.</i> [2013]) and included simplified categories compared to those included in the prior appraisals in line with clinician feedback.^{12, 79}

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	Resource use was included for post-progression treatments Unit costs: NHS National Schedule of costs	included Unit costs: NHS National Schedule of costs	
Measure of health effects	QALYs	QALYs	In line with the NICE reference case. ¹⁰⁵
Source of costs	- Intervention costs were based on the UK list price including a PAS discount - Other treatment costs were sourced from the BNF or eMIT database - PSSRU - NHS National Schedule of Costs	- Intervention costs were based on the UK list price including a PAS discount - Other treatment costs were sourced from the BNF - PSSRU - National Schedule of Costs	Cost inputs were taken from established sources of NHS costs and are aligned with the prior appraisals.

In the prior appraisals, the committee decided that only the EAG model was appropriate for decision making. Given that the same EAG model was used in TA539 and TA449, only one set of values is presented.^a The company submission included utility values from Swinburn et al (2012)³⁵

Abbreviations: BNF: British National Formulary; BSC: best supportive care; CT: computerised tomography; GI: gastrointestinal; eMIT: electronic market information tool; HCRU: healthcare and resource use; HRQoL: health-related quality of life; IPD: individual patient data; OS: overall survival; NET: neuroendocrine tumour; NHS: National Health Service; PAS: patient access scheme; PD: progressed disease; PF: progression free; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour; PSSRU: Personal Social Services Research Unit; PRRT: peptide receptor radionuclide therapy; SLR: systematic literature review; SSA: somatostatin analogue; TA: technology appraisal; QALY: quality-adjusted life year.

Source: NICE TA449;⁴ NICE TA539.³

3.2.3 *Intervention technology and comparators*

Intervention

The intervention of interest is cabozantinib (60 mg), administered orally once daily (QD) as a continuous therapy. This dose is in line with the anticipated licensing of cabozantinib ([REDACTED]) as well as the current marketing authorisation in other indications: renal cell carcinoma (RCC), hepatocellular carcinoma (HCC) and differentiated thyroid cancer (DTC).¹ It is advised the cabozantinib is administered until disease progression or unacceptable toxicity.

Comparator

As noted in Section 1.1 BSC represents the most appropriate comparator in this appraisal. Cabozantinib is anticipated to be used in UK clinical practice in line with the population enrolled in the CABINET trial, which informed the anticipated marketing authorisation for cabozantinib in this indication, and which reflects a heavily pre-treated population with the highest unmet need for new treatment options. After progression on SSAs, the treatment pathway is highly individualised, with systemic treatments restricted to subgroups based on specific patient characteristics. Chemotherapy regimens are not commonly used in Grade 1 and 2, well-differentiated tumours given high treatment burden and a lack of robust efficacy data. For many patients who have progressed on subsequent systemic therapy, the only remaining treatment option is BSC. On the basis of the marketing authorisation for cabozantinib, clinical experts experienced in the treatment of patients with NETs in the UK also considered BSC to represent the most appropriate comparator for this appraisal.¹²

Efficacy data for BSC included in the model were derived from the placebo arm of the CABINET trial, where patients receive only SSAs as CCT and no systemic anticancer therapy. This is akin to BSC which focuses primarily on symptomatic management of disease and maintaining quality of life. Clinician feedback suggested this approach was appropriate considering no other treatments, other than SSAs, were relevant for BSC.^{12, 79} UK clinicians specifically highlighted that although both lanreotide and octreotide are used, in practice the market share of lanreotide is far higher.¹² Market share estimates, which align with the feedback received from clinicians, suggest [REDACTED]% and [REDACTED]% of patients receive lanreotide and octreotide, respectively.¹²

The administration and dosing regimens of SSAs, lanreotide and octreotide in UK clinical practice, are summarised in Table 23.

Table 23: Details of administration of interventions included in the model

Intervention	Dosing regimen	Proportion of cohort	Duration of treatment	Admin. route	Source
Cabozantinib	60 mg per day in a 28-day cycle (continuous)	100%	Until disease progression or unacceptable toxicity	Oral	Cabozantinib SmPC ¹
BSC (concomitant SSAs)	Lanreotide: 120, 90 or 60 mg every 28 days	■	Indefinitely	Deep SC injection	BNF, 2025 ¹⁰⁸
	Octreotide: 30, 20 or 10 mg every 4 weeks	■	Indefinitely	Deep IM injection	BNF, 2025 ¹⁰⁹

Abbreviations: BSC: best supportive care; IM: intramuscular; mg: milligram; SC: subcutaneous; SmPC: summary of product characteristics.

Source: Cabozantinib SmPC;¹ BNF, 2025. Lanreotide;¹⁰⁸ BNF, 2025. Octreotide.¹⁰⁹

3.3 Clinical parameters and variables

3.3.1 Baseline characteristics

The baseline characteristics for the model population are provided in Table 24. These inputs were based on the baseline characteristics of the intention to treat (ITT) population who were enrolled in the CABINET trial. The baseline characteristics of patients in the CABINET trial are expected to be in line with the patient population in which cabozantinib is anticipated to be used in in UK clinical practice.

Age and sex are included in the model to determine general population mortality inputs. Body weight and body surface area (BSA) are included in the model in order to calculate the drug acquisition costs of FOLFOX that is dosed based on weight or BSA (see Section 3.5.1).

Table 24: Baseline characteristics for the model population

Model parameter	pNETs	epNETs	Source
Mean age, years (SE)	60.22 (1.13)	63.09 (0.80)	CABINET CSR ²
Percentage female	42.11%	51.72%	
Body weight, kg (SE)	80.81 (2.07)	78.85 (1.45)	
Body surface area, m ² (SE)	1.95 (0.03)	1.91 (0.03)	Ipsen Data on File; calculated from CABINET IPD

Abbreviations: CSR: clinical study report; IPD: individual patient data, SE: standard error

Source: Ipsen. Data on File. CABINET CSR. Data Cut-Off 24 August 2023;² Ipsen Data on File; calculated from CABINET IPD

It should be noted that there were some differences in cohort allocation between the OPEN registration system and EDC. As a result, a small number of pNET patients were allocated to the epNET cohort, and vice versa, during enrollment in CABINET (3 epNET patients included in the pNET cohort and 7 pNET patients included in the epNET cohort). This can occur where lesions are present at multiple sites. However, post-hoc analyses using corrected cohorts revealed consistent results with the ITT population. Therefore, given that the ITT analyses maintain randomisation, these form the key evidence base for inclusion in this submission.

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3.3.2 *Extrapolation of survival inputs*

Efficacy inputs for cabozantinib and BSC were informed by CABINET using the cabozantinib and placebo arms, respectively. For BSC (placebo arm), this represented the concomitant use of SSAs only given that concomitant systemic anticancer therapy was not permitted.²

As the follow-up period from CABINET (see Section 2.3.2) was shorter than the model time horizon, extrapolation from the observed time-to-event data was required. Extrapolation of PFS and OS for cabozantinib and BSC was performed using ITT analysis datasets derived from the CABINET time-to-event individual patient data (IPD) dataset (ADTTE) in both pNETs and epNETs. This dataset corresponded to a median follow-up of 89.1 months for OS.² For PFS in the cabozantinib and placebo arms respectively, this corresponded to a median follow-up of 23.2 and 25.2 months in pNETs and 23.3 and 23.0 months in epNETs.²

Survival parameters were generated for the standard parametric extrapolations as detailed in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14: exponential, Weibull, log normal, log logistic, Gompertz and generalised gamma.⁹⁹

Model selection: Internal validity of survival functions

The goodness-of-fit criteria (including the Akaike information criterion [AIC] and the Bayesian information criteria [BIC]) were estimated for each parametric function. The choice of distribution for the base case for all OS and PFS curves, as per the recommendations provided in NICE DSU TSD14 and TSD21, was informed considering:

- **AIC/BIC tests:** the AIC and the BIC provide useful statistical tests of the relative fit of different parametric survival models. These tests weight the improved fit of models with the potentially inefficient use of additional parameters. Lower AIC and BIC values indicate better fit of the selected model
- **Graphical assessment of fit:** visual inspection can evaluate how well a parametric survival model fits with the observed Kaplan–Meier curves. The parametric survival model that most closely follows the Kaplan–Meier curve could be considered the best fit
- **Visual inspection of hazard plots:** The hazard profiles of the time-to-event data were assessed using diagnostic plots to identify which extrapolation was suitable (i.e. relatively aligned with the hazard profiles of one of the six standard extrapolations). Inspection of the Schoenfeld and log-cumulative hazard plots was conducted to determine if there was any violation of the proportional hazards (PH) assumption

Model selection: External validation based on clinical expert feedback and comparison to external data

Clinical validation

Given the similarity in visual and statistical fit of parametric models to the observed data for cabozantinib and BSC, clinical plausibility of the various long-term OS extrapolations explored was a primary factor informing selection of the distributions for the base case. Feedback was obtained from five UK clinical experts in NETs through pre-read questionnaire and subsequent discussions via teleconference.

In the teleconference, clinicians were asked to provide lower, upper and most likely estimates for the proportion of patients they would expect to be alive at 5, 10 and 15 years when receiving BSC or cabozantinib, respectively. Clinical experts were provided with relevant baseline characteristics from CABINET and landmark survival data derived from CABINET Kaplan–Meier data for cabozantinib and BSC (adjusted for crossover) to inform their estimates.

Using the results of the questionnaire, candidate distributions that were deemed potentially clinically plausible were identified (i.e. those that did not predict survival above or below the upper and lower values elicited from the experts, respectively). There was broad consistency between the individual assessments provided by the experts, albeit with greater variation for the survival predictions for epNETs.

See Section 3.14 for further details on the collection of clinical expert opinion.

Real-world evidence

In order to further validate survival extrapolations from CABINET, evidence from prior HTAs in NETs (in particular TA449), and reported long-term survival data identified from a targeted literature review (TLR) of non-interventional studies was investigated.⁴ 28 publications reporting on 25 unique studies were identified (deprioritising studies only reporting individual patient data), of which nine studies included outcomes solely for patients with pNETs, and the remaining 15 studies enrolled patients with non-stratified NETs, encompassing both pNETs and epNETs. The majority of studies were conducted at a single centre, were single arm and had small sample sizes. Details of the TLR can be found in Appendix M.

Limited long-term survival data were identified, with median OS and PFS typically reported across studies, rather than percentage survival at specific time points. Additionally, due to differences in treatment line, there was limited applicability to the CABINET trial population across the identified studies. However, one RWE study identified in the TLR (Fröss-Baron et al. [2021]) showed that survival beyond 12 years was possible for patients with advanced pNETs that were heavily pre-treated with chemotherapy and undergoing treatment with ¹⁷⁷Lu-dotatate. In this study, around 20% of patients survived beyond 12 years, which suggests that long-term survival is realistic for some CABINET patients, and approximately 5% of patients were progression-free after 12 years.¹¹⁰ Patients were slightly younger in this study (mean age at baseline: 57.1 years, range 29-79 years) than the CABINET pNET population (mean age at baseline: 60.2 years, range: 29-79 years), and average time since diagnosis was only 36 months as opposed to between 57 and 112 months for CABINET. However, the fact that a substantial proportion of a heavily pre-treated population survived beyond 12 years of onset of PRRT treatment, including a proportion of those who received two lines of prior chemotherapy, suggests that some CABINET patients might achieve similar long-term survival.

The NICE for the appraisal of everolimus (TA449) reported data from the Surveillance, Epidemiology, and End Results (SEER) program indicating that the 15-year survival rate of patients who were diagnosed with distant NETs in the US since 1973 was 6% for pNET patients and 5% for GI/lung NET patients.⁴ However, there are challenges in comparing the SEER data with the CABINET population. On the one hand, patients in CABINET were diagnosed between 5 and 10 years, on average, before entering the trial and progressed on at least one prior Food and Drug Administration (FDA)-approved treatment whereas, for the SEER data presented in the everolimus submission, patients were followed from diagnosis, which suggests that shorter survival would be expected in the CABINET population.⁴ On the other hand, the SEER data

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included patients regardless of tumour grade whereas CABINET eligibility criteria were restricted to well- or moderately differentiated tumours which is associated with a better prognosis of survival. Additionally, the SEER data presented in the everolimus submission reached back as far as 1973 and improvements observed in survival over time in patients with NETs indicate that a longer survival would be expected in the CABINET population.

Despite limited external data to assess validity of the survival extrapolations, a substantial proportion of patients (48% of epNET patients and 34% of pNET patients) died during follow-up, thereby providing reasonable data maturity and a suitable basis for OS extrapolations from the CABINET trial. Similarly for PFS, a substantial proportion of patients (55% of epNET patients and 66% of pNET patients) progressed during follow-up, thereby providing a suitable basis for PFS extrapolations from the CABINET trial. From the external data that are available, it is reasonable to consider that a proportion of CABINET patients would be alive after 15 years.

3.3.3 Progression-free survival

As described in Section 3.2.2, the proportion of patients in each health state at each four-week model cycle was determined for each therapy directly from cumulative survival probabilities for PFS. PFS curves were bounded by OS to avoid logical inconsistencies.

Initially, in line with NICE TSD 14, the PH assumption was assessed. Schoenfeld residual, log-cumulative hazard and smoothed hazard plots are presented in Appendix K for cabozantinib and BSC. Overall, the plots show little evidence of violation of the PH assumption for both pNETs and epNETs. All Schoenfeld tests had p-values higher than 0.1, suggesting that there was not sufficient evidence to reject the null hypothesis of proportional hazards in pNET or epNET cohorts. The PH assumption between cabozantinib and BSC for PFS was therefore considered appropriate; for consistency with approach to OS (see Section 3.3.4), PFS for BSC was derived by applying the PFS HR from the CABINET trial to the cabozantinib PFS curve. PFS extrapolations were also fitted separately for the cabozantinib and placebo arms to explore the impact of independent modelling in scenarios.

It is noted that choice of parametric extrapolation for the cabozantinib treatment arm (to which relevant HRs would be applied) was not limited to proportional hazards models, but also considered functions such as accelerated failure time (AFT) models. The purpose of this was to maximise choice from a range of potentially clinically valid extrapolations. Whilst the combining of HRs with survival probabilities estimated from an AFT model is technically mixing assumptions on how treatment effects would (theoretically) be applied in the survival model (acting on the time scale for an AFT model) and how they are modelled in the comparative analysis (acting on the hazard scale). However, there is no reason to artificially constrain the comparator curves to the same form. If the estimated curves for the comparators are clinically valid, the conflating of technical assumptions is immaterial.

Cabozantinib

To inform long-term estimates of PFS in the model for cabozantinib, it was necessary to extrapolate PFS data through the application of parametric survival functions. A substantial proportion of patients (55% of epNET patients and 66% of pNET patients) progressed during follow-up, thereby providing a suitable basis for PFS extrapolations. The selection of the most appropriate extrapolation for cabozantinib PFS was informed by the recommendations of NICE DSU TSD 14.⁹⁹ Specifically, goodness-of-fit statistics were calculated and assessed to

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understand which parametric form had the best statistical fit to the KM data. Assessment of visual fit was also conducted.

The model fit statistics (AIC and BIC) for the parametric survival functions explored for the cabozantinib PFS data are presented in Table 25 and Table 26 for pNETs and epNETs, respectively. Visual assessment of the parametric survival functions to the KM data for cabozantinib was performed using the extrapolations presented in Figure 20 and Figure 21.

Table 25: Model fit statistics for PFS parametric survival functions for cabozantinib (pNETs)

Function	PFS			
	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	252.16	5	254.32	4
Weibull	249.95	3	254.27	3
Lognormal	249.10	1	253.42	1
Loglogistic	249.29	2	253.61	2
Gompertz	252.53	6	256.85	5
Generalised gamma	250.74	4	257.22	6

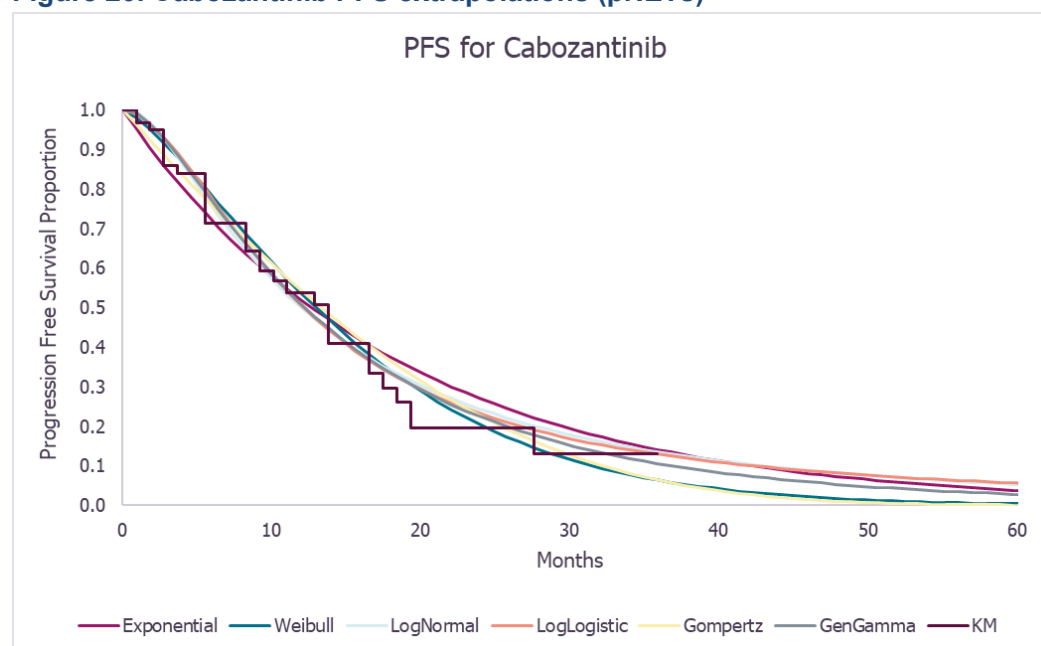
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; pNET: pancreatic neuroendocrine tumour; ITT: intent-to-treat; PFS: progression-free survival.

Table 26: Model fit statistics for PFS parametric survival functions for cabozantinib (epNETs)

Function	PFS			
	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	509.11	6	512.01	6
Weibull	498.02	4	503.82	3
Lognormal	493.57	1	499.37	1
Loglogistic	495.67	3	501.47	2
Gompertz	505.51	5	511.31	5
Generalised gamma	495.44	2	504.13	4

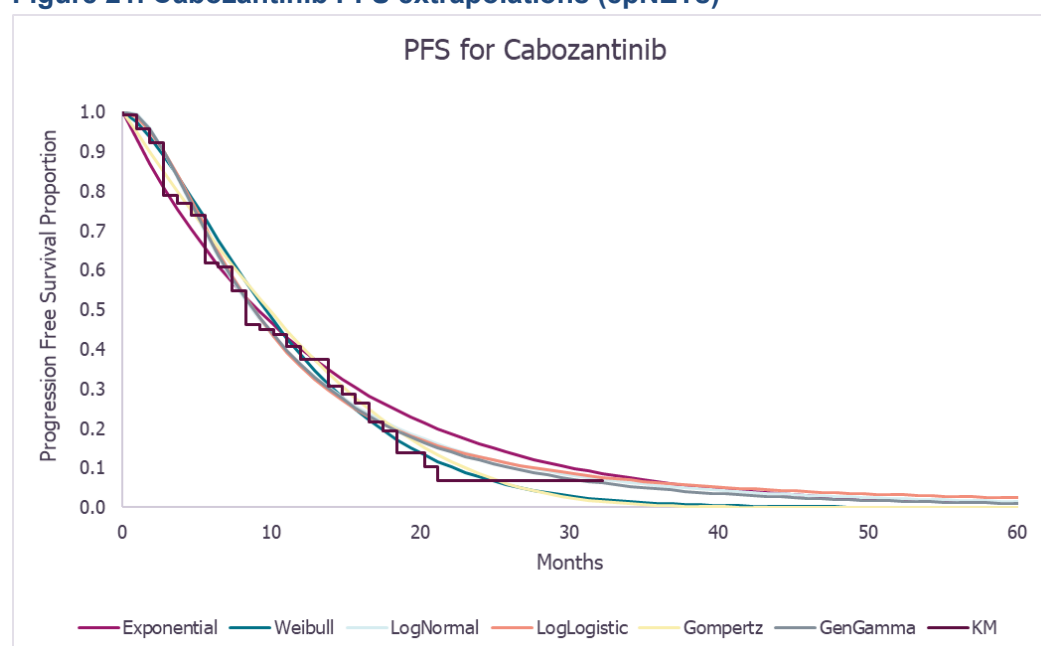
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; epNET: extra-pancreatic neuroendocrine tumour;; PFS: progression-free survival.

Figure 20. Cabozantinib PFS extrapolations (pNETs)



Abbreviations: KM: Kaplan-Meier; PFS: progression free survival, pNET: pancreatic neuroendocrine tumour.

Figure 21. Cabozantinib PFS extrapolations (epNETs)



Abbreviations: epNET: extra pancreatic neuroendocrine tumour; KM: Kaplan-Meier; PFS: progression free survival.

There were no substantial differences between the AIC and BIC values for the fitted PFS curves, suggesting a similar goodness of fit to the KM data for all curves. The majority of extrapolations showed a difference in points <5 within AIC and BIC values, which is generally accepted to indicate similar fit,^{111, 112} with the exception of the exponential curves in both populations and Gompertz curve in epNETs.

With the exception of the exponential curve, all extrapolations appeared to provide a similar fit to the observed KM data in the assessment of visual fit and were shown to have plausible long-term

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PFS rates. Whilst there were limited relevant external data available to validate the extrapolations from CABINET, available data suggests that it is plausible a small proportion of patients treated with an effective treatment option can achieve progression-free survival in the long term, even in heavily pre-treated populations. Acknowledging the differences in study populations described above, in Fröss-Baron 2021, patients with advanced pNETs that were heavily pre-treated with chemotherapy and undergoing treatment with ¹⁷⁷Lu-dotatate achieved a median PFS of 24 months (95% CI: 17,28), with more than 20% of patients remaining progression-free at 36 months and approximately 5% progression-free after 12 years.¹¹⁰

The lognormal model was therefore selected for the base case analysis for both pNET and epNET cohorts given it was associated with the best statistical fit, a suitable hazard profile, acceptable fit to the KM curve and a plausible long-term PFS rate (as shown in Table 27). The Gompertz and Weibull models were explored in scenario analyses to extrapolate cabozantinib PFS data in the pNET and epNET populations, respectively, representing the most conservative estimates of PFS (3.11.3), whilst providing reasonable statistical and visual fit to the KM data and hazard profile.

Table 27: Extrapolated landmark PFS rates for base case and scenarios (cabozantinib)

Population	Distribution	Extrapolated PFS rate at			
		Month 12	Month 36	Month 72	Month 120
pNET	Base case: Lognormal	0.50116	0.13553	0.03618	0.01044
	Scenario: Gompertz	0.54467	0.06469	0.00002	<0.00001
epNET	Base case: Lognormal	0.36098	0.05605	0.00897	0.00164
	Scenario: Weibull	0.38618	0.01027	<0.00001	<0.00001

Derived directly from the CEM, and therefore including the impact of any bounds to avoid logical inconsistencies. Shaded highlighting indicates a survival rate of less than 0.01.

Abbreviations: epNET: extra-pancreatic neuroendocrine tumour; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour.

BSC

Given there was little evidence of violation of the PH assumption for both pNETs and epNETs, for consistency with the approach to OS (see Section 3.3.4), PFS for BSC in the base case analysis was derived by applying the HR from the CABINET trial to the cabozantinib PFS curve (lognormal in both populations). The HRs applied are outlined in Table 28. Stratified HRs were selected as this was the preferred measure in CABINET. The appropriateness of these HRs was assessed by evaluating the proportional hazards assumption using Schoenfeld residuals and log cumulative hazard plots to ensure that the effect of treatment on the hazard rate is consistent over time.

Table 28: PFS HRs (95% CI) for cabozantinib versus BSC

Population	Measure	ITT Analysis
pNET	Stratified HR (95% CI) ^a	0.23 (0.12, 0.42)
epNET	Stratified HR (95% CI) ^b	0.38 (0.25, 0.58)

^a Stratification factors per OPEN for pNET: concomitant SSA use and prior sunitinib use; ^b Stratification factors per OPEN for epNET: concomitant SSA use and primary site (midgut/unknown vs non-midgut GI/lung/other).

Abbreviations: epNET: extra-pancreatic neuroendocrine tumour; ITT: intent-to-treat; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour.

PFS extrapolations were also fitted separately for the cabozantinib and placebo arms to explore the impact of independent modelling in scenarios. Lognormal functions were selected to directly extrapolate placebo PFS data in these scenarios, on the basis that they were associated with the best statistical fit, a suitable hazard profile, acceptable fit to the KM curve and a plausible long-term PFS rate (as shown in Table 29). Full details of survival extrapolations explored are presented in Appendix K.

Table 29: Extrapolated landmark PFS rates for base case and scenarios (BSC)

Population	Distribution ^a	Extrapolated PFS rate at			
		Month 12	Month 36	Month 72	Month 120
pNET	Base case: HR applied to cabozantinib curve	0.04715	0.00015	<0.00001	<0.00001
	Scenario: lognormal	0.05538	0.00049	0.00001	<0.00001
epNET	Base case: HR applied to cabozantinib curve	0.06830	0.00051	0.00000	<0.00001
	Scenario: lognormal	0.08845	0.00196	0.00006	<0.00001

^a Derived directly from the CEM, and therefore including the impact of any bounds to avoid logical inconsistencies. Shaded highlighting indicates a survival rate of less than 0.01.

Abbreviations: epNET: extra-pancreatic neuroendocrine tumour; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour.

3.3.4 Overall survival

As outlined in Section 3.2.2, the proportion of patients in each health state at the beginning of each 4-week cycle was determined directly from cumulative survival probabilities for OS. Mortality for patients with NETs is expected to be higher than the mortality of the general population when matched for age and gender. Therefore, in each model cycle, the OS curve was capped by the general age and gender-adjusted population mortality rate (Office for National Statistics [ONS] life tables for England¹¹³) to ensure, the hazard of death for the modelled population was not lower than the hazard of death for the general population.

As outlined in NICE TSD 14, the PH assumption was investigated through inspection of Schoenfeld, log cumulative and smoothed hazard plots (presented in Appendix K for cabozantinib and BSC). These showed there was no compelling evidence of PH violation for the pNET and epNET cohorts. Thus, the PH assumption between cabozantinib and BSC for OS was therefore considered appropriate and OS for BSC was derived by applying the IPCW-adjusted HRs from the CABINET trial to the cabozantinib OS curve. Further details on the IPCW adjustment are provided below. OS extrapolations were also fitted separately for the cabozantinib and placebo arms to explore the impact of independent modelling in scenarios.

Cabozantinib

In the model, long-term estimates of OS for cabozantinib were derived through extrapolation of OS data from CABINET through the application of parametric survival functions. By the data cutoff date, 34% of patients (n=32) in the pNET cohort and 48% of patients (n=97) in the epNET cohort had died across the cabozantinib and placebo arms.² The relative maturity of the data provided a suitable basis for OS extrapolations. The selection of the most appropriate extrapolation for cabozantinib OS was informed by the recommendations of NICE DSU TSD 14.⁹⁹ Specifically, goodness-of-fit statistics were calculated and assessed to understand which

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parametric form had the best statistical fit to the KM data. Assessment of visual fit was also conducted.

The model fit statistics (AIC and BIC) for the parametric survival functions explored for the cabozantinib PFS data are presented in Table 30 and Table 31 for pNETs and epNETs, respectively. Visual assessment of the parametric survival functions to the KM data for cabozantinib was performed using the extrapolations presented in Figure 24 and Figure 25.

Table 30: Model fit statistics for OS parametric survival functions for cabozantinib (pNETs)

Function	OS			
	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	216.35	1	218.51	1
Weibull	217.10	2	221.42	2
Lognormal	217.71	5	222.02	5
Loglogistic	217.20	3	221.52	3
Gompertz	217.60	4	221.92	4
Generalised gamma	219.05	6	225.53	6

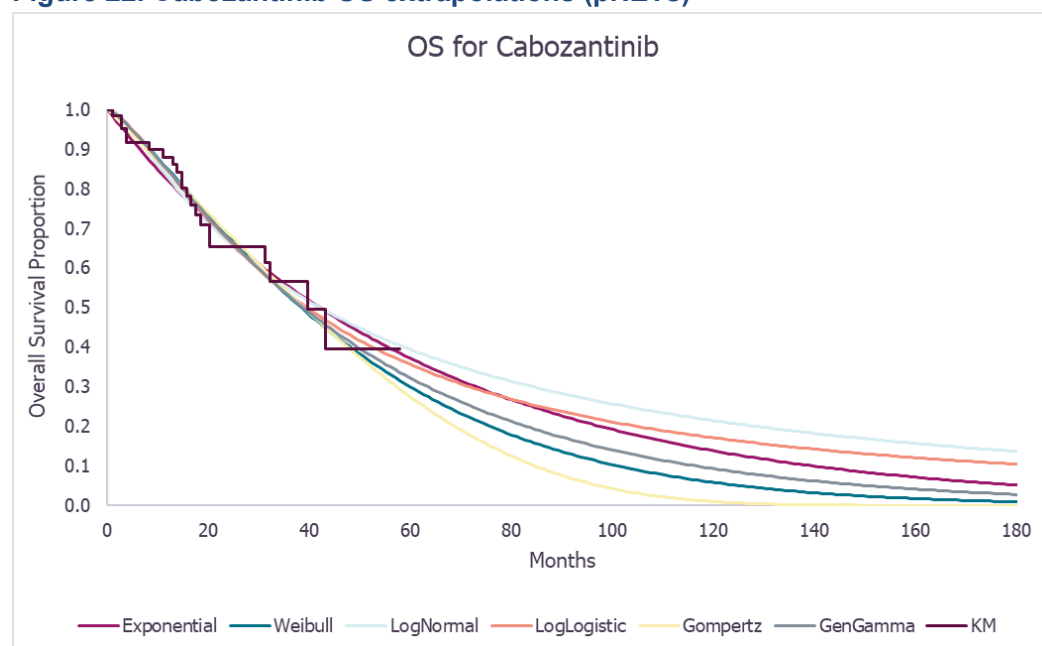
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; pNET: pancreatic neuroendocrine tumour; ITT: intent-to-treat; OS: overall survival.

Table 31: Model fit statistics for OS parametric survival functions for cabozantinib (epNETs)

Function	OS			
	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	545.83	6	548.73	4
Weibull	542.23	2	548.02	2
Lognormal	542.63	3	548.43	3
Loglogistic	542.13	1	547.92	1
Gompertz	545.06	5	550.85	5
Generalised gamma	543.30	4	551.99	6

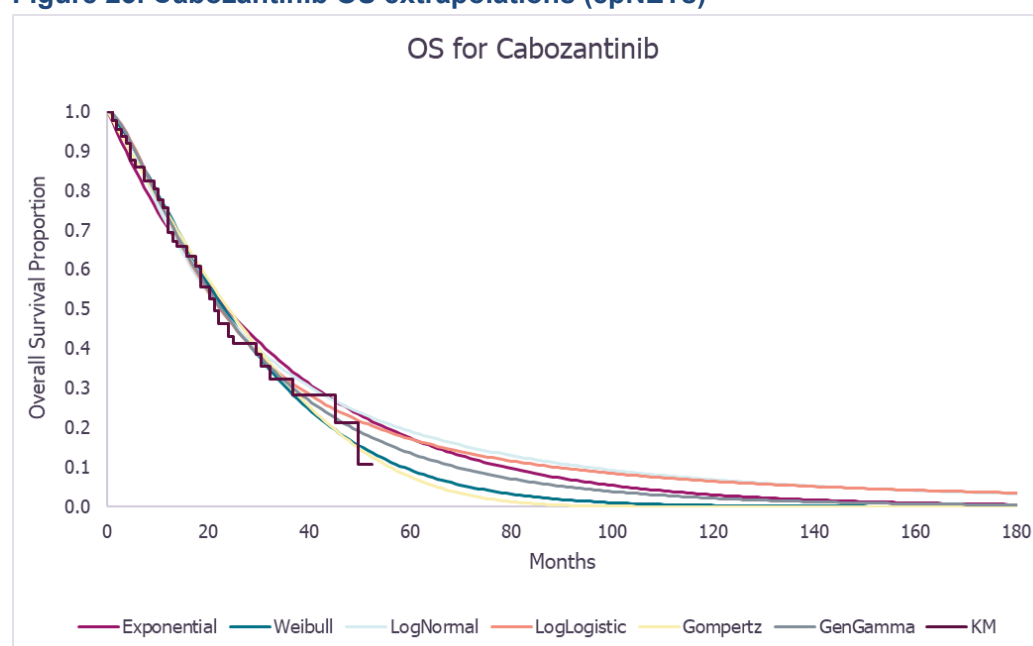
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; epNET: extra-pancreatic neuroendocrine tumour; ITT: intent-to-treat; OS: overall survival.

Figure 22. Cabozantinib OS extrapolations (pNETs)



Abbreviations: KM: Kaplan-Meier; OS: overall survival; pNET: pancreatic neuroendocrine tumour.

Figure 23. Cabozantinib OS extrapolations (epNETs)



Abbreviations: epNET: extra pancreatic neuroendocrine tumour; KM: Kaplan-Meier, OS: overall survival.

There were no substantial differences between the AIC and BIC values for the fitted OS curves, with the majority of extrapolations showing a difference of <5 points, suggesting a similar goodness of fit to the KM data for all curves. Additionally, all extrapolations appeared to provide a similar fit to the observed KM data in the assessment of visual fit. As such, the selection of the base case curves was informed by clinical expert opinion; given OS for BSC was derived by applying the IPCW-adjusted HRs from the CABINET trial to the cabozantinib OS curve, base case curve selection for cabozantinib was informed by clinical plausibility across cabozantinib and BSC, simultaneously, as discussed below.

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BSC

In CABINET, unblinding and crossover from placebo to cabozantinib were permitted after confirmation of progressed disease by central radiology review. As such, ITT analysis results may have overestimated the OS of placebo patients and underestimated the relative benefits in OS for patients receiving cabozantinib. A crossover-adjusted HR was therefore applied to the cabozantinib curve in the base case analysis rather than using direct extrapolations or applying the ITT HR.

In line with NICE DSU TSD 16 and 24, the rank-preserving structural failure time model (RPSFTM), IPCW and two-stage approaches were explored to adjust for crossover:^{114, 115}

- Unlike the RPSFTM and IPCW methods, the two-stage approach separately models post-progression survival in patients eligible to switch (i.e., patients in the placebo arm who progressed). As there were very small numbers of patients eligible for crossover, and OS events among these patients were few, it was not possible to robustly adjust for a sufficient number of prognostic factors to balance differences between patients who did and did not switch and thus it was concluded that the two-stage method was not feasible.
- The RPSFTM approach aims to adjust the survival of placebo switchers by assuming that switchers are comparable to patients randomised to cabozantinib and the effect of cabozantinib is the same across both regardless of when the treatment was initiated. However, the extent to which this key assumption of RPSFTM holds is unclear. Namely, Latimer et al. 2024 suggested that RPSFTM may perform relatively poorly compared with other crossover adjustment methods when ITT analyses provided HRs close to 1,⁹⁵ which is the case for the epNET and pNET cohorts in CABINET.
- In contrast, by accounting for prognostic factors in the estimation of weights and treatment effects, IPCW results do not only correct bias induced by crossover but also potential bias resulting from imbalances in prognostic factors between treatment arms in the epNET subgroups. Additionally, IPCW does not suffer from the same limitation as RPSFTM in being able to adequately adjust a HR close to 1. Thus, the IPCW results provide the most robust estimate of the true treatment effect of cabozantinib for OS.

Full details of the models explored and the rationale for the selection of IPCW are presented in Appendix L.

IPCW analyses can occasionally generate extreme weights, which can be mitigated by truncation. Therefore, both untruncated and truncated results (based on truncated weights) were generated. However, these results were very similar and diagnostic histograms outlined showed that extreme weights had not been generated. Therefore, the untruncated values were selected as most appropriate (Table 32) as they are based on the full results from the weight estimation model and do not include any arbitrary truncation. Full details of the methodology and results of the IPCW analysis are presented in Appendix L.

No crossover-adjusted survival extrapolations were generated. While it would be possible to generate BSC extrapolations from RPSFTM to complement the ITT extrapolations for cabozantinib, the IPCW and two-stage methods require adjusting for baseline covariates which would also affect the survival extrapolations of the cabozantinib arm. As this would lead to different cabozantinib extrapolations used across different analysis types, crossover-adjusted HRs were used instead to generate crossover-adjusted survival extrapolations for BSC based on

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the ITT extrapolations for cabozantinib. The appropriateness of applying these HRs was assessed by evaluating the proportional hazards assumption using Schoenfeld residuals and log cumulative hazard plots to ensure that the effect of treatment on the hazard rate is consistent over time (as described above).

Stratified HRs were produced as this was the preferred measure as per the CABINET CSR. The base case analysis modelled the survival of BSC using a hazard ratio (HR) applied to the cabozantinib survival curve. The cabozantinib survival curve was selected to ensure clinical plausibility of long-term survival estimates across both cabozantinib BSC arms of the model, as described above.

Table 32. OS hazard ratios (cabozantinib vs BSC)

Population	Measure	ITT Analysis (95% CI)	IPCW (95% CI)
pNET	Stratified HR	0.95 (0.45, 2.00)	0.74 (0.36, 1.52)
epNET	Stratified HR	0.86 (0.56, 1.31)	0.65 (0.39, 1.07)

Stratified HRs were based on the relevant stratification factors for each population (pNET: concomitant SSA use and prior sunitinib use; epNET: concomitant SSA use and primary site [midgut/unknown vs non-midgut GI/lung/other]).

Abbreviations: BSC: best supportive care; epNET: extra pancreatic neuroendocrine tumour; GI: gastrointestinal; HR: hazard ratio; IPCW: inverse probability coefficient weighting; ITT: intention-to-treat; NET: neuroendocrine tumour; OS: overall survival; pNET: pancreatic neuroendocrine tumour; SSA: somatostatin analogue.

Source: Ipsen Data on File, 2024 (CABINET CSR).²

Base case assumptions for OS: cabozantinib and BSC

As outlined in Section 3.14, five independent clinician interviews were conducted to help inform the most appropriate curve selections. TSD21 notes that retrospective assessment of the plausibility of extrapolations is inherently subjective and as a result may be prone to personal bias.¹¹⁶ As such, clinicians were asked to provide predictions of survival, which were subsequently used to inform parametric curve selection. Clinicians were asked to provide a most plausible estimate, as well as upper and lower limits, of overall survival (life expectancy) for cabozantinib and BSC at 5-, 10- and 15-years post treatment initiation. The baseline characteristics of patients included in the CABINET trial, and available landmark OS data were provided as context to inform predictions. Predictions across clinicians were aggregated through simple averages (i.e. assuming equal weight for each prediction). The predicted survival associated with each parametric extrapolation was compared against the average clinician estimates, as outlined in Table 33 and Table 34.

Given the base case of the model applied a crossover-adjusted HR to the cabozantinib curve for BSC, the most appropriate extrapolation for both cabozantinib was selected considering clinical plausibility across cabozantinib and BSC simultaneously. Consideration of the clinician estimates alongside the internal validity of the curves, as outlined above, was also considered.

Clinical expert feedback suggested that long term survival following treatment with cabozantinib was possible for a proportion of patients. It was estimated that 19.2% and 10.8% of pNETs patients would survive to 10 and 15 years after cabozantinib treatment versus 6.0% and 2.0% after BSC, respectively. This is broadly aligned with RWE for patients with NETs; acknowledging the differences in study populations described above, in Fröss-Baron 2021, 20% of patients with advanced pNETs that were heavily pre-treated with chemotherapy and undergoing treatment with ¹⁷⁷Lu-dotatate survived beyond 12 years, suggesting that long-term survival in heavily pre-treated patients is realistic.¹¹⁰ Clinical expert feedback suggested that a smaller proportion of

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epNETs patients would achieve long term survival, estimating 10.5% and 3.5% survival at 10 and 15 years after cabozantinib treatment versus 3.8% and 1.5% after BSC, respectively. This reflects the poorer prognosis for this patient population.

For pNETs, the exponential curve was selected as most appropriate for the base case given that the predicted survival was in line with all clinicians' estimates for BSC and all except the 15-year survival estimate for the cabozantinib curve. Survival predicted by the exponential curve falls below the clinicians' lowest plausible estimate at 15 years for cabozantinib, thereby representing a conservative selection. This curve was also associated with the best statistical fit across AIC and BIC, a suitable hazard profile and acceptable visual fit to the KM curve. The loglogistic model was explored in a scenario, given that the predicted survival was in line with all clinicians' estimates for cabozantinib and all except the 15-year survival estimate for the BSC curve. This curve was also associated with very similar statistical fit (ranked third for AIC and BIC), a suitable hazard profile and acceptable fit to the KM curve.

The loglogistic function was selected as most appropriate given the predicted survival was in line with all clinicians' estimates for cabozantinib and all except the 10-year survival estimate for the BSC curve. The loglogistic model was also associated with the best statistical fit across AIC and BIC, a suitable hazard profile and an acceptable visual fit to the KM curve. The lognormal model was explored in a scenario, since it was the next best aligned with the clinician estimates, had very similar statistical fit (ranked third for AIC and BIC), a suitable hazard profile and an acceptable visual fit to the KM curve.

The selected extrapolations for the base case are displayed in Table 40.

Table 33: Clinician and parametric survival landmark estimates for OS for cabozantinib and BSC (pNETs)

Category	Curve	OS %		
		5	10	15
Cabozantinib				
Average clinician estimates	Lower plausible limit	24.1%	13.4%	6.8%
	Most likely	36.0%	19.2%	10.8%
	Upper plausible limit	44.0%	23.6%	15.0%
Extrapolations	Exponential	37.3%	13.9%	5.1%
	Weibull	30.1%	5.9%	0.9%
	Log-logistic	35.6%	17.2%	10.4%
	Lognormal	39.5%	21.5%	13.6%
	Generalised gamma	32.3%	9.3%	2.7%
	Gompertz	27.6%	1.0%	0.0%
BSC				
Average clinician estimates	Lower plausible limit	11.0%	2.8%	0.5%
	Most likely	20.0%	6.0%	2.0%
	Upper plausible limit	27.8%	9.8%	2.8%
Cabozantinib curve + HRs	Exponential	26.2%	6.9%	1.8%
	Weibull	19.6%	2.1%	0.2%
	Log-logistic	24.6%	9.1%	4.6%

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	Lognormal	28.3%	12.4%	6.7%
	Generalised gamma	21.6%	4.0%	0.8%
	Gompertz	17.4%	0.2%	0.0%

Light red shading indicates that the predicted survival of the selected curve falls below the lower plausible limit of the clinician's estimate of overall survival. Light green shading indicates that the curves predict survival that exceeds the clinician's upper estimate of overall survival.

Abbreviations: BSC: best supportive care; HR: hazard ratio; NET: neuroendocrine tumour; OS: overall survival; pNET: pancreatic neuroendocrine tumour.

Table 34: Clinician and parametric survival landmark estimates for OS for cabozantinib and BSC (epNETs)

Category	Curve	OS %		
		5	10	15
Cabozantinib				
Average clinician estimates	Lower plausible limit	12.3%	6.0%	1.0%
	Most likely	21.1%	10.5%	3.5%
	Upper plausible limit	24.0%	13.8%	4.7%
Extrapolations	Exponential	17.4%	3.0%	0.5%
	Weibull	9.4%	0.3%	0.0%
	Loglogistic	17.2%	6.4%	3.5%
	Lognormal	19.2%	6.8%	3.2%
	Generalised gamma	13.6%	2.1%	0.4%
	Gompertz	7.6%	0.0%	0.0%
BSC				
Average clinician estimates	Lower plausible limit	5.8%	2.0%	0.5%
	Most likely	10.8%	3.8%	1.5%
	Upper plausible limit	15.5%	6.8%	2.3%
Cabozantinib curve + HRs	Exponential	6.7%	0.4%	0.0%
	Weibull	2.6%	0.0%	0.0%
	Loglogistic	6.6%	1.4%	0.5%
	Lognormal	7.8%	1.6%	0.5%
	Generalised gamma	4.6%	0.3%	0.0%
	Gompertz	1.9%	0.0%	0.0%

Light red shading indicates that the predicted survival of the selected curve falls below the lower plausible limit of the clinician's estimate of overall survival. None of the curves predicted survival that exceeds the clinician's upper estimate of overall survival.

Abbreviations: BSC: best supportive care; epNET: extrapancreatic neuroendocrine tumour; HR: hazard ratio; NET: neuroendocrine tumour; OS: overall survival.

3.3.5 Time to treatment discontinuation

In the base case analysis, time on treatment was informed by time to treatment discontinuation (TTD) data from the respective arms of CABINET.

Initially, in line with NICE TSD 14, the PH assumption was assessed. Schoenfeld residual, log cumulative hazard and smoothed hazards plots are presented in Appendix K. Overall, the plots show limited evidence of violation of the proportional hazards assumption for the pNET cohort. The p-value of the Schoenfeld test was 0.121, suggesting that the evidence was not strong

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enough to reject the null hypothesis of proportional hazards. There was no compelling evidence of PH violation for epNETs. The PH assumption between cabozantinib and BSC for TTD was therefore considered appropriate; for consistency with approach to PFS ad OS (see Section 3.3.3 and 3.3.4), TTD for BSC was derived by applying the HR from the CABINET trial to the cabozantinib TTD curve. ITT HRs for TTD were calculated using stratified and unstratified Cox models, retaining the original CABINET strata. TTD extrapolations were also fitted separately for the cabozantinib and placebo arms to explore the impact of independent modelling in scenarios. All TTD curves were bounded by PFS given clinician feedback suggested that treatment would not occur beyond progression.⁷⁹

Cabozantinib

To inform long-term estimates of TTD in the model for cabozantinib, it was necessary to extrapolate TTD data through the application of parametric survival functions. The majority of patients (77% in pNETs and 83% in epNETs) had discontinued treatment by the most recent data cut-off (August 2023).² The relative maturity of the data provided a suitable basis for TTD extrapolations. The selection of the most appropriate extrapolation for cabozantinib TTD was informed by the recommendations of NICE DSU TSD 14.⁹⁹ Specifically, goodness-of-fit statistics were calculated and assessed to understand which parametric form had the best statistical fit to the KM data. Assessment of visual fit was also conducted.

The model fit statistics (AIC and BIC) for the parametric survival functions explored for the cabozantinib TTD data are presented in Table 35 and Table 36 for pNETs and epNETs, respectively. A visual assessment of the survival functions to the KM data for cabozantinib was performed using the extrapolations presented in Figure 24 and Figure 25.

Table 35: Model fit statistics for TTD parametric survival functions for cabozantinib (pNETs)

Function	TTD			
	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	343.86	1	346.00	1
Weibull	345.81	2	350.10	2
Lognormal	349.65	6	353.94	5
Loglogistic	347.33	4	351.62	4
Gompertz	345.82	3	350.11	3
Generalised gamma	347.58	5	354.01	6

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; pNET: pancreatic neuroendocrine tumour; ITT: intent-to-treat; PFS: progression-free survival; TTD: time to treatment discontinuation.

Table 36: Model fit statistics for TTD parametric survival functions for cabozantinib (epNETs)

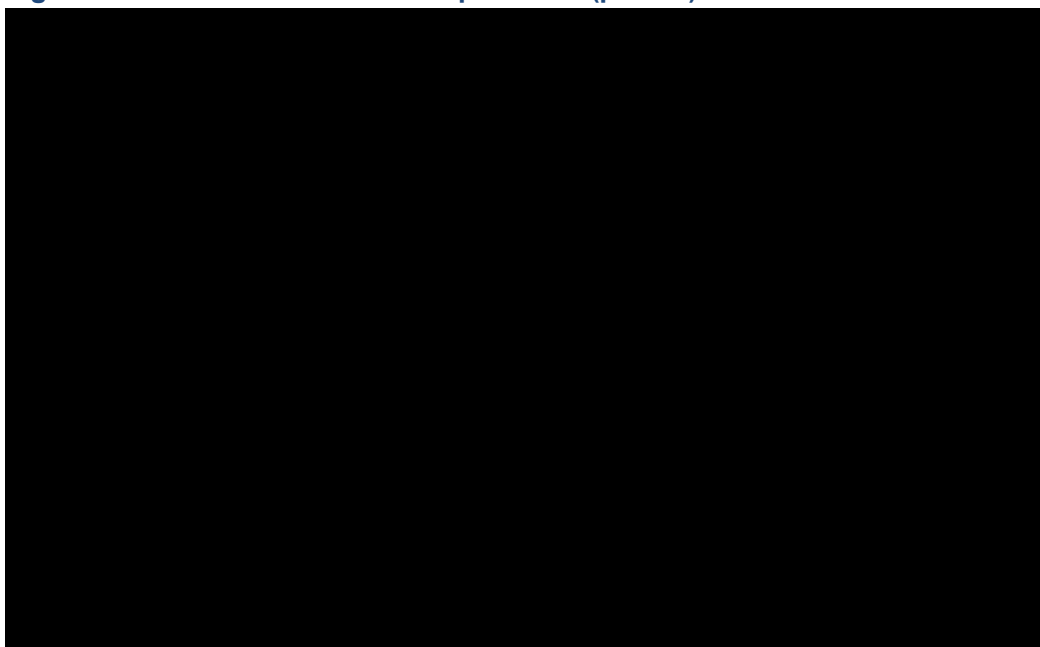
Function	TTD			
	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	689.89	1	692.78	1
Weibull	691.21	3	696.97	3
Lognormal	704.09	6	709.85	6
Loglogistic	703.96	5	709.73	5

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Gompertz	690.30	2	696.07	2
Generalised gamma	692.98	4	701.63	4

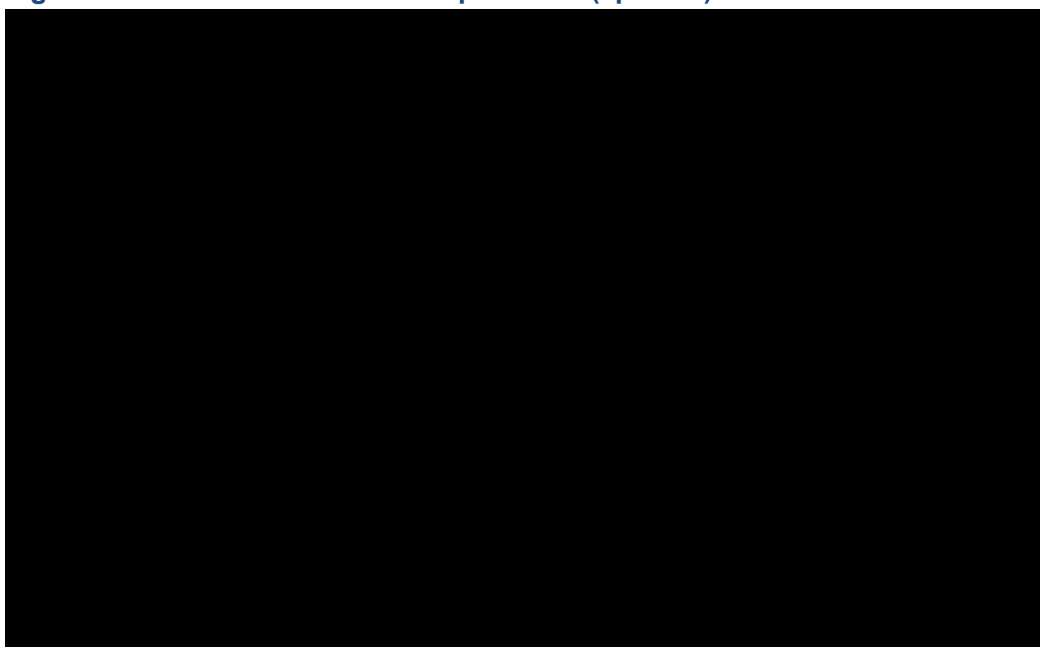
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; epNET: extra-pancreatic neuroendocrine tumour; ITT: intent-to-treat; PFS: progression-free survival; TTD: time to treatment discontinuation.

Figure 24. Cabozantinib TTD extrapolations (pNETs)



Abbreviations: KM: Kaplan-Meier; pNET: pancreatic neuroendocrine tumour; TTD: time to treatment discontinuation.

Figure 25. Cabozantinib TTD extrapolations (epNETs)



Abbreviations: epNET: extra pancreatic neuroendocrine tumour; KM: Kaplan-Meier; TTD: time to treatment discontinuation.

The differences between AIC and BIC values for the fitted TTD curves was not substantial, suggesting a similar goodness of fit to the KM data for all curves (difference in points <5 between Company evidence submission template for cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment

all curves aside from the generalised gamma curve in pNETs and the lognormal and loglogistic curves in epNETs). This was also reflected in the visual assessment of the fit of functions to the observed KM data, which all aside from the loglogistic, appeared to provide a similar fit and were provide plausible long-term TTD rates.

The exponential curve was selected as most appropriate, as presented in Table 40, for the base case in both populations as it had the best statistical fit, a suitable hazard profile and acceptable fit to the KM curve in all cases.

The Weibull and Gompertz functions were explored in scenario analyses to extrapolate cabozantinib TTD data in pNETs and epNETs, respectively. These represented the most conservative estimates of TTD, whilst providing reasonable statistical and visual fit to the KM data and hazard profile.

Table 37: Extrapolated landmark TTD rates for base case and scenarios (cabozantinib)

Population	Distribution	Extrapolated TTD rate at			
		Month 12	Month 36	Month 72	Month 120
pNET	Base case: Exponential	██████	██████	██████	██████
	Scenario: Weibull	██████	██████	██████	██████
epNET	Base case: Exponential	██████	██████	██████	██████
	Scenario: Gompertz	██████	██████	██████	██████

Derived directly from the CEM, and therefore including the impact of any bounds to avoid logical inconsistencies. Shaded highlighting indicates a survival rate of less than 0.01.

Abbreviations: epNET: extra-pancreatic neuroendocrine tumour; pNET: pancreatic neuroendocrine tumour; TTD: time to treatment discontinuation.

BSC

To align with the approach with PFS and OS (see Section 3.3.3 and 3.3.4), BSC TTD was modelled in the base case using HRs (based on the placebo arm of CABINET), applied to the cabozantinib curves (exponential in both populations). The HRs applied are outlined in Table 38. The appropriateness of these HRs was assessed by evaluating the proportional hazards assumption using Schoenfeld residuals and log cumulative hazard plots to ensure that the effect of treatment on the hazard rate is consistent over time.

Table 38: TTD HRs (95% CI) for cabozantinib versus BSC

Population	Measure	ITT Analysis
pNET	Stratified HR (95% CI) ^a	██████████
epNET	Stratified HR (95% CI) ^b	██████████

^a Stratification factors per OPEN for pNET: concomitant SSA use and prior sunitinib use; ^b Stratification factors per OPEN for epNET: concomitant SSA use and primary site (midgut/unknown vs non-midgut GI/lung/other).

Abbreviations: BSC: best supportive care; epNET: extra pancreatic neuroendocrine tumour; HR: hazard ratio; ITT: intent-to-treat; pNET: pancreatic neuroendocrine tumour; TTD: time to treatment discontinuation.

TTD extrapolations were also fitted separately for the cabozantinib and placebo arms to explore the impact of independent modelling in scenarios. The Weibull and loglogistic functions were explored to directly extrapolate BSC TTD data in pNETs and epNETs, respectively, in these scenarios, on the basis that they were associated with good statistical fit, a suitable hazard profile, acceptable fit to the KM curve and a plausible long-term TTD rate (as shown in Table 39). Full details of survival extrapolations explored are presented in Appendix K.

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Table 39: Extrapolated landmark TTD rates for base case and scenarios (BSC)

Population	Distribution	Extrapolated TTD rate at			
		Month 12	Month 36	Month 72	Month 120
pNET	Base case: HR applied to cabozantinib curve				
	Scenario: Weibull				
epNET	Base case: HR applied to cabozantinib curve				
	Scenario: Loglogistic				

Derived directly from the CEM, and therefore including the impact of any bounds to avoid logical inconsistencies. Shaded highlighting indicates a survival rate of less than 0.01.

Abbreviations: epNET: extra-pancreatic neuroendocrine tumour; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour.

3.3.6 Summary of curve selections

The summary of extrapolation curves for cabozantinib and BSC PFS, OS and TTD data chosen for the base case analysis is provided below in Table 40.

Table 40: Summary of extrapolation curve choices in the base case analysis

Clinical endpoint	Cabozantinib		BSC		Section
	pNETs	epNETs	pNETs	epNETs	
PFS	Lognormal	Lognormal	HR applied to cabozantinib curve	HR applied to cabozantinib curve	Section 3.3.3
OS	Exponential	Loglogistic	IPCW-adjusted HR applied to cabozantinib curve	IPCW-adjusted HR applied to cabozantinib curve	Section 3.3.4
TTD	Exponential	Exponential	HR applied to cabozantinib curve	HR applied to cabozantinib curve	Section 3.3.5

Abbreviations: epNET: extra-pancreatic neuroendocrine tumour; IPCW: inverse probability of censoring weights; OS: overall survival; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour; TTD: time to treatment discontinuation.

3.3.7 Adverse events

In the base case, all treatment-related AEs (TRAEs) that occurred at Grade 3 or above in in >5% of patients in either the cabozantinib or the placebo arm in the CABINET trial were applied in the model for cabozantinib and BSC, respectively, as outlined in Table 41 below. The approach of limiting to TRAEs at Grade 3+ that occur above 5% is a common approach in health economic models and aims to capture only those AEs that are likely to occur with sufficient frequency and severity that they have an impact on costs and/or quality of life. The per cycle probability of TRAEs was calculated based on the overall frequency of adverse event and mean trial follow-up as outlined in Table 41 below. Given AEs were treatment-related, these were applied based on state occupancy of ToT.

Table 41: Summary of TRAEs and their respective frequencies included in the economic model in the base case analysis

Adverse Event	pNETs		epNETs	
	Cabozantinib (n=63)	BSC (n=83)	Cabozantinib (n=63)	BSC
	% patients	% patients	% patients	% patients
Mean follow-up (months)	25.7	27.6	24.4	24.21
Fatigue	11.1%	3.2%	12.9%	7.5%
Diarrhoea	6.4%	0.0%	10.6%	4.5%
Hypertension	19.1%	9.7%	20.5%	3.0%
Stomatitis	6.4%	0.0%	0.0%	0.0%
PPE syndrome	9.5%	0.0%	0.0%	0.0%
Nausea	8.0%	3.2%	0.0%	0.0%
Vomiting	6.4%	0.0%	0.0%	0.0%
Small intestinal obstruction	0.0%	6.5%	0.0%	0.0%
Embolism	6.4%	0.0%	0.0%	0.0%

Abbreviations: epNET: extra-pancreatic neuroendocrine tumour; pNET: pancreatic neuroendocrine tumour; TRAE: treatment-related adverse event.

Some adverse events were grouped, after removing any events that did not meet the 5% cut off, due to their similar effect and associated cost, as displayed in Table 42.

Table 42: Summary of TRAEs groupings included in the economic model in the base case analysis

TRAE Group	TRAEs included
Pain	Pain, abdominal pain, flank pain
Fatigue	Fatigue, asthenia, anaemia
Blood result abnormality	Lymphocyte count decreased, platelet count decreased, blood alkaline phosphatase increased, blood creatinine increased, neutropenia, thrombocytopenia, lymphopenia, leukopenia, platelet count decreased
Embolism	Embolism, pulmonary embolism

Abbreviations: TRAE: treatment-related adverse event.

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life data from clinical trials

In the CABINET trial, patients completed the European Organisation for Research and Treatment Cancer (EORTC) quality of life questionnaire (QLQ-C30), EORTC quality of life questionnaire with gastrointestinal neuroendocrine tumours (QLQ-GI.NET21) and the Patient Global Impression of Change (PGIC) at baseline and every 12 weeks until disease progression or the start of a new anticancer therapy.⁸⁸

Given that EuroQol-5 dimension (EQ-5D) was not collected in the CABINET trial, EORTC QLQ-C30 data was mapped onto EQ-5D utility index scores to generate utility values for the economic model in line with the NICE manual for health economic evaluation.^{117, 118}

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3.4.2 Mapping

The domains of the EORTC QLQ-C30 were mapped onto EQ-5D using a published mapping algorithm, from which utility values were estimated.¹¹⁸ The same approach was taken in TA539.³
¹¹⁸ Values for pNETs and epNETs were included and are outlined in Section 3.4.5.

3.4.3 Health-related quality-of-life studies

An SLR was conducted in May 2024 and updated in January 2025 to identify all relevant literature published on HRQoL outcomes in patients with pNETs or epNETs who have experienced treatment failure or disease progression following prior treatment.

The SLR identified eight relevant studies, with seven reporting HRQoL data and only one reporting health state utility values (Mujica-Mota et al. [2018]).^{101,119-125} Mujica-Mota et al. (2018) was a publication of the external assessment group (EAG) report for the prior NICE appraisals (TA449 and TA539) and reported utility values using the sources outlined in Table 22.¹⁰¹ These values were not included in the economic model as utility values were available directly from the CABINET trial for the PF health state. For the PD health state, given the utility values derived from CABINET data were deemed implausible due to being higher than in PF, clinician feedback suggested that applying a relative decrement using Swinburn *et al.* (2012) provided the most plausible utility values.³⁵ However, the model did also include scenarios using the ERASMUS values for the PD health state, as were included in Mujica-Mota et al. (2018).^{101, 107}

Full details of the HRQoL SLR search strategy, study selection process and results are reported in Appendix F.

3.4.4 Adverse reactions

To capture the negative effects of AEs (specifically TRAEs) on HRQoL, a QALY decrement was applied additively per cycle for the duration that patients spend on treatment. The overall QALY decrement is calculated based on the AE incidence per model cycle as outlined in Table 41, for any TRAE at Grade ≥3 occurring in 5% of patients in either arm of the CABINET trial.

The utility decrements were derived from Swinburn et al. (2012), as this study investigated advanced NETs specifically, and a combination of those from previously published technology appraisals in oncology and other oncology indications such as non-small-cell lung (NSCLC) and pancreatic cancer (TA898, TA476, TA911).^{35, 126-128} It should be noted that Swinburn et al. (2012) was not a primary publication identified or included in the utility studies SLR and was instead included in prior economic evaluations identified in the SLR focussing on economic evaluations.³⁵

For each disutility, a utility decrement was calculated based on the duration the disutility is applicable for. These were also sourced from appraisal in other oncology indications including NSCLC and pancreatic cancer (TA911, TA476 and TA789).¹²⁸⁻¹³⁰ Where values were not identified by targeted searches, the durations were calculated as an average of all other AE durations as outlined in.

The disutility per TRAE and the disutility duration is outlined in Table 43. The inclusion of AE disutilities in the base case is based on clinician feedback which suggested that the main

difference in quality of life between patients (in the same health state) would be reflected by the impact of AEs.⁷⁹

Table 43: Treatment-related adverse event disutility decrements applied in the cost-effectiveness model

Treatment-related adverse event	Disutility	Duration (days)	Disutility source	Duration source
Fatigue	-0.073	23.80	NICE TA911 (derived from Nafees et al. (2008)) ¹³¹	NICE TA911 ¹³²
Diarrhoea	-0.171	5.50	Swinburn et al. (2012) ³⁵	NICE TA911 ¹³²
Hypertension	-0.085	15.00	NICE TA911 ¹³²	NICE TA911 ¹³²
Stomatitis	-0.214	18.12	Swinburn et al. (2012) ³⁵	Average of all other TRAE durations
PPE syndrome	-0.188	18.12	Swinburn et al. (2012) ³⁵	Average of all other TRAE durations
Nausea	-0.061	10.50	Swinburn et al. (2012) ³⁵	NICE TA789 ¹³⁰
Vomiting	-0.061	2.00	Swinburn et al. (2012) ³⁵	NICE TA789 ¹³⁰
Small intestinal obstruction	-0.255	18.12	NICE TA1011 ¹³³	Average of all other TRAE durations
Embolism	-0.370	51.90	NICE TA476 ¹²⁸	NICE TA476 ¹²⁸

Abbreviations: NICE: National Institute for Health and Care Excellence; PPE: plantar erythrodysaesthesia; TA: technology appraisal; TRAE: treatment-related adverse event.

3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

As outlined in Section 3.4.1, HRQoL data was collected in CABINET from patients using the EORTC QLQ-C30, QLQ-GI.NET21 and PGIC questionnaires. These were collected at baseline and every 12 weeks until disease progression or the start of a new anticancer treatment. In some cases where data were collected at timepoints outside of 12-week intervals; an algorithm was used where windows were defined around each 12-weekly timepoint to assess each response to a planned timepoint. Crossover patients were also not permitted to be included in the QoL sub study. The numbers of patients included in the QoL sub study are outlined in Table 44.

Table 44: Numbers of patients who were included in the CABINET QoL sub study

Population	pNETs		epNETs	
Treatment arm	Cabozantinib	Placebo	Cabozantinib	Placebo
EORTC	55	28	113	58
PGIC	49	19	88	43

Available QoL data do not necessarily imply availability at baseline, but rather at least one response during the course of the CABINET trial. Two patients included in the HRQoL sub study were randomised after the 24th August 2023 data cut-off and are not included in the summary of available data above.

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; epNET, extra-pancreatic neuroendocrine tumours; GI: gastrointestinal; NET: neuroendocrine tumours; PGIC, Patient Global Impression of Change; pNET, pancreatic neuroendocrine tumours; QLQ: quality of life questionnaire.

Utility values were applied to the PF and PD health states to estimate HRQoL. As described in 3.4.2, the individual patient data (IPD) from EORTC QLQ-C30 data collected in CABINET were mapped to EQ-5D using the response mapping algorithm from Longworth et al. (2014) to estimate utility values for the PF and PD health states.¹¹⁸ Descriptive statistics for the utility values are outlined in Table 45.

Table 45: Descriptive statistics for EQ-5D health state utility values derived from CABINET

Health state	Statistic	pNETs		epNETs	
		Baseline	Post-baseline	Baseline	Post-baseline
PF	Number of observations	■	■	■	■
	Number of participants	■	■	■	■
	Mean utility (SD)	■■■■■	■■■■■	■■■■■	■■■■■
PD	Number of observations	NA	■	NA	■
	Number of participants		■		■
	Mean utility (SD)		■■■■■		■■■■■

Abbreviations: epNET, extra-pancreatic neuroendocrine tumours; pNET, pancreatic neuroendocrine tumours; PD, progressive disease; PF, progression-free; SD, standard deviation.

The primary analysis included a regression model to derive the utility values for the health states in the CEM whilst adjusting for baseline utility and was stratified by cohort. Secondary analyses investigated the impact of adjusting for relevant covariates, including prognostic factors and treatment, in the model. Exploratory analyses suggested that there were convergence issues when including both a random slope for time and a random intercept by individual; as such, models fitted only included a random intercept by individual. Given HRQoL was collected until disease progression or the start of new anticancer therapy, there were limited data available in the PD health state. Whilst models were fitted for both health states, limited data availability meant it was not feasible to robustly assess the PD health state. The estimated utility across the PF and PD health states within the full cohorts were similar with differences of less than ■■■ (Table 46); ■■■ compared with ■■■ and ■■■ compared with ■■■ for pNETs and epNETs respectively).

Table 46: Summary of utility values: primary regression analysis

Model	Health State	Utility Value	SE
pNET ^a	PF	■■■	■■■
	PD	■■■	■■■
epNET ^b	PF	■■■	■■■
	PD	■■■	■■■

^a Includes patients with non-pancreas tumour site that were initially misclassified to the pNET cohort; ^b Includes patients with pancreas primary tumour site that were initially misclassified to the epNET cohort, and are in the unknown/other subgroup..

Abbreviations: CI: confidence interval; epNET: extrapancreatic neuroendocrine tumours; pNET: pancreatic neuroendocrine tumours; PD: progressive disease; PF: progression-free; SE: standard error.

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Values derived from CABINET for the PD health state were based on very limited numbers of observations. These were also deemed clinically implausible given the utility value was higher in the PD state for pNETs than in PF. Therefore, alternative sources of utility were required for PD and explored in scenarios, as outlined in Table 47.

This included Swinburn et al. (2012) which reported on a time trade-off (TTO) approach in which health state vignettes in NETs were developed based on clinician and patient interviews using EQ-5D questionnaires.³⁵ The company submission in the prior appraisal, TA449, also used these values to define the PF and PD utility values.⁴

The PD utility values derived from HRQoL data collected in ERASMUS, a single-arm study of PRRT in pNET and GI NET patients, was also considered.¹⁰⁷ Using utility values from ERASMUS was also the approach adopted in a prior appraisal (TA539) for the progressed disease state only.^{3, 107} Other values were included in the prior appraisals (TA449 and TA539) that were derived from IPD in the A618111 and RADIANT-4 trials which investigated sunitinib in pNETs and everolimus in lung and GI NETs, respectively.^{3, 4} However, the values from A618111 were redacted in the submission so could not be incorporated into the model. Although utility values derived from RADIANT-4 were reported, these data are derived specifically from a population with non-functional epNETs.

Clinician feedback suggested that using a relative decrement applied to the CABINET PF data would be more reflective of the patient population, and provided more clinically plausible utility estimates than using values directly from either source.¹² Therefore, the base case applied a relative decrement to the CABINET PF data, using values derived from Swinburn *et al.* (2012), which was considered to reflect a plausible decrement in utility for progression, particularly in this highly pre-treated patient population.³⁵ Scenarios explored the impact of including direct values as well as the decrement from ERASMUS, as outlined in Table 47. Treatment specific utility values were not explored given clinician feedback highlighted that the main difference in quality of life beyond progression status would be captured by the impact of AEs.⁷⁹

Table 47: Summary of utility values for pNETs and epNETs in PF and PD

Input	pNET utility input	epNET utility input	Source
Health states utility (base case: CABINET + Swinburn et al. [2012] relative decrement)			
Pre-progression	■	■	CABINET (Ipsen. Data on File)
Post-progression	■	■	Swinburn <i>et al.</i> (2012) ³⁵
Health states utility (scenario analysis: CABINET trial + Swinburn et al. (2012) vignettes)			
Pre-progression	■	■	CABINET (Ipsen. Data on File)
Post-progression	0.612	0.612	Swinburn <i>et al.</i> (2012) ³⁵
Health states utility (scenario analysis: CABINET trial + ERASMUS relative decrement)			
Pre-progression	■	■	CABINET (Ipsen. Data on File)
Post-progression	■	■	ERASMUS ¹⁰⁷
Health states utility (scenario analysis: CABINET trial + ERASMUS)			
Pre-progression	■	■	CABINET (Ipsen. Data on File)
Post-progression	0.790	0.740	ERASMUS ¹⁰⁷

Abbreviations: epNET: extra-pancreatic neuroendocrine tumour; pNET: pancreatic neuroendocrine tumour; TRAE: treatment-related adverse event; SE: standard error.

Source: Swinburn *et al.* (2012)³⁵; ERASMUS.¹⁰⁷

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Age adjustment of utility values

In the base case, general population utilities from the Health Survey England (HSE) 2014, as recommended by the NICE DSU, were applied multiplicatively to the health state utility values.¹³⁴ This accounted for the changing health of the patient population as patients age in the model, based on a gender-adjusted weighted average general population utility.

3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted in May 2024 and updated in January 2025 to identify all relevant literature published on cost and HCRU in adult patients with pNETs or epNETs who have experienced treatment failure/disease progression following prior treatment. The full methods and results of the HCRU SLR are reported in Appendix G.

Of the eight studies included in the SLR, two reported results for the overall population in addition to stratification for pNETs and epNETs.^{37, 135} Of these, Casciano et al. (2013) reported resource use in multiple countries, including the UK, and was therefore deemed more appropriate for consideration to inform inputs in the model than Jalbert et al. (2020) that was primarily based in the US.^{37, 135}

The economic model included drug acquisition, drug administration, CCT, subsequent treatment, AE, resource use and end of life costs.

3.5.1 Intervention and comparators' costs and resource use

Cabozantinib acquisition and administration costs

Treatment costs for cabozantinib and BSC were modelled based on time on treatment (ToT) which was informed by TTD in the base case (Section 3.3.5), and based on the recommended dosing schedules outlined in Section 3.2.3. As discussed in Section 3.2.3, BSC was assumed to consist of only SSAs as CCT and no systemic anticancer therapy. Concomitant SSAs were also modelled alongside treatment cabozantinib (i.e. SSAs are modelled as a backbone therapy).

The list price for cabozantinib is the same as reported by the British National Formulary (BNF) but will be provided at a simple PAS discount of [REDACTED] on the list price of £5,143.00 per pack. Drug acquisition costs for cabozantinib included in the cost-effectiveness analysis are presented in Table 48.

Table 48: Drug acquisition unit costs and dosing schedules for cabozantinib

Treatment	Form	Strength/unit	Pack size	Dosing schedule	Cost per pack (list)	Cost per pack (PAS)	Source
Cabozantinib	Tablet	60 mg	30	60 mg per day in a 28-day cycle (continuous)	£5,143.00	[REDACTED]	Cabozantinib 60 mg tablets- Ipsen Ltd, BNF 2025 ³⁰

Abbreviations: BNF: British National Formulary; BSC: best supportive care; mg: milligram; NR: not reported; PAS: patient access scheme.

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Source: BNF, 2025. Cabozantinib.

Given the flat-pricing of cabozantinib, dose holds were deemed more appropriate to apply within the model to ensure acquisition costs were reflective of how treatments were received by patients in practice rather than the recommended dosing intensity (RDI). This had no impact on administration costs. For cabozantinib, this was calculated using the mean total dose hold length and the mean dose exposure, defined as the time between the first and last dose, for all patients who had a dose hold due to any reason from CABINET.² The mean dose exposure was selected over the mean safety follow-up which includes post-progression periods when patients were not treated, thus underestimating the dose hold percentage. The mean dose exposure aligns more closely with TTD and therefore provides a more accurate estimation of dose holds in this patient population. The dose hold setting was applied in the base case for cabozantinib. Dose holds were not applied for SSAs across the cabozantinib or BSC arms of the model. A summary of dose holds for pNETs and epNETs included in the model is outlined in Table 49. The total costs per cycle for cabozantinib are summarised in Table 50.

Table 49: Dose holds for cabozantinib and BSC

Treatment	pNETs	epNETs	Source
Cabozantinib	████	████	Ipsen Data on File; calculated from CABINET IPD

Abbreviations: BSC: best supportive care; epNETs: extra-pancreatic neuroendocrine tumours; IPD: individual patient data; pNETs: pancreatic neuroendocrine tumours.

Source: Ipsen Data on File; calculated from CABINET IPD

Table 50: Treatment acquisition cost per cycle for cabozantinib

Treatment	Cycle length, days	Cost per treatment cycle (pNETs)	Cost per treatment cycle (epNETs)	Source
Cabozantinib 60 mg daily (PAS price)	4 weeks	████	████	Ipsen. Data on File.

Abbreviations: epNET: extra-pancreatic neuroendocrine tumour; mg: milligram; PAS: patient access scheme; pNET: pancreatic neuroendocrine tumour.

Source: Ipsen. Data on File.

Administration costs associated with cabozantinib are presented in Table 51. Cabozantinib is orally administered and so was not anticipated to incur any direct administration costs. To align with prior appraisals in this indication, a cost was applied on the assumption that pharmacist time would be required to dispense the drug, as is in line with the prior appraisals in this indication (TA539 and TA449).^{3, 4} This was calculated using 12 minutes of a band 8b advanced hospital pharmacist's time from the personal social services research unit (PSSRU).¹³⁶

Table 51: Treatment administration costs per cycle for cabozantinib

Treatment	Unit Cost	Cycle length, days	Cost per treatment cycle		Source
			pNETs	epNETs	
Cabozantinib 60 mg daily	£16.20	4 weeks	£15.12	£15.12	PSSRU, 2023. Calculated as 12 minutes of hospital pharmacist time at £81 per hour ^{3, 136}

Abbreviations: mg: milligram; PSSRU: Personal Social Services Research Unit.

Source: PSSRU, 2023.¹³⁶

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Concomitant treatments

Only concomitant SSA usage, and no systemic anticancer therapy, was permitted in the CABINET trial. Clinician feedback suggested it was appropriate to not consider any other treatments, other than SSAs, as concomitant therapy.^{12, 79} Therefore concomitant SSA is the only therapy modelled concomitantly for each treatment.

In the PF health state, the proportion receiving CCT in pNETs and epNETs was derived directly from the cabozantinib and placebo arms of CABINET, as outlined in Table 52. This formed the basis of the acquisition cost for BSC.

Table 52: Proportion of patients receiving concomitant therapy included in cost effectiveness model

Treatment	pNETs	epNETs	Source
Cabozantinib	54.7%	68.7%	CABINET CSR ²
BSC	54.8%	69.6%	

Abbreviations: epNETs: extra-pancreatic neuroendocrine tumours; pNETs: pancreatic neuroendocrine tumours.

Source: Ipsen. Data on File, 2024 (CABINET CSR; Table 14.3.2.1.a.1 and Table 14.3.1.2.b.1).²

Acquisition costs for lanreotide and octreotide were weighted based on the market shares outlined in Section 3.2.3 (■% and ■%, respectively) as well as the expected distribution of pack strengths (outlined in Table 54). Octreotide was assumed to have the same market shares as lanreotide across the three strengths. Unit costs were derived from the list prices extracted from the BNF, as the eMIT only contained the short-acting (daily) injections rather than the relevant long-acting (monthly) injections as is relevant for this population. The administration and dosing regimens of SSAs (lanreotide and octreotide) in UK clinical practice are summarised in Table 23. These, alongside the unit costs, were used to derive the per cycle cost of CCT SSA for both cabozantinib and BSC, as presented in Table 53 below.

Table 53: Treatment acquisition costs per cycle for CCT SSA

Treatment	pNETs	epNETs
Cabozantinib	■	■
BSC	■	■

Abbreviations: epNETs: extra-pancreatic neuroendocrine tumours; pNETs: pancreatic neuroendocrine tumours.

Administration costs were assumed to be equal for both SSAs and are detailed in Table 55.

Table 54: Drug acquisition unit costs and dosing schedules for CCT SSAs

Treatment	Form	Strength/unit	Pack size	Dosing schedule	Proportion included	Cost per pack (list)	Source
Lanreotide	Vial	120 mg	1	Lanreotide: 120, 90 or 60 mg every 28 days	■	£937.00	Lanreotide 120 mg/0.5 ml solution- Ipsen Ltd, BNF 2025 ⁵
		90 mg	1		■	£736.00	Lanreotide 90 mg/0.5 ml solution- Ipsen Ltd, BNF 2025 ⁵
		60 mg	1		■	£551.00	Lanreotide, 60 mg/0.5 ml solution- Ipsen Ltd, BNF 2025 ⁵
Octreotide	Vial	30 mg	1	Octreotide: 30, 20 or 10 mg every 4 weeks	■	£898.57	Olatuton- Teva UK Ltd, BNF 2025 ¹³⁷
		20 mg	1		■	£719.40	Olatuton- Teva UK Ltd, BNF 2025 ¹³⁷
		10 mg	1		■	£494.74	Olatuton- Teva UK Ltd, BNF 2025 ¹³⁷

Abbreviations: BNF: British National Formulary; BSC: best supportive care; mg: milligram; NR: not reported; PAS: patient access scheme.

Source: BNF, 2025. Cabozantinib; BNF, 2025. Lanreotide. BNF, 2025. Octreotide.

Costs for administering CCT SSAs were determined based on clinician feedback, which indicated that these treatments are primarily delivered in patients' homes.⁷⁹ Thorn et al. (2020) noted that managing conditions at home includes costs such as one hour of Band 6 community staff time and reimbursement for five miles of travel by the NHS. As of 2023, staff are reimbursed at 5p per mile.^{136, 138, 139} It was assumed that both lanreotide and octreotide incur the same administration cost. The unit and per cycle costs of administration are presented in Table 55.

Table 55: Administration costs for CCT SSAs

Treatment	Unit Cost	Cycle length, days	Cost per treatment cycle		Source
			pNETs	epNETs	
CCT SSA	£55.95	4 weeks	£30.68	£38.92	Thorn et al. 2020; PSSRU 2023, calculated as 1 hour of band 6 community-based scientific and professional staff time at £53 per hour and 5 miles reimbursed at 59p; NHS Employers. ^{136, 138, 139}

Abbreviations: BSC: best supportive care; mg: milligram; PSSRU: Personal Social Services Research Unit.
Source: PSSRU, 2023.¹³⁶

Subsequent treatments

Patients who progressed from the modelled line of therapy in the CEM could receive subsequent therapy. For simplicity, subsequent treatment costs included treatment acquisition and treatment administration only (i.e. treatment-specific monitoring and resource use, and adverse events were not included for subsequent treatments). Costs were applied as a one-off cost in the model upon disease progression and were based on the percentage of patients expected to receive subsequent treatment, the distribution of subsequent treatments expected to be received, and the duration of each subsequent treatment. The distributions and durations of subsequent treatment used within the CEM were assumed to have no meaningful impact on survival outcomes, which was based on the extrapolated CABINET trial data.

The proportion of patients receiving subsequent treatment was derived directly from CABINET data. The subsequent treatments deemed relevant for inclusion in the model for both cabozantinib and BSC were those received in at least 5% of patients in only the cabozantinib arm. Those received in the cabozantinib arm were assumed to be relevant for BSC.

Clinician feedback suggested that the distribution of subsequent treatments from CABINET was not entirely reflective of UK clinical practice, and that a more equal distribution across all treatments in both arms would be more appropriate, as well as a lower proportion of everolimus use.¹² Therefore, this approach was adopted in the base case as presented in Table 50. A scenario using the distributions reported in CABINET was explored for completeness, excluding those received in less than 5% of patients. For this scenario, the distributions were re-weighted to ensure that all those included summed to 100% (excluding SSAs, which are taken concomitantly). External beam radiation therapy was not considered a relevant subsequent treatment based on clinical feedback.¹² For BSC, subsequent treatments were also reweighted to account for the exclusion of those crossing over to open-label cabozantinib.

Subsequent treatments were assumed to include other systemic treatment options (sunitinib, everolimus, PRRT, and chemotherapy regimens). However, clinical experts highlighted that their use in later lines is considered on an individual patient basis (according to specific patient

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characteristics and prior treatment history) and cannot be considered routine practice; re-challenge with regimens used in earlier treatment lines may be attempted but is not in line with NHS guidelines.¹²

Clinician feedback indicated that concomitant SSAs would be continued indefinitely throughout both the PF and PD health states.¹² Therefore, SSAs were included as concomitant therapy alongside subsequent treatments and were applied for a duration of 26.09 weeks and in the same proportion as those in the PF health state (as shown in Table 52).³⁴ A scenario was also included which explored the use of pooled estimates of those receiving CCT SSAs alongside subsequent treatment in the CABINET trial (23.08% and 21.64% in pNETs and epNETs, respectively). This was included on the basis of clinician feedback which suggested it was reasonable to assume that the percentages are similar between treatment arms.¹²

The distribution and duration of all other subsequent treatments are detailed in Table 56.

Table 56: Distribution and duration of subsequent treatments

	pNETs		epNETs	
	Cabozantinib	BSC	Cabozantinib	BSC
Proportion of patients receiving subsequent treatment (out of those who progress)	51.02%	35.29%	40.54%	45.00%
Distribution of subsequent treatments¹²				
Sunitinib	22.50%	22.50%	N/A	N/A
Everolimus	10.00%	10.00%	10.00%	10.00%
PRRT	22.50%	22.50%	30.00%	30.00%
CAPTEM	22.50%	22.50%	30.00%	30.00%
FOLFOX	22.50%	22.50%	30.00%	30.00%

^a Concomitant SSAs (lanreotide and octreotide) are included as per the market shares outlined in Section 3.2.3.

Abbreviations: BSC: best supportive care; CAPTEM: capecitabine and temozolomide; CSR: clinical study report; FOLFOX: folinic acid, fluorouracil and oxaliplatin; NET: neuroendocrine tumour; pNET: pancreatic neuroendocrine tumour; PRRT: peptide receptor radionuclide therapy.

Source: Ipsen Data on File, 2024 (CABINET CSR);² Ipsen, Data on File (Clinician Validation Report).¹²

Acquisition and administration costs for subsequent treatment were based on the dosing schedules of subsequent treatments depicted in Table 57 and calculated using the unit costs in Table 58 and Table 59. Patients not receiving subsequent treatment were assumed to incur no further treatment costs. A commercial discount for ¹⁷⁷Lu dotatate is applicable in UK clinical practice, however given this was not available to the company, this has not been included.

Table 57: Subsequent treatment dosing schedules

Intervention	Planned dosage per treatment cycle	Duration of treatment (weeks)	Administration route	Source
Sunitinib	37.5 mg to be taken per day in a 28-day cycle (continuous)	43.48	Oral	Sunitinib Accord SmPC ¹⁴⁰ ; duration from Rinzivillo et al (2018) ¹⁴¹
Everolimus	10.0 mg to be taken per day in a 28-day cycle (continuous)	39.13	Oral	Affinitor SmPC ¹⁴² ; duration from

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				Dasari et al (2019) ¹⁴³
PRRT	4 IV infusions, 8 weeks apart ^a	32.00	IV	Lutathera SmPC ¹⁴⁴
CAPTEM	750 mg/m ² taken orally twice a day on days 1–14 (capecitabine) and 100 mg/m ² days 10–14 (temozolomide) for a treatment period of 28-days	54.79	Oral	Sahu et al. (2019); eMIT, 2024 ^{145, 146} ; duration taken from Arrivi et al, (2022) ¹⁴⁷
FOLFOX ^b	IV infusions of oxaliplatin (85 mg/m ²) and folinic acid (100 mg/m ²) day 1 followed by two IV administrations of fluorouracil for 10 minutes (400 mg/m ²) and then a 46-hr continuous infusion (2400 mg/m ²)	54.79	IV	Faure et al. (2017); eMIT, 2024 ^{146, 148} ; duration assumed the same as CAPTEM

^a The interval between infusions could be increased up to 16 weeks, increasing the treatment cycle length to 64 weeks;¹⁴⁴ ^b The BSA values outlined in Section 3.3.1 have been used to calculate the acquisition cost of FOLFOX which uses weight-based dosing.

Abbreviations: CAPTEM: capecitabine and temozolomide; FOLFOX: folinic acid, fluorouracil and oxaliplatin; NET: neuroendocrine tumour; pNET: pancreatic neuroendocrine tumour; PRRT: peptide receptor radionuclide therapy.

Table 58: Unit costs subsequent treatments

Treatment	Form	Strength/unit	Pack size	Cost per pack (list)	Source
Sunitinib	Tablet	50 mg	30	£89.07	eMIT, 2024 ¹⁴⁶
Everolimus	Tablet	10 mg	30	£283.71	eMIT, 2024 ¹⁴⁶
PRRT	Vial	7.40 GBq	1	£17,875.00	NICE, TA539 ³
CAPTEM	Tablet	500 mg (CAP) and 250 mg (TEM)	120 (CAP), 5 (TEM)	£39.87 (total)	eMIT, 2024 ¹⁴⁶
FOLFOX	Vial	350 mg (folinic acid), 5000 mg (fluorouracil), 200 mg (oxaliplatin)	10, 1 and 1 respectively	£78.55 (total)	eMIT, 2024 ¹⁴⁶

Abbreviations: CAPTEM: capecitabine and temozolomide; eMIT: electronic market information tool; FOLFOX: folinic acid, fluorouracil and oxaliplatin; IV: intravenous; NICE: National Institute for Health and Care Excellence; PRRT: peptide receptor radionuclide therapy.

Source: BNF, 2025. Cabozantinib; BNF, 2025. Lanreotide. BNF, 2025. Octreotide.

Table 59: Treatment administration costs per cycle for subsequent treatments

Treatment	Cycle length, days	Unit costs	Source
Sunitinib	28	£16.20	Aligned with TA539; PSSRU 2023; Calculated as 12 minutes of band 8b hospital pharmacist time at £81 per hour ^{3, 136}
Everolimus	28	£16.20	

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PRRT	224	£1,237.70	NHS National Schedule of Costs 2023/24, RN52Z - Delivery of Other Radionuclide Therapy ¹⁴⁹
CAPTEM	28	£16.20	Aligned with TA539; PSSRU 2023; Calculated as 12 minutes of band 8b hospital pharmacist time at £81 per hour ^{3, 136}
FOLFOX	14	£755.35	Aligned with TA948; NHS National Schedule of Costs 2023/24, SB14Z (Delivery of More Complex Parenteral Chemotherapy at First Attendance), Total HRG (£598.22) and WF01A (Non-Admitted Face-to-Face Attendance, Follow-up, Medical Oncology [Non-Consultant Led]) (£157.13) ⁴

Abbreviations: CAPTEM: capecitabine and temozolomide; FOLFOX: folinic acid, fluorouracil and oxaliplatin; HRG: healthcare resource group; IV: intravenous; NICE: National Institute for Health and Care Excellence; NHS: National Health Service; PRRT: peptide receptor radionuclide therapy; PSSRU: Personal Social Services Research Unit.

Source: NICE TA449;⁴ NICE TA539;³; PSSRU 2023;¹³⁶ NHS National Schedule of Costs 2023/24.¹⁴⁹

3.5.2 *Health-state unit costs and resource use*

The model included resource use costs based on health states, defined by the modelled ToT. The types of resource and frequency of use in the PF and PD health states included were based on Casciano et al. (2013) in the base case, as presented in Table 60.¹³⁵ The types of resource use included were consolidated based on feedback from clinicians who suggested that a simpler approach would be more reflective of clinical practice than that presented in the prior appraisals (TA449 and TA539).^{3, 4, 79} For example, the multiple biomarker tests included in the prior appraisals were deemed unnecessary, so the one laboratory test included from Casciano et al. (2013) was more appropriate.¹³⁵

The frequency of resource use per four-week cycle was derived using the baseline and first progression periods to represent the PFS and PD states respectively. The follow-up duration for the baseline and first progression period (13 and nine months respectively) were used to derive the rate. The second progression follow-up duration was excluded from the calculation of four-week rate for the PD state on the assumption that the frequencies likely underestimate actual resource use as they represent the percentage of patients utilising the resource use rather than frequency of usage.

The resource use cost applied for the PFS and PD health states were calculated by multiplying the unit cost of each resource (provided in Table 60) with the relevant resource frequency for each health state. It was assumed that resource use did not differ by treatment, however the model also included the flexibility for users to input treatment specific resource use frequencies.

A scenario was also included which adjusted the resource use frequency estimates based on UK clinical expert feedback; feedback was mixed, but some clinicians suggested resource use may be more frequent than reported in Casciano et al. (2013).¹² This scenario included altering the frequency of lab tests and visits to be equivalent to the model cycle length and all imaging to be every 3 months in the PF health state. In PD, the frequency of visits was increased to once per month and lab tests to every other month. All costs were based on the NHS National Schedule of Costs 2023/24 and are outlined in Table 60.¹⁴⁹

Table 60: Resource use per 28 day cycle by health state: base case

Resource ¹³⁵	Unit Cost ¹³⁶	Cost source	pNETs		epNETs	
			Frequency (PF)	Frequency (PD)	Frequency (PF)	Frequency (PD)
CT scan	£142.33	NHS National Schedule of Costs 2023/24, RD22Z (Computerised Tomography Scan of one area, with pre and post contrast), total HRGs ¹⁴⁹	0.11	0.15	0.13	0.16
Hospitalisation	£792.05	NHS National Schedule of Costs 2023/24, average of non-elective inpatient short stays ¹⁴⁹	0.04	0.06	0.03	0.06
Laboratory test	£3.10	NHS National Schedule of Costs 2023/24, PATH05 - Haematology (Directly Accessed Pathology Services) ¹⁴⁹	0.07	0.08	0.05	0.06
Ultrasound	£70.49	NHS National Schedule of Costs 2023/24, weighted average of RD40Z - RD43Z (Ultrasound Scan with and without Contrast), total HRGs ¹⁴⁹	0.06	0.05	0.05	0.05
Other imaging	£38.63	NHS National Schedule of Costs 2023/24, 812 - Diagnostic Imaging (Outpatient Attendance) ¹⁴⁹	0.05	0.05	0.05	0.04
Visit	£174.37	NHS Reference Costs 23/24, weighted average 370 - Medical Oncology Service, WF01A/C - Non-Admitted Face-to-Face Attendance/Non-Face-to-Face Attendance, Follow-Up (Outpatient Attendance) ¹⁴⁹	0.25	0.31	0.21	0.28

Resource use included was not treatment dependent and differed based on health-state only.

Abbreviations: CT: computed tomography; epNETs: extrapancreatic neuroendocrine tumours; HRG: healthcare resource group; NETs: pancreatic neuroendocrine tumours; NHS: National Health Service; PF: progression-free; PD: progressed disease.

Source: Casciano, 2013;¹³⁵ NHS National Schedule of Costs. 2023/24.¹⁴⁹

3.5.3 Adverse reaction unit costs and resource use

AE costs are included within the model, reported in Table 61, are based on the modelled time on treatment. These were derived from the NHS National Schedule of Costs and aligned with the prior NICE appraisals (TA539 and TA449).^{3, 4, 149} The overall AE management costs were calculated as a cost per four-week cycle. The rate was derived using the mean duration of follow-up observed in CABINET and the probability of each adverse event, as presented in Section 3.3.7.

Table 61: Costs per adverse event applied in the cost-effectiveness model

Adverse event	Unit cost	Source
Fatigue	£766.57	Assumed to be the same as anaemia; NHS National Schedule of Costs 2023/24, weighted average SA01G–SA01K: Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia (Non-Elective Inpatient Short Stay) ¹⁴⁹
Diarrhoea	£566.83	NHS National Schedule of Costs 2023/24, weighted average FD10A–FD10M: Non-Malignant Gastrointestinal Tract Disorders with and without Interventions (Non-Elective Inpatient Short Stay) ¹⁴⁹
Hypertension	£404.67	NHS National Schedule of Costs 2023/24, EB04Z: Hypertension (Non-Elective Inpatient Short Stay) ¹⁴⁹
Stomatitis	£519.16	NHS National Schedule of Costs 2023/24, weighted average CB02A–CB02F: Non-Malignant, Ear, Nose, Mouth, Throat, Head or Neck Disorders, with and without Interventions (Non-Elective Inpatient Short Stay) ¹⁴⁹
PPE syndrome	£511.89	NHS National Schedule of Costs 2023/24, weighted average JD07A–JD07K: Skin Disorders with and without Interventions (Non-Elective Inpatient Short Stay) ¹⁴⁹
Nausea	£508.69	NHS National Schedule of Costs 2023/24, FD10M: Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2 (Non-Elective Inpatient Short Stay) ¹⁴⁹
Vomiting	£508.69	NHS National Schedule of Costs 2023/24, FD10M: Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2 (Non-Elective Inpatient Short Stay) ¹⁴⁹
Small intestinal obstruction	£4,584.00	NHS National Schedule of Costs 2023/24, weighted average of FF20A–FF22D (Complex/Very Major/Major Small Intestine Procedures), non-elective inpatient short stay ¹⁴⁹
Embolism	£663.75	NHS National Schedule of Costs 2023/24, weighted average DZ09J–DZ09Q: Pulmonary Embolus with and without Interventions (Non-Elective Inpatient Short Stay) ¹⁴⁹

Abbreviations: PPE: palmar-plantar erythrodysesthesia.

Source: NHS National Schedule of costs, 2023/24.¹⁴⁹

3.5.4 Miscellaneous unit costs and resource use

A one-off terminal care cost of £13,314.00 was applied in the cycle that death occurred for both pNETs and epNETs to account for the cost associated with the additional disease management required in the months prior to death. Despite prior NICE appraisals (TA449 and TA539) using an end-of-life study (Round et al. (2015)), the cost used in the economic model is derived from the

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end-of-life care cost in latest version of the PSSRU unit costs of health and social care (2023).^{3, 4, 150} This is a more recently derived value, and is thought to more closely align with current clinical practice given that it is an exact cost to the NHS for end-of-life care compared with the estimates derived from the systematic literature review conducted by Round et al. (2015).^{3, 4, 150}

3.6 Severity

A summary of the features of the QALY shortfall analysis are provided in Table 62 and Table 63.

The expected quality-adjusted life expectancy (QALE) for the general population was calculated in line with the methods provided by Schneider *et al.* (2022).¹⁵¹ Baseline characteristics for the QALY shortfall analysis were aligned with the modelled population. The total life expectancy for the general population was calculated using population mortality data from the Office for National Statistics for 2021–2023.¹¹³ The total life expectancy was quality-adjusted using UK population norm values for EQ-5D using data from HSE, 2014 and modelled results reported by Hernández Alava *et al.* (2020) through the NICE DSU.¹⁵² Utilities were discounted at a rate of 3.5% per year in line with the NICE guide to the methods of technology appraisal.¹⁵³

The results of the QALY shortfall analysis are summarised in Table 63. For the epNETs population, the proportional QALY shortfall compared to the population receiving treatment with BSC was above the threshold of 0.85, therefore, a severity modifier of 1.2 should be considered for base case results for this comparison. Whilst not meeting the threshold to qualify for a severity weighting, the proportional QALY shortfall compared to the population receiving treatment with BSC remained high (0.82) in the pNETs population, reflecting the high unmet need for new treatment options across NETs as a whole.

As the guidance for the only prior appraisals in this indication (TA449 and TA539) were published in 2017 and 2018 respectively, no prior appraisals in the indication of interest to this submission used severity modifiers.^{3, 4}

Table 62: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)		Reference to section in submission
	pNETs	epNETs	
Sex distribution	42.11%	51.72%	Section 3.3.1
Starting age	60.22	63.09	

Abbreviations: CSR: clinical study report; epNETs: extrapancreatic neuroendocrine tumours; pNETs: pancreatic neuroendocrine tumours; QALY: quality-adjusted life years;

Source: Ipsen. Data on File. CABINET CSR. Data Cut-Off 24 August 2023²

Table 63: Summary of QALY shortfall analysis

Population	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment (BSC)	Absolute QALY shortfall	Proportional shortfall	Severity weighting
pNETs	12.61	2.23	10.39	0.82	1.00

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epNETs	11.61	1.13	10.48	0.90	1.20

Abbreviations: QALY: quality-adjusted life year.

3.7 *Uncertainty*

Crossover to cabozantinib may have underestimated the relative benefits versus placebo in OS for patients receiving cabozantinib, introducing uncertainty in the cost-effectiveness analysis. An IPCW adjustment was conducted, which required adjustment of all prognostic factors and included all baseline and clinical biomarkers predictive of treatment switching. The IPCW results were deemed to provide the most robust estimates of the relative effect for cabozantinib versus placebo on OS across all populations. Resulting extrapolations for BSC (derived via application of the HRs to the cabozantinib curve) produced estimates of long term survival that were consistent with predictions made by clinical experts experienced in the treatment of NETs.

There remains some uncertainty in the modelled utility values; the PD utility values derived directly from the CABINET data were based on a very limited number of observations, and were higher than those in PF and therefore deemed clinically implausible. In the absence of plausible utility values derived from the CABINET trial, a relative decrement to the CABINET PF data based on values derived from Swinburn *et al.* (2012) was used to inform the base case PD utility value. Whilst the values in the Swinburn publication were not derived directly from patients in line with the reference case (instead estimated from a TTO approach in which health state vignettes in NETs were developed based on clinician and patient interviews and EQ-5D questionnaires) the decrement applied was considered plausible by clinical experts,¹² particularly for the heavily pre-treated population of relevance for this appraisal, and scenarios exploring alternative decrements were explored for completeness.

The long-term survival extrapolations of OS data from the CABINET trial may pose another possible source of uncertainty. This was mitigated through conducting detailed individual consultations with UK clinical experts in NETs to ensure that the selected extrapolations produced clinically plausible long-term survival estimates; there was strong consensus between the preferred models based on statistic and visual fit (internal validity) and clinical plausibility (external validity).¹² Additionally, the PFS data at the final data cut-off could be considered relatively mature given that between 50% and 81% of patients had experienced a PFS event (see Section 2.6.1). Therefore, the long-term survival extrapolations are not expected to represent a substantial source of uncertainty for the base case analysis.

3.8 *Managed access proposal*

N/A – No further data cuts are planned for the CABINET trial, and available data are relatively mature.

3.9 *Summary of base-case analysis inputs and assumptions*

3.9.1 *Summary of base-case analysis inputs*

The base-case analysis inputs used in the model are summarised in Table 64.

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Table 64: Summary of variables applied in the economic model (base case analysis)

Variable	Value (pNETs)	Value (epNETs)	Reference to section in submission
Model settings			
Perspective	NHS and PSS		N/A
Discount rate (costs)	3.5%		
Discount rate (benefits)	3.5%		
Time horizon	Lifetime: ~40 years ^a		
Patient characteristics			
Starting age, years	60.22	63.1	Section 3.3.1
Percentage female	42.11%	51.72%	
Body weight, kg	80.81	78.85	
Body surface area, m ²	1.95	1.91	
Clinical inputs			
OS for cabozantinib	Exponential	Loglogistic	Section 3.3.4
OS for BSC	IPCW-adjusted HRs applied to cabozantinib curve	IPCW-adjusted HRs applied to cabozantinib curve	
PFS for cabozantinib	Lognormal	Lognormal	Section 3.3.3
PFS for BSC	HRs applied to cabozantinib curve	HRs applied to cabozantinib curve	
TTD for cabozantinib	Exponential	Exponential	Section 3.3.5
TTD for BSC	HRs applied to cabozantinib curve	HRs applied to cabozantinib curve	
AE rates	Grade 3 or 4 AEs regardless of study-drug relationship that occurred in ≥5% of patients in CABINET		Section 3.3.7
Utility inputs			
Utility for PF health state	■	■	Section 3.4.5
Utility for PD health state	■	■	
AE disutilities			
Fatigue	-0.073		Section 3.4.4
Diarrhoea	-0.171		
Hypertension	-0.085		
Stomatitis	-0.214		
PPE syndrome	-0.188		
Nausea	-0.061		
Vomiting	-0.061		
Small intestinal obstruction	-0.255		
Embolism	-0.370		
AE disutility durations (days)			

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Fatigue	23.80			Section 3.4.4	
Diarrhoea	5.50				
Hypertension	15.00				
Stomatitis	18.12				
PPE syndrome	18.12				
Nausea	10.50				
Vomiting	2.00				
Embolism	51.90				
Drug acquisition and administration costs (per cycle)					
Cabozantinib price (with PAS) 30 x 60 mg tablets			Section 3.5.1		
BSC (derived from CABINET CCT SSA costs in PF)					
Cabozantinib administration cost	£15.12				
BSC administration cost	£30.68	£38.92			
Concomitant therapy					
PF	CABINET (pre-progression)			Section 3.5.1	
PD					
Subsequent treatment					
Proportion of patients receiving subsequent treatment	Derived from the CABINET trial			Section 3.5.1	
Treatment distribution					Even distribution based on feedback from UK clinicians
Resource use frequencies					
Resource	PF	PD	PF	PD	Section 3.5.2
CT scan	0.11	0.15	0.16	0.16	
Hospitalisation	0.04	0.06	0.03	0.06	
Laboratory test	0.07	0.08	0.05	0.06	
Ultrasound	0.06	0.05	0.05	0.05	
Other imaging	0.05	0.05	0.05	0.04	
Visit	0.25	0.31	0.21	0.28	
Resource use unit costs					
CT scan	£142.33			Section 3.5.2	
Hospitalisation	£792.05				
Laboratory test	£3.10				
Ultrasound	£70.49				
Other imaging	£38.63				
Visit	£174.37				
Adverse events costs					
Fatigue	£766.57			Section 3.5.3	

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Diarrhoea	£566.83	
Hypertension	£404.67	
Stomatitis	£519.16	
PPE syndrome	£511.89	
Nausea	£508.69	
Vomiting	£508.69	
Embolism	£663.75	
Miscellaneous costs		
End of life cost	£13,314.00	Section 3.5.4

^a A lifetime horizon was Calculated by 100 minus the average age a patient enters as outlined above.

Abbreviations: AE: adverse event; BSC: best supportive care; CT: computed tomography; epNETs: extrapancreatic neuroendocrine tumours; HR: hazard ratio; IPCW: inverse-probability-of-censoring weights; NHS: National Health Service; OS: overall survival; PAS: patient access scheme; PD: progressed disease; PF: progression-free; PFS: progression-free survival; pNETs: pancreatic neuroendocrine tumours; PPE: plantar erythrodysesthesia; PSS: Personal Social Services; TTD: time to treatment discontinuation.

3.9.2 Assumptions

A summary of all the model assumptions and justifications is provided in Table 65.

Table 65: Base-case assumptions

Subject	Base-case assumption	Justification	Addressed in scenario analysis
Cabozantinib OS	The cabozantinib curve (directly extrapolated) and BSC curves (IPCW-adjusted HR applied to the cabozantinib curve) were selected in parallel using clinician estimates of long-term survival alongside model fit statistics and assessment of visual fit. The selected curves were as follows: pNETs: exponential epNETs: loglogistic	Given BSC OS values may have been confounded by crossover from placebo to cabozantinib, directly extrapolating from the placebo arm would likely overestimate survival for BSC. Therefore, it was necessary to adjust the efficacy data and apply the adjusted-HRs to the cabozantinib curve. Given OS for BSC was derived by applying the IPCW-adjusted HRs from the CABINET trial to the cabozantinib OS curve, base case curve selection for cabozantinib was informed by clinical plausibility across cabozantinib and BSC, simultaneously. Both the exponential and loglogistic functions predicted OS values that were reflective of the clinicians' estimates of long-term survival. These were also associated with the best statistical fit, a suitable hazard profile and acceptable visual fit to the KM curve.	Scenarios were included to explore alternative curve selections for OS that were also plausible based on clinician estimates of long-term survival (loglogistic for pNETs and lognormal for epNETs).
BSC OS	Curves for BSC were derived by applying IPCW-adjusted HRs to the cabozantinib curves	ITT OS values for BSC were confounded by patients crossing over to cabozantinib. Therefore, using the direct extrapolations for the ITT OS analyses would likely overestimate BSC OS. Applying an IPCW-adjusted HRs to the cabozantinib arm was deemed the only appropriate method.	N/A
Health-state utility values	Utility values are health-state and not treatment specific	QoL is based on values specific to health states as patients within a single health state (e.g. PF) are assumed to represent a homogenous state of	N/A

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		being, and therefore, have an equivalent quality of life. Any differences in quality of life between patients in the same health state but on treatments is expected to be due to adverse events, which are reflected in the treatment-related adverse event disutilities, as validated at an advisory board. ⁷⁹	
PD utility values	In the PF health state, these were derived directly from the CABINET data whereas the PD utility value was derived by applying a relative decrement calculated from Swinburn et al. (2012) ³⁵ to the PF value	UK clinicians highlighted that applying a relative decrement to the CABINET PF data for the PD health state would be more reflective of the trial population. Whilst both the relative decrement from Swinburn et al. (2012) and ERASMUS were deemed to provide plausible estimates, Swinburn et al. (2012) values were selected in the base case due to being used in the prior appraisals (TA449 and TA539), and given the heavily pre-treated nature of the CABINET trial population. ^{4, 35, 40, 107}	The model included scenarios to explore the effect of using direct utility values from the Swinburn Vignettes and ERASMUS trial, as well as a relative decrement from the ERASMUS trial. In all cases, PF utility was retained as the values from CABINET.
AE disutilities	AE disutilities were include in the base case. Where disutilities and durations could not be sourced for specific AEs, these were assumed to be equivalent to similar AEs from a NICE TA in another oncology indication. Where disutility durations could not be sourced that were identical to those included in the model, and no similar AEs could be used for assumptions, the values were calculated as an average of all other sourced durations.	Given clinician feedback suggested that the main difference in quality of life for patients beyond health state would be reflected in AEs, it was appropriate to model AE disutilities in the base case. It is reasonable to assume, in the absence of data, that the disutilities associated with AEs, and the duration they are applied for, could be similar across oncology indications. Calculating the average of all other AE disutilities and durations where there was a lack of data, was the approach taken in the prior TAs (TA539 and TA449).^{3, 4}	A scenario was explored excluding AE disutilities.
Concomitant therapy	Concomitant therapy use was based on the CABINET trial, and an equal	Clinician feedback suggested that concomitant SSA use would be continued indefinitely and	Pooled estimates of SSA use alongside subsequent treatment in CABINET were

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distribution (PD)	distribution assumed across PF and PD health states.	therefore it was reasonable to assume that the percentages are similar between health states.	used to derive the distribution of concomitant therapy in the PD health state.
Subsequent treatment distribution	The proportion of patients receiving subsequent treatment was derived from CABINET, and the distribution of treatments was split more evenly between individual subsequent treatment regimens.	Clinician feedback suggested that the proportion of patients receiving subsequent treatment in CABINET is reflective of UK clinical practice, however the distribution did not seem entirely plausible, and could be an artefact of the limited patient numbers from which these data were derived. ¹² A more even distribution between all potentially relevant treatments was suggested to be more reflective, with a lower proportion expected for everolimus. ¹²	A scenario was explored where the distribution of subsequent treatments was as reported in CABINET.
Resource use	Resource use values were derived from a literature source, Casciano et al. (2013), adapted based on clinician feedback. ¹³⁵	Feedback from clinicians suggested that the extensive list of biomarker tests included in the prior submissions was too complex for UK clinical practice and that a simple approach would be more appropriate.⁷⁹ There was a lack of consensus regarding the expected frequency of resource use across experts consulted, thus was deemed more robust to use those directly in the literature source for the base case analysis.	A scenario was explored which adjusted the frequency of resource use in each health state based on clinician feedback. This included aligning the visits and lab tests with the treatment (and model) cycle length as well as the frequency of all imaging to every three months in PF.
Oral admin costs	Oral administration was assumed to incur an ongoing cost for dispensing of the drug	This is aligned with prior appraisals (TA539 and TA449). ^{3,4}	A scenario which set the administration of oral drugs to zero was explored.

Abbreviations: AE: adverse event; BSC: best supportive care; CSR: clinical study report; epNET: extra-pancreatic neuroendocrine tumour; HR: hazard ratio; IPCW: inverse probability of censoring weights; ITT: intention-to-treat; KM: Kaplan-Meier; OS: overall survival; PD: progressed disease; PF: progression free; pNET: pancreatic neuroendocrine tumour; TA: technology appraisal; QoL: quality of life.

3.10 Base-case results

3.10.1 Deterministic base-case cost-effectiveness analysis results

The base case deterministic cost-effectiveness results for cabozantinib versus BSC and incremental net health benefits are presented in Table 66 and Table 67 at list and PAS price for pNETs population and the same in Table 68 and Table 69 for epNETs.

Although cabozantinib was found to be associated with higher costs, it was also associated with a higher number of life years and QALYs gained than BSC. Cabozantinib was found to be cost-effective compared to BSC in both pNETs and epNETs at a willingness to pay (WTP) threshold of £30,000 per QALY and produced an ICER well below the threshold of £20,000 in the epNET cohort. At PAS price, the deterministic ICER of cabozantinib versus BSC was £24,815 for pNETs and £12,849 for epNETs with a 1.2x severity modifier applied (£15,419 excluding the severity modifier).

Cabozantinib yielded an INHB of 0.14 and 0.34 in pNETs and epNETs, respectively. These results do not include a severity modifier which is provided for epNETs only, in Table 70 and Table 71 at list and PAS price, respectively, given pNETs did not qualify. With the 1.2 modifier applied in the epNETs group, cabozantinib yielded an INHB of 0.49.

Given that there is only one relevant comparator, BSC, a fully incremental analysis was not conducted. The clinical outcomes and disaggregated base case cost-effectiveness results (by cost category, including health states) and QALYs (by health state) are presented in Appendix H.

pNETs

Table 66: Deterministic base case results (cabozantinib list price, pNETs)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incr. £/QALY	Incr. NHB at £30k
Cabozantinib	████	4.38	████	-	-	-	-	-
BSC	████	3.36	2.23	████	1.02	████	████	████

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; NMB: net monetary benefit; QALY: quality-adjusted life year.

Table 67: Deterministic base case results (cabozantinib PAS price, pNETs)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incr. £/QALY	Incr. NHB at £30k
Cabozantinib	████	4.38	████	-	-	-	-	-
BSC	████	3.36	2.23	████	1.02	████	£24,815	0.14

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; NMB: net monetary benefit; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

epNETs

Table 68: Deterministic base case results (cabozantinib list price, epNETs)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incr. £/QALY	Incr. NHB at £30k
Cabozantinib	████	2.95	████	-	-	-	-	-
BSC	████	1.84	1.13	████	1.11	████	████	████

Abbreviations: BSC: best supportive care; epNET: extra-pancreatic neuroendocrine tumour; ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; NMB: net monetary benefit; QALY: quality-adjusted life year.

Table 69: Deterministic base case results (cabozantinib PAS price, epNETs)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incr. £/QALY	Incr. NHB at £30k
Cabozantinib	████	2.95	████	-	-	-	-	-
BSC	████	1.84	1.13	████	1.11	████	£15,419	0.34

Abbreviations: BSC: best supportive care; epNET: extra-pancreatic neuroendocrine tumour; ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; NMB: net monetary benefit; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

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Table 70: Deterministic base case results (cabozantinib list price, epNETs; 1.2 severity modifier applied)

Intervention	Incr. costs (£)	Incr. QALYs	ICER incr. £/QALY	Incr. NHB at £30k
versus BSC	██████	██	██████	████

Abbreviations: BSC: best supportive care; epNET: extra-pancreatic neuroendocrine tumour; ICER: incremental cost-effectiveness ratio; NHB: net health benefit; NMB: net monetary benefit; QALY: quality-adjusted life year.

Table 71: Deterministic base case results (cabozantinib PAS price, epNETs; 1.2 severity modifier applied)

Intervention	Incr. costs (£)	Incr. QALYs	ICER incr. £/QALY	Incr. NHB at £30k
Versus BSC	██████	██	£12,849	0.49

Abbreviations: BSC: best supportive care; epNET: extra-pancreatic neuroendocrine tumour; ICER: incremental cost-effectiveness ratio; NHB: net health benefit; NMB: net monetary benefit; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

3.11 *Exploring uncertainty*

Parameter uncertainty in the model was assessed via both probabilistic and deterministic sensitivity analyses the results of which are presented in Sections 3.11.1 and 3.11.2, respectively. In addition, key assumptions in the model were explored in several probabilistic scenario analyses, the results of which are presented below.

Overall, it is considered that all relevant uncertainties included in the analyses have been adequately accounted for and the base case results were found to be robust to uncertainty in the key model inputs and assumptions.

3.11.1 *Probabilistic sensitivity analysis*

A probabilistic sensitivity analysis (PSA) was included in the model to allow the methodological, parametric and structural uncertainties to be evaluated. This analysis produced cost-effectiveness acceptability curves (CEAC), to represent the probability that cabozantinib is cost-effective compared to BSC at the WTP threshold using a range of different threshold values, as well as a scatter plot and convergence plot.

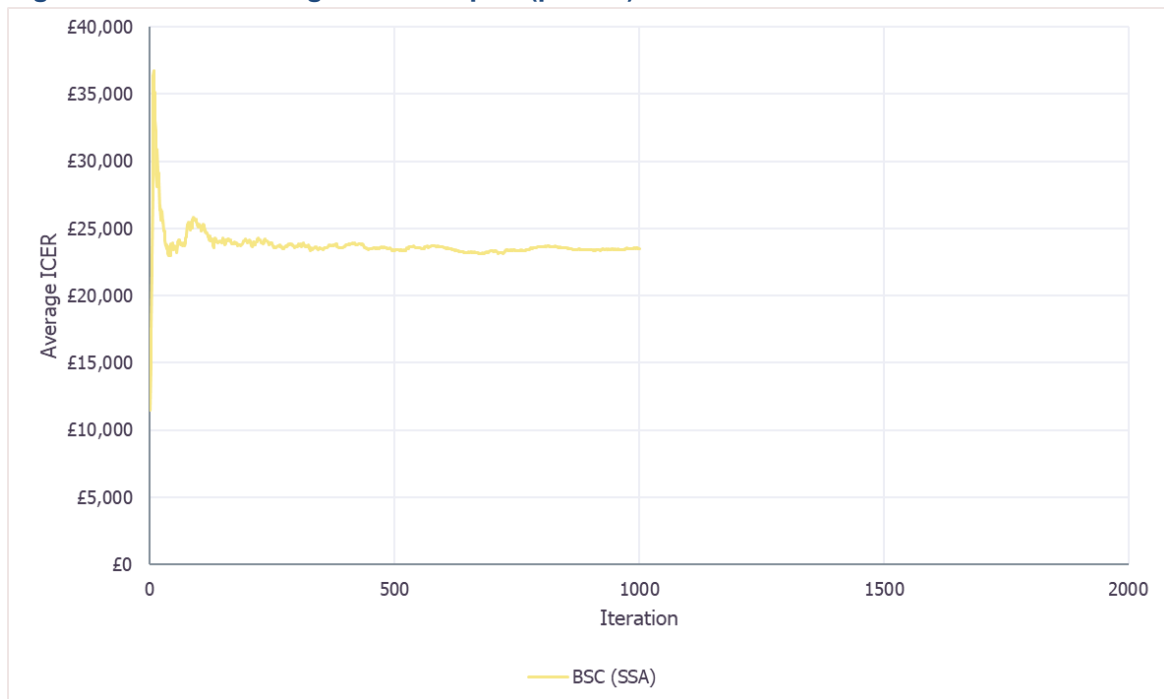
During the PSA, the model ran 1,000 iterations, with estimates of model parameters based on the uncertainty in the source data (where data availability permitted) as detailed in the PSA tab of the CEM. Where no such data were available, the model applied a user-defined percentage of the mean value as the standard error. A convergence plot is provided in Figure 26 and Figure 29 for pNETs and epNETs, respectively, which represents the change in the ICER over time and therefore the number of simulations required before a consistent ICER is reached.

The base case probabilistic cost-effectiveness results for cabozantinib versus BSC and net health benefits are presented in Table 72 for pNETs and Table 73 for epNETs. Closely aligned with the deterministic base case results, in the probabilistic analysis, cabozantinib was found to remain cost-effective versus BSC at a WTP of £30,000 and £20,000 per QALY for pNETs and epNETs, respectively, and yielding an INHB of 0.19 and 0.22 (with a 1.2 severity modifier applied).

Scatter plots showing the results of each iteration from the PSA on the cost-effectiveness plane are presented in Figure 27 and Figure 30 at PAS price for pNETs and epNETs (including a 1.2 severity modifier), respectively. Cost-effectiveness acceptability curves are presented in Figure 28 for pNETs and Figure 31 for epNETs. In the PSA, cabozantinib was found to have a ■■■% and ■■■% (including a 1.2 severity modifier) probability of cost-effectiveness versus BSC in pNET and epNET groups, respectively, at a WTP threshold of £30,000 per QALY.

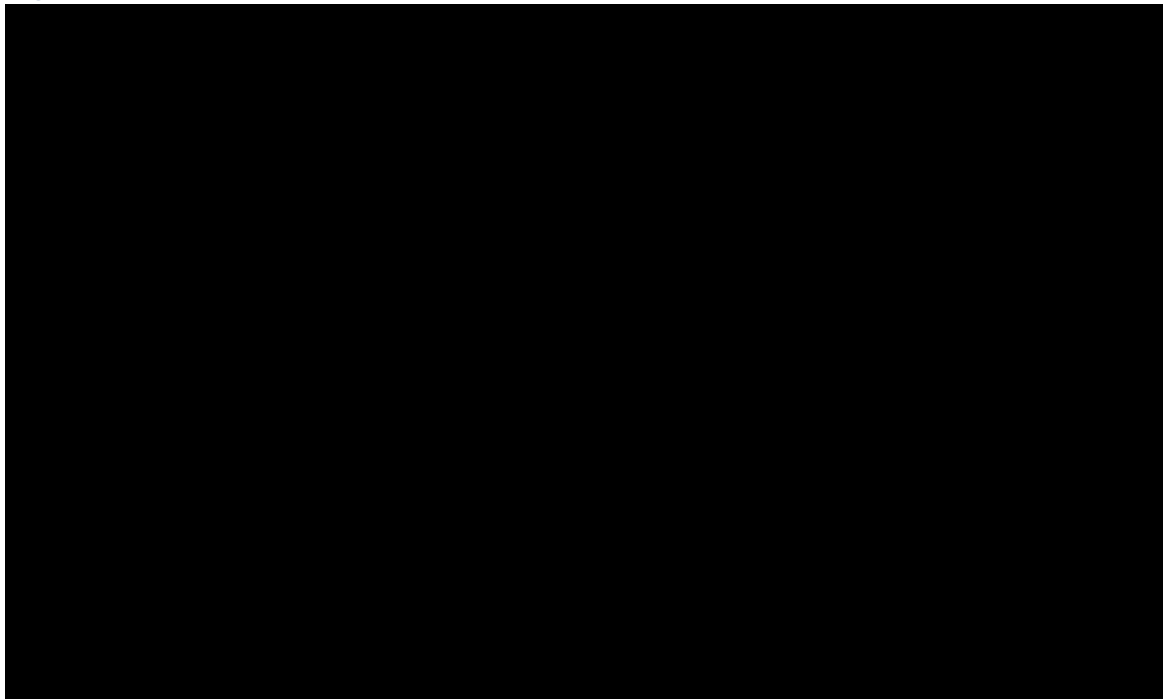
pNETs

Figure 26: PSA convergence ICER plot (pNETs)



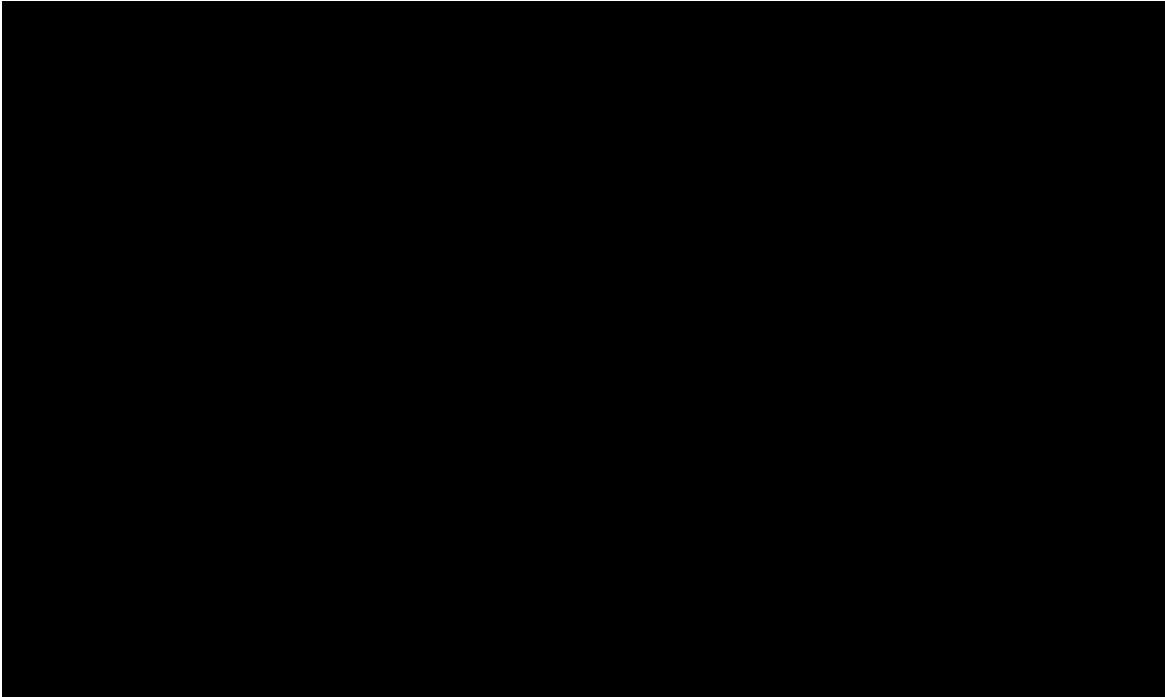
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; pNETs: pancreatic neuroendocrine tumours; PSA: probabilistic sensitivity analysis; SSA: somatostatin analogues

Figure 27: Cost-effectiveness scatter plot cabozantinib versus BSC (SSA) (pNETs)



Abbreviations: BSC: best supportive care; pNETs: pancreatic neuroendocrine tumours; QALY: quality-adjusted life years; SSA: somatostatin analogues; WTP: willingness to pay.

Figure 28: Cost-effectiveness acceptability curve (pNETs)



Abbreviations: BSC: best supportive care; pNETs: pancreatic neuroendocrine tumours; SSA: somatostatin analogues.

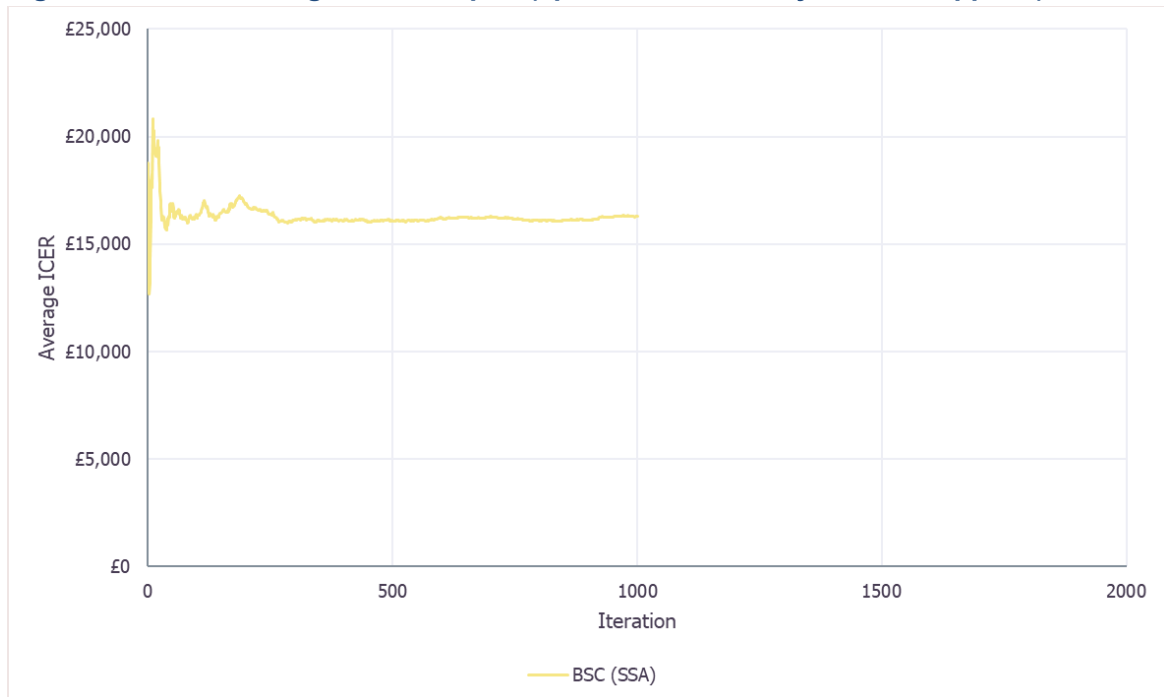
Table 72: Probabilistic base-case results (cabozantinib PAS price, pNETs)

Intervention	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. £/QALY	Incr. NHB at £30k
Cabozantinib						
BSC		2.22			£23,512	0.19

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; PAS: patient access scheme; pNET: pancreatic neuroendocrine tumour; QALYs: quality-adjusted life years

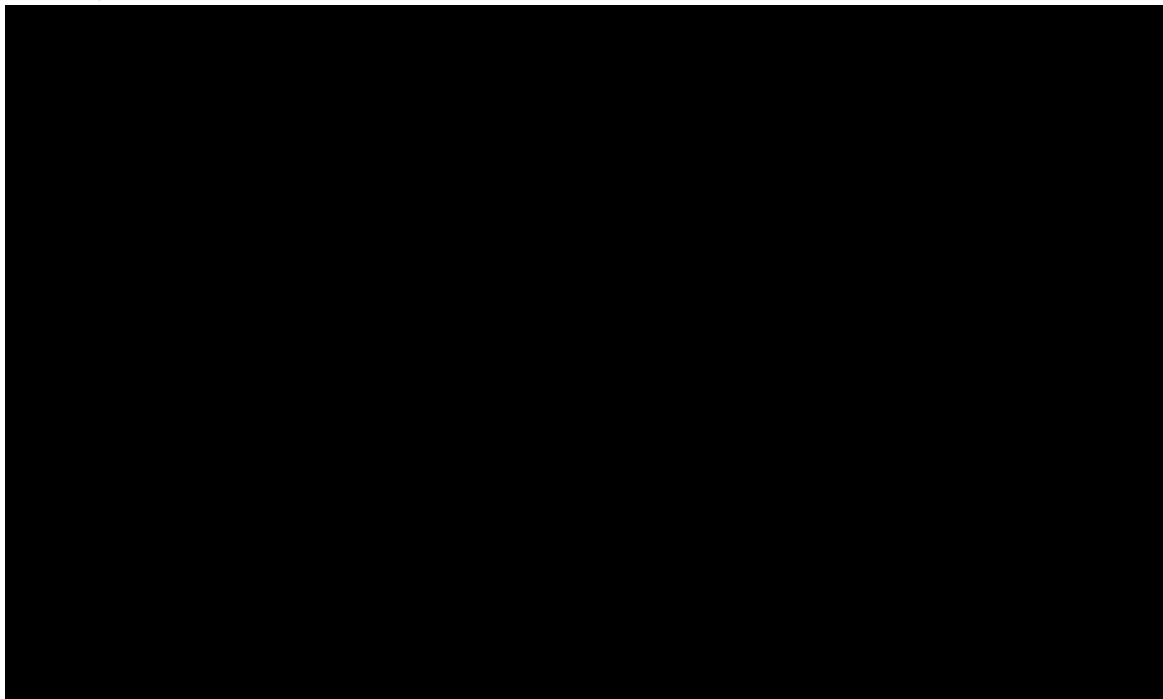
epNETs

Figure 29: PSA convergence ICER plot (epNETs; 1.2 severity modifier applied)



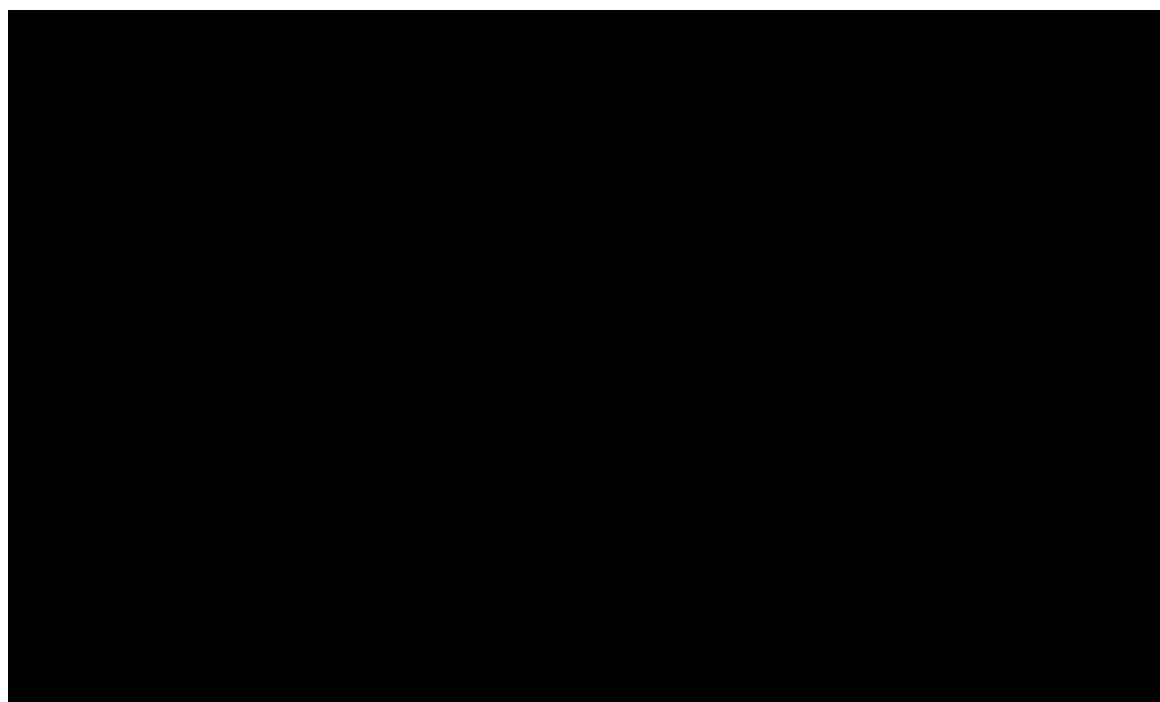
Abbreviations: BSC: best supportive care; epNETs: extrapancreatic neuroendocrine tumours; ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; SSA: somatostatin analogues

Figure 30: Cost-effectiveness scatter plot cabozantinib versus BSC (SSA) (epNETs; 1.2 severity modifier applied)



Abbreviations: BSC: best supportive care; epNETs: extrapancreatic neuroendocrine tumours; QALY: quality-adjusted life years; SSA: somatostatin analogues; WTP: willingness to pay.

Figure 31: Cost-effectiveness acceptability curve (epNETs; 1.2 severity modifier applied)



Abbreviations: BSC: best supportive care; epNETs: extrapancreatic neuroendocrine tumours; SSA: somatostatin analogues.

Table 73: Probabilistic base-case results (cabozantinib PAS price, epNETs; 1.2 severity modifier applied)

Intervention	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. £/QALY	Incr. NHB at £30k
Cabozantinib	██████	██████				
BSC	██████	1.15	██████	██████	£13,561	0.22

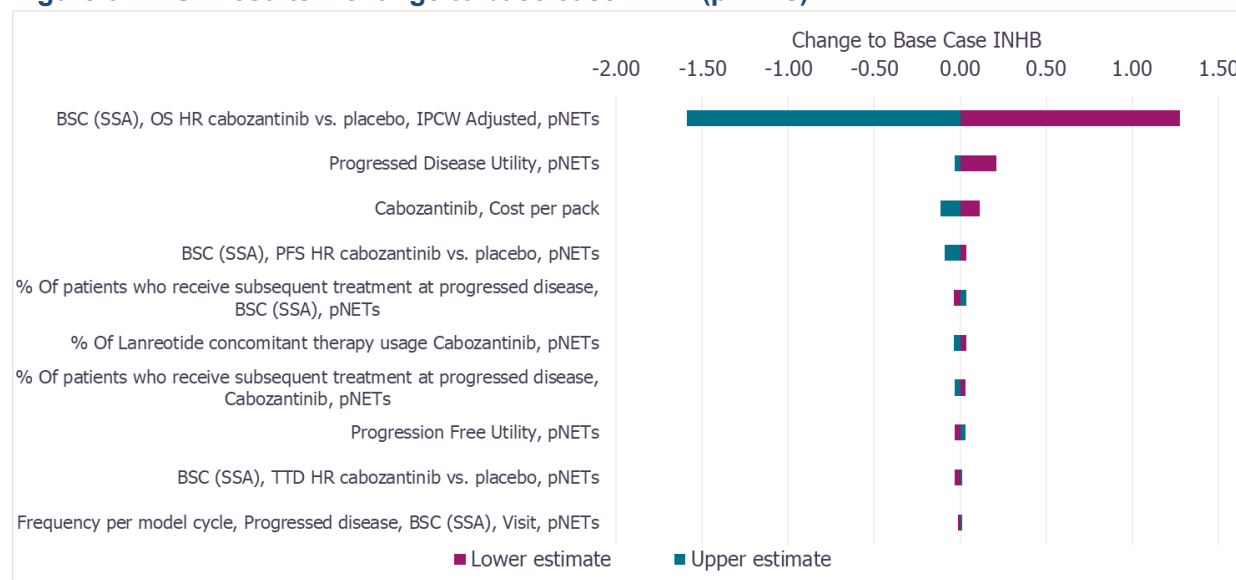
Abbreviations: epNET: extra-pancreatic neuroendocrine tumour; ICER: incremental cost-effectiveness ratio; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years

3.11.2 *Deterministic sensitivity analysis*

A deterministic sensitivity analysis (DSA) was included in the model to allow users to explore which parameters were the principal drivers of cost-effectiveness within the CEM. This was achieved by setting each parameter value to upper and lower bounds based on either reported CIs or an assumed variation of 20% either side of the mean. The results are in the form of tornado plots displaying the top ten parameters to which INHB was found to be most sensitive and are presented in Figure 32 and Figure 33 for pNETs and epNETs, respectively. Tornado plots displaying the top ten parameters most influential parameters for the ICER are presented in the economic model, but are not intuitive, given changes in ICER quadrant between the bounds of the OS IPCW-adjusted HR (given 95% CIs span 1). Of the parameters explored in the DSA, the OS HR had the largest impact on the INHB in both pNETs and epNETs, given this is key for driving the QALYs in the CEM. However, the IPCW results were deemed to provide the most robust estimates of the relative effect for cabozantinib versus placebo on OS across all populations.

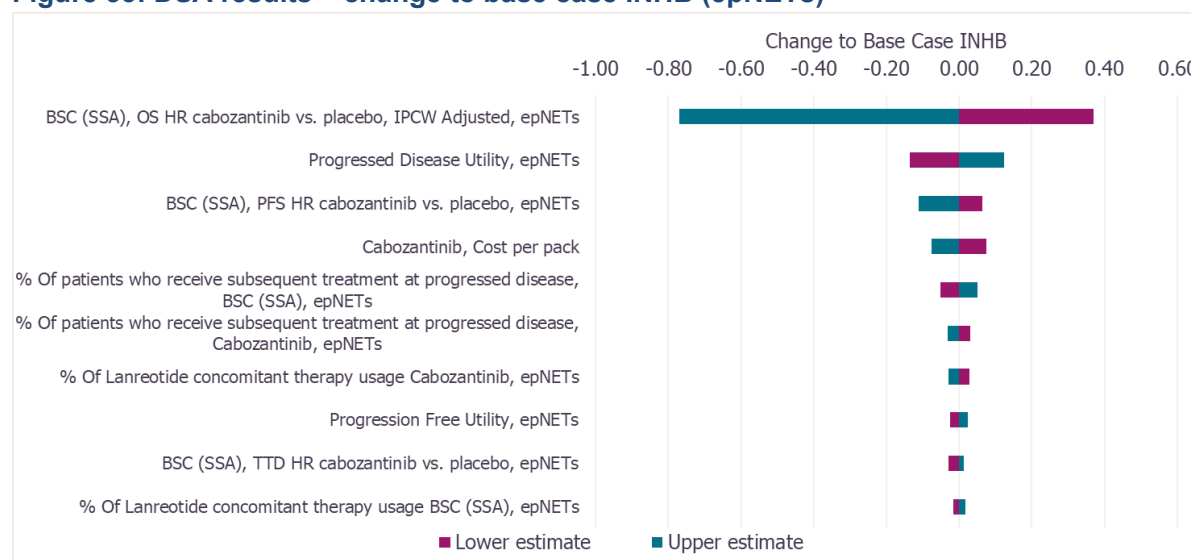
In pNETs, the cost per pack of cabozantinib as well as the progressed disease utility also had a notable impact on the INHB in comparison to other parameters. For epNETs, the BSC HR for PFS as well as the cost per pack of cabozantinib and progressed disease utility had a notable impact on INHB. All other parameters had limited impact on the INHB.

Figure 32: DSA results – change to base case INHB (pNETs)



Abbreviations: BSC: best supportive care; DSA: deterministic sensitivity analyses; HR: hazard ratio; INHB: incremental net health benefit; incremental cost-effectiveness ratio; IPCW: inverse probability of censoring weighting; OS: overall survival; pNETs: pancreatic neuroendocrine tumours; PFS: progression-free survival; SSA: somatostatin analogue; TTD: time to death.

Figure 33: DSA results – change to base case INHB (epNETs)



Abbreviations: BSC: best supportive care; DSA: deterministic sensitivity analyses; HR: hazard ratio; INHB: incremental net health benefit; incremental cost-effectiveness ratio; IPCW: inverse probability of censoring weighting; OS: overall survival; epNETs: extrapancreatic neuroendocrine tumours; PFS: progression-free survival; SSA: somatostatin analogue; TTD: time to death.

3.11.3 Scenario analysis

Several scenario analyses were conducted to assess the impact of the uncertainty associated with key inputs and assumptions in the economic model and how the incremental results change depending on these key inputs and assumptions. The key scenarios that can be explored in this model, and their rationale for inclusion, are outlined in Section 3.9.2. Results from the scenario analysis are presented in Table 74 for pNETs and Table 75.

Cabozantinib remained cost-effective across all scenarios explored for pNET and epNET populations. Overall, sensitivity analysis results demonstrate the base case results to be robust to uncertainties in inputs and assumptions.

Table 74: Scenario analysis results for cabozantinib versus BSC, pNETs

Scenario		Cabozantinib versus BSC		
		Incr. costs, £	Incr. QALYs	ICER (£/QALY)
Base case				
	Cost-effectiveness analysis	██████	██	£24,815
Discounting				
1	Discount rate for costs and benefits: 6.0%	██████	██	£27,210
2	Discount rate for costs and benefits: 1.5%	██████	██	£22,869
Utilities				
3	CABINET trial (PF) and Swinburn Vignettes (PD)	██████	██	£24,662
4	CABINET trial (PF) and ERASMUS relative decrement (PD)	██████	██	£25,452
5	CABINET trial (PF) and ERASMUS (PD)	██████	██	£25,394
Disutilities				
6	AE disutilities: exclude	██████	██	£24,730
Cabozantinib curve selection				
7	Alternative PFS/TTD curve selection for cabozantinib: PFS: Gompertz, TTD: Weibull	██████	██	£26,845
8	Alternative OS curve selection for cabozantinib (based on clinical validation): loglogistic	██████	██	£20,850
BSC survival method				
9	PFS/TTD: Direct extrapolation: PFS: Lognormal, TTD: Weibull	██████	██	£24,759
Costs				
10	Administration costs for orally administered drugs: £0	██████	██	£24,587
11	Subsequent treatment distribution source: Ipsen Data on File, CABINET CSR	██████	██	£20,722
12	CCT in PD distribution source: Ipsen Data on File, CABINET CSR (pooled SSA use alongside subsequent treatment)	██████	██	£25,490
13	Resource use source: Casciano et al. 2013 (adjusted frequency)	██████	██	£27,677

Abbreviations: AE: adverse event; BSC: best supportive care; CCT: concomitant therapy; CSR: clinical study report; ICER: incremental cost-effectiveness ratio; OS: overall survival; PD: progressed disease; PF: progression free; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumours; TTD: time to treatment discontinuation; QALY: quality-adjusted life year.

Table 75: Scenario analysis results for cabozantinib versus BSC, epNETs (with 1.2 severity modifier applied)

Scenario		Cabozantinib versus BSC		
		Incremental costs, £	Incr. QALYs	ICER (£/QALY)
Base case				
	Cost-effectiveness analysis	██████	██	£12,849
Discounting				
1	Discount rate for costs and benefits: 6.0%	██████	██	£13,783
2	Discount rate for costs and benefits: 1.5%	██████	██	£12,067
Utilities				
3	CABINET trial (PF) and Swinburn Vignettes (PD)	██████	██	£12,578
4	CABINET trial (PF) and ERASMUS relative decrement (PD)	██████	██	£12,016
5	CABINET trial (PF) and ERASMUS (PD)	██████	██	£11,590
Disutilities				
6	AE disutilities: exclude	██████	██	£12,841
Cabozantinib curve selection				
7	Conservative PFS/TTD curve selection cabozantinib: PFS: Weibull, TTD: Gompertz)	██████	██	£13,809
8	Alternative curves aligned with clinical validation for cabozantinib: OS: Lognormal)	██████	██	£12,956
BSC survival method				
9	PFS/TTD: Direct extrapolation, PFS: Lognormal, TTD: Loglogistic	██████	██	£13,273
Costs				
10	Administration costs for orally administered drugs: £0	██████	██	£12,711
11	Subsequent treatment distribution source: Ipsen Data on File, CABINET CSR	██████	██	£10,507
12	CCT in PD distribution source: Ipsen Data on File, CABINET CSR (pooled SSA use alongside subsequent treatment)	██████	██	£13,522
13	Resource use source: Casciano et al. 2013 (adjusted frequency)	██████	██	£15,431

Abbreviations: AE: adverse event; BSC: best supportive care; CCT: concomitant therapy; CSR: clinical study report; epNET: extra-pancreatic neuroendocrine tumour; ICER: incremental cost-effectiveness ratio; OS: overall survival; PD: progressed disease; PF: progression free; PFS: progression-free survival; TTD: time to treatment discontinuation; QALY: quality-adjusted life year.

3.12 Subgroup analysis

N/A – No subgroups were considered relevant to this appraisal. Consequently, no subgroup analyses were included in the economic analysis.

3.13 Benefits not captured in the QALY calculation

It should be noted that the current treatment pathway is highly individualised, with treatments often being restricted to specific populations or on the basis of distinct disease characteristics such as functional status and SSTR positivity. Given the broad anticipated marketing authorization of cabozantinib, which is not restricted on the basis of patient characteristics, cabozantinib has the potential to provide a much-needed additional, effective treatment option in an all-comers population. This could meet a key unmet need in this patient population that often face limited treatment options once they have progressed through multiple prior lines of therapy and has the potential to simplify the treatment paradigm in UK practice.

Two-thirds of patients with NETs report having a caregiver (a close family member or friend to help them manage day-to-day NET-associated activities), and caregiver burden is likely to be increased for patients with progressive disease. The economic model does not capture any HRQoL decrement borne by caregivers, and thus does not capture any corresponding beneficial impact of effective treatment with cabozantinib.³²

3.14 Validation

3.14.1 Validation of cost-effectiveness analysis

Clinical validation

Clinician input was sought during the development of the UK cost-effectiveness model, as noted throughout the submission, to ensure that the inputs and assumptions used were relevant to UK clinical practice.¹² Five independent interviews were conducted with UK clinicians who were experts in the treatment of patients with NETs. This helped to confirm the validity of the selected model inputs and clinical plausibility of the outcomes predicted by the model. The full report for the clinician interviews is provided in the reference pack.¹²

In particular, clinicians were asked to provide upper and lower biologically plausible estimates of life-expectancy for the patient population of interest treated with both cabozantinib and BSC, in line with NICE DSU TSD21.¹¹⁶ This, alongside model fit statistics and the assessment of visual fit was used to determine the most appropriate survival extrapolations for OS.

Validation of other inputs and assumptions, such as the proportion of patients receiving CCT and subsequent therapy, as well as the appropriate distribution of treatments for the latter, was conducted from clinician interviews. These clinicians also provided feedback regarding the most appropriate types and frequency of resource use in UK clinical practice.

Model predictions were also compared against available survival data from published real-world evidence sources and prior NICE technology appraisals.

Technical validation

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The model programming was checked by a health economist who was not involved in the original development of the model. This involved a cell-by-cell quality control check of all formulae used in the model and stress testing of the model to ensure that it behaves as expected when extreme values are used.

3.15 Interpretation and conclusions of economic evidence

Summary of the cost-effectiveness evidence

To conduct the cost-effectiveness analysis, a *de novo* PSM was constructed from the perspective of NHS and PSS in England.

The deterministic base-case analysis revealed that cabozantinib was found to be cost-effective versus BSC at the WTP threshold of £30,000 and £20,000 for pNETs and epNETs, respectively. At cabozantinib PAS price, this yielded a positive INHB of 0.14 for pNETs and 0.34 for epNETs (0.49 when considering the 1.2x severity modifier). Therefore, cabozantinib can be considered a cost-effective use of NHS resource for patients with advanced NETs that have progressed after prior systemic therapy.

To assess the robustness of the base case analysis for key inputs and assumptions, a number of sensitivity and scenario analyses were explored. Of parameters explored in the deterministic sensitivity analysis (DSA), the IPCW-adjusted OS HR was found to be the most influential parameters on the ICERs versus BSC. The IPCW results were deemed to provide the most robust estimates of the relative effect for cabozantinib versus placebo on OS across all populations. In the PSA, cabozantinib was found to have a ■■■% and ■■■% probability of cost-effectiveness versus BSC in pNET and epNET groups, respectively, at a WTP threshold of £30,000 per QALY.

Scenario analyses were conducted to explore the impact of alternative discount rates, utility values, parametric models for cabozantinib OS, PFS and TTD, independent modelling of PFS and TTD for BSC, administration and subsequent treatment costs, and resource use. In all of the scenario analyses conducted, the ICERs for cabozantinib at PAS price (with the x1.2 severity modifier applied in the epNET cohort) were found to be below a cost-effectiveness threshold of £30,000 per QALY in the pNET group, and well below the threshold of £20,000 in the epNET group.

Strengths

UK clinical experts in NETs highlighted that cabozantinib would be used in UK clinical practice in line with the CABINET trial population, which informs the anticipated marketing authorisation of cabozantinib and the proposed treatment pathway. They also verified the proposed positioning of cabozantinib to be suitable, considering BSC as the only appropriate comparator, and highlighted that this poses an important therapy to address the unmet need in this patient population. Clinician input was sought during the development of the UK cost-effectiveness model, as noted throughout the submission, to ensure that the inputs and assumptions used were relevant to UK clinical practice.¹² The results of this economic analysis are therefore considered highly relevant to decision-making in NHS clinical practice.

The model also closely aligns with the NICE reference case, adopting an NHS and PSS perspective, as well as utilising a lifetime horizon to ensure all costs and QALY gains associated Company evidence submission template for cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment

with the interventions are fully captured as well as discounting costs and benefits at 3.5% per annum.¹⁰⁵ Costs included in the analysis were derived from UK sources (e.g. NHS Schedule of Costs, PSSRU and the BNF). Where possible, the parameters and assumptions used in the model were aligned with the only other prior NICE appraisals in this indication (TA539 and TA449).^{3, 4}

Limitations

As discussed in Section 3.7, there are some remaining sources of uncertainty in the economic model, including the impact of crossover from the placebo arm of the CABINET trial to open-label cabozantinib, which may have underestimated the relative benefits versus placebo in OS for patients receiving cabozantinib. However, adjustment for the impact of crossover was explored in line with NICE DSU TSD 16 and 24, and the results of the preferred IPCW analysis inform the OS benefit for cabozantinib versus BSC in the economic model. Resulting extrapolations for BSC (derived via application of the HRs to the cabozantinib curve) produced estimates of long term survival that were consistent with predictions made by clinical experts experienced in the treatment of NETs, and can therefore be considered robust.

There remains some uncertainty in the modelled utility values, due to a limited number of observations reported in the CABINET trial for the PD health state. Literature values were used to inform the utility value for the PD health state in line with sources applied in prior appraisals, and scenarios exploring alternative values did not alter the conclusions of the cost-effectiveness analysis.

Long-term survival extrapolations of OS data from the CABINET trial may pose another possible source of uncertainty. However, detailed individual consultations with UK clinical experts in NETs were conducted to ensure selected extrapolations were clinically plausible, and there was strong consensus between the preferred models based on statistic and visual fit (internal validity) and clinical plausibility (external validity).¹² Therefore, the long-term survival extrapolations are not expected to represent a substantial source of uncertainty for the base case analysis.

Conclusions

In the UK, there is a high unmet need in patients with advanced neuroendocrine tumours that have progressed after prior systemic treatment. Many of these patients have limited treatment options other than BSC to delay disease progression and improve prognosis. Given the heterogenous nature of NETs, the current treatment pathway is highly individualised and dependent on multiple disease characteristics. However, the broad anticipated marketing authorisation of cabozantinib offers a treatment option that is not restricted to any specific subgroup, or on the basis of a specific disease characteristic. Based on the results of the CABINET trial, cabozantinib is associated with increased PFS and OS compared to BSC. Overall, the base case analysis found cabozantinib to be cost-effective versus BSC at a WTP of £30,000 per QALY.

Appendices

Appendix A: Summary of product characteristics (SmPC) and UK public assessment report

Appendix B: Identification, selection and synthesis of clinical evidence

Appendix C: Subgroup analyses

Appendix D: Adverse reactions

Appendix E: Published cost-effectiveness studies

Appendix F: Health-related quality-of-life studies

Appendix G: Cost and healthcare resource identification, use and validation

Appendix H: Clinical outcomes and disaggregated results from the model

Appendix I: Price details of treatments included in the submission

Appendix J: Additional evidence from the CABINET trial

Appendix K: Assessment of proportional hazards

Appendix L: Adjustment for crossover in CABINET

Appendix M: Targeted literature review for RWE studies

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment

ID6474

April 2025

Template version	Date amended	Changes since previous version
2.0	14 April 2025	

File name	Version	Contains confidential information	Date
ID6474_Cabozantinib in NETs_SIP	Final	No	14/04/2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [IJTAHC journal article](#)

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

1a) Name of the medicine (generic and brand name):

Response:

Generic name – Cabozantinib (Brand name – Cabozantinib Ipsen)¹

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Response:

Cabozantinib will be used to treat adults with **unresectable** or **metastatic extra-pancreatic (epNET)** and **pancreatic neuroendocrine tumours (pNET)** who have progressed after systemic treatment. More information on the population can be found in Section B.1.1 of the company submission.¹

Please note that further explanations for the words and phrases highlighted in **bold** are provided in the glossary (**Section 4b**).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Response:

The **Medicines and Healthcare products Regulatory Agency (MRHA)** is reviewing whether cabozantinib should be approved and granted marketing authorisation as a treatment for adults with advanced epNETs and pNETs who have progressed after systemic treatment. The marketing authorisation for cabozantinib is therefore pending. More information on this can be found in Section B.1.2 of the company submission.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response:

Ipsen has an ongoing collaborative partnership with Neuroendocrine Cancer UK (NCUK) and UK and Ireland Neuroendocrine Tumour Society (UKINETS), comprising various projects at a global and UK level.

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Response:

What are neuroendocrine tumours (NETs)?

A neuroendocrine tumour is a rare tumour that can develop in many different organs of the body. It affects the cells that release hormones into the bloodstream (neuroendocrine cells).² Most neuroendocrine tumours develop slowly over some years. They may not cause symptoms in the early stages and it is not unusual for people to find that a neuroendocrine tumour has already spread to another part of the body when they are diagnosed.³

What are signs and symptoms of NETs?

The symptoms of a NET depend on where in the body it is and what hormones it produces. For example, a tumour in the digestive system (gastrointestinal NET) may cause diarrhoea, constipation or stomach pains. A tumour in the lung (pulmonary NET) may cause wheezing or a persistent cough. Some tumours may lead to abnormally large amounts of hormones being released into the bloodstream. These are known as "functional tumours" and can cause symptoms such as diarrhoea, flushing, cramps, wheezing, low blood sugar (hypoglycaemia), changes in blood pressure and heart problems.⁴

What is the impact of NETs?

NETs are rare, affecting 35 per 100,000 people in England. NETs are diagnosed in 4.8 per 100,000 people every year. However, this is steadily increasing globally. NETs can occur at any age, but the average age of people living with NETs in England is 62.⁵

As there are many different symptoms that can occur, it can make diagnosis and management complicated. On average, people wait up to five years for a diagnosis,⁶ visiting their GP an average of 11 times with NETs related symptoms* and hospital an average of three times prior to diagnosis**.

Neuroendocrine cancers are a complicated set of conditions, and life expectancy can vary greatly depending on various factors, including the type and stage of the cancer, treatment options, and individual health circumstances.⁸ Studies have shown that the majority of people with neuroendocrine cancers are diagnosed with advanced cancer, requiring urgent, accurate diagnostic assessments and increased healthcare requirements.^{9, 10, 11} Long delays to diagnosis and poor access to specialist care can result in significant anxiety, poorer quality of life and threat to survival.^{12, 13, 14, 15}

Less than 25% of patients living with Stage 4 NETs (advanced NETs) are expected to survive up to five years from diagnosis, compared with over 75% of patients with Stage 1 and Stage 2 disease, and over 50% of patients with Stage 3 disease.¹⁶

What is meant by primary tumour location and why does it matter?

The primary tumour location is the place or organ in the body where the cancer first started growing. NETs can have primary locations throughout the body, but the most common primary locations are: gastrointestinal tract, pancreas, lungs and adrenal glands.

What is tumour staging?

Staging is a way of confirming how advanced the cancer is and how far it has spread.¹⁶

- Stage 1: Early stage, tumour is small and hasn't spread beyond the part of the body or organ where it started growing.
- Stage 2: Tumour is larger or has spread to nearby tissues.
- Stage 3: Tumour has spread to nearby lymph nodes or tissues.
- Stage 4: Cancer has spread to distant parts of the body (metastatic).

What is tumour grade and why does it matter?

In addition to staging, NETs are also graded based on how abnormal the cancer cells look under a microscope and how quickly the cells are likely to grow and spread. Grades range from 1 to 3,

where a higher grade indicates faster growth. The grade of the cancer will help the healthcare team to decide the right course of treatment and care to manage symptoms and quality of life.¹⁶

- Grade 1: Slow-growing, well-differentiated cells.
- Grade 2: Moderately fast-growing, intermediate grade.
- Grade 3: Rapidly growing, **poorly differentiated** cells.

** reported by 80% of people surveyed*

***reported by 58% of people surveyed*

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Response:

A significant number of tests and investigations are available to accurately diagnose and grade NETs. Multiple tests are needed to confirm a diagnosis. A combination of the following may be used based on an individual's symptoms and medical history:

- **Endoscopic procedures**
- **Imaging scans**
- **Tumour biopsy and histopathology**
- Blood and urine tests
- **Biomarker testing**
- **Genetic testing**

Findings from these tests are used to identify the **primary tumour location**, determine the **grade of cancer** and ultimately inform treatment decisions.¹⁷

There is no single test that can confirm a diagnosis of NETs.¹⁸ The diversity of NETs causes significant challenges at the point of diagnosis, including choosing the right diagnostic tests. NETs are often misdiagnosed, and diagnosis is frequently delayed.^{6, 10, 19} Delays can be caused by the complexity of tumour presentation and significant number of possible primary sites. As a result, choosing the most appropriate diagnostic tests is difficult, and administration of a variety of tests can cause delays to diagnosis.¹⁰

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
 - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
 - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Response:

Treatments

The aim of treatment for adults with unresectable or metastatic epNETs and pNETs who have progressed after systemic treatment²⁰ is to control symptoms and tumour growth whilst maintaining quality of life.

Somatostatin Analogues (SSAs) are often prescribed first, before any other types of treatment, except in the case of grade 3 NETs, regardless of primary tumour location. SSAs are a type of **systemic therapy** (a treatment that travels through the bloodstream to reach cells all over the body).

As NETs presents differently in almost every patient, the decisions around which treatments to use, in which order, can be complicated and must be personalised for each individual patient. There is not one clear or consistent route to making treatment decisions after the cancer has progressed on SSA treatment.

Systematic therapies that are used after SSAs are only given to patients with specific types of NETs, depending on the primary tumour site and grade, and can include **everolimus** (for **progressive pNETs** and **non-functional progressive** gastrointestinal [GI] or lung NETs), **sunitinib** (for **progressive pNETs** only) and **lutetium oxodotreotide** (¹⁷⁷Lu-dotatate, for **SSTR-positive progressive** gastroenteropancreatic [GEP] NETs).^{21, 22}

Different types of **chemotherapy** may be considered for **off-label** use, but healthcare teams may decide to save this treatment option for higher-grade NETs, given they can be toxic and impact quality of life.

There are limited treatment options following progression on **SSAs** and further **systemic treatment**, and for many patients the only remaining option is **best supportive care**.

Unmet need

There are several recommended **systemic treatment** options after **SSAs**, these are often used only for patients with very specific types of NETs.

As many as 66% of patients progress to a second type of systemic therapy and 56% progress to third type of systemic therapy, meaning there is a significant need for more, effective treatment options for patients who have progressed on previous treatments.²³

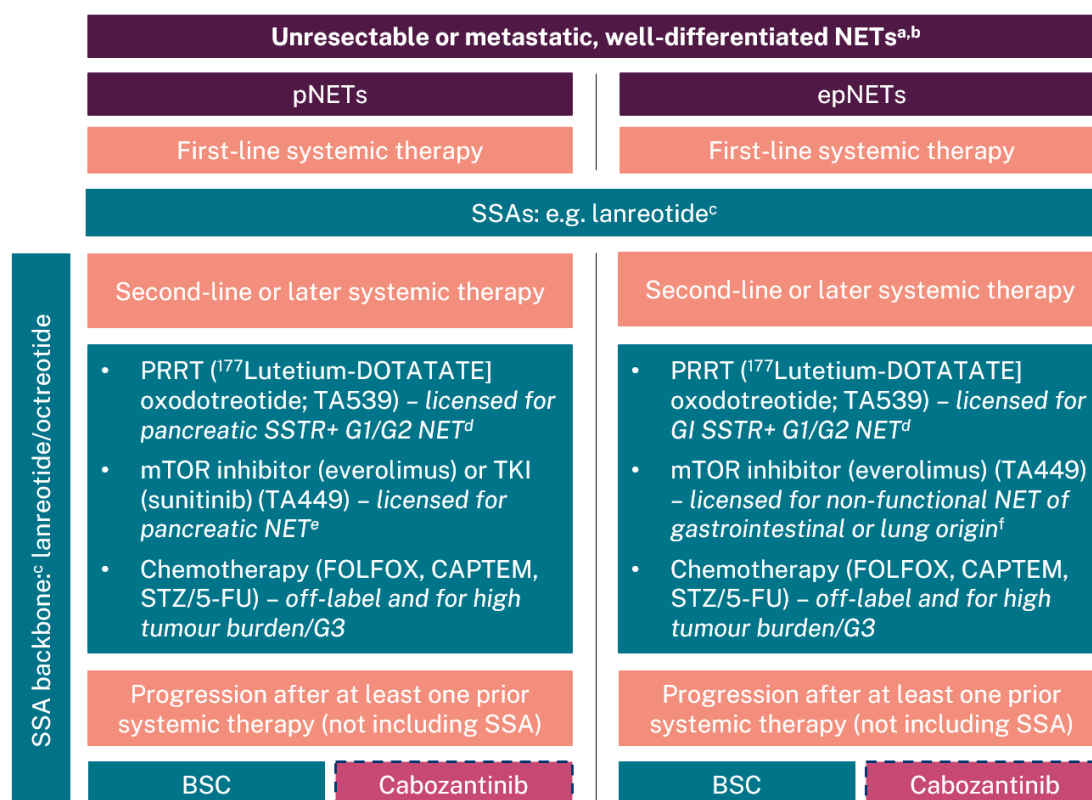
For patients with unresectable or metastatic NETs who have progressed after SSAs and the systemic therapy that follows, there is a significant unmet need for therapies that extend **progression-free survival** (PFS) after the NETs has started to grow and progress, regardless of primary tumour location, **tumour grade** and **SSTR expression status**. An effective treatment that delays progression would also delay the impact on **quality of life** that may come with progression of the disease.

Quality of Life (QoL) is worse in patients with progressive disease compared to those with stable disease, and therefore treatments should delay progression to maintain QoL for as long as possible.

Proposed position of cabozantinib

The proposed indication for cabozantinib in this submission is to treat adults with unresectable or metastatic epNETs and pNETs who have progressed after systemic therapy.

Figure 1: Proposed positioning of cabozantinib in the recommended NETs sequence of treatment options in the UK



^aPatients with G3/poorly differentiated tumours typically have a truncated treatment pathway, mostly with chemotherapy at first line; ^bThe NHS does not reimburse re-treatment with the same treatment class; ^cSomatostatin analogues (lanreotide/octreotide) are not licensed for use in Lung NETs and they are used off-label; ^d¹⁷⁷Lutetium-DOTATE is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic NETs in adults. ^eEverolimus and sunitinib are recommended, within their marketing authorisations, as options for treating well- or moderately differentiated unresectable or metastatic NETs of pancreatic origin in adults with progressive disease; ^fEverolimus is recommended, within its marketing authorisation, as an option for treating well-differentiated (grade 1/2) non-functional unresectable or metastatic NETs of gastrointestinal or lung origin in adults with progressive disease.

Abbreviations: BSC: best-supportive care; CAPTEM: capecitabine and temozolomide; epNET: extra-pancreatic neuroendocrine tumour; FOLFOX: folinic acid + fluorouracil + oxaliplatin; G: grade; GI: gastrointestinal; ¹⁷⁷Lu-DOTATATE; mTOR: mammalian target of rapamycin; NET: neuroendocrine tumour; pNET: pancreatic neuroendocrine tumour; PRRT: peptide receptor radionuclide therapy; SSA: somatostatin analogue; SSTR: somatostatin receptor; STZ: streptozocin; TA: Technology Appraisal; TKI: tyrosine kinase inhibitor.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Response:

Patients with **NETs** experience a significant clinical burden, with symptoms often impacting their daily life. Throughout clinical trials to investigate a medicine's effectiveness and safety, patients are able to describe their symptoms and quality of life, both **quantitatively** and **qualitatively**. These methods often stem from questionnaires that ask patients to score how they are feeling at certain time points, either of the day or of their treatment cycle.^{6, 13}

Beyond clinical trials, patient input plays a vital role in shaping treatment guidelines and healthcare policies. The Role of Patient Support Groups in Neuroendocrine cancer population bioequivalence (PBE) studies have shown that symptoms such as gastrointestinal problems (diarrhoea, constipation), pain, fatigue, and hormonal imbalances (e.g., flushing, hypoglycaemia) significantly affect daily living and overall well-being of people living with NETs.

In addition, the emotional toll of delayed diagnosis is a common theme, with many patients reporting prolonged diagnostic delays of up to five years, leading to frustration and a sense of isolation.⁷

PBE also highlights the significant burden on caregivers, who face not only the challenges of providing care but also emotional and physical strain due to the chronic nature of NETs and its treatment

Patients desire improvement in many aspects of NETs care, including availability of a wider range of NET-specific treatment options, better access to NETs experts or specialist centres, and a more knowledgeable, better-coordinated NETs medical team.¹³

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Response:

Cabozantinib is a medicine that may stop tumour growth and disease progression, in patients with NETs.²⁴

Cabozantinib works in a unique way by focusing on many different targets at the same time, that may be contributing to NET growth and survival.²⁴

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Response:

Cabozantinib will be used as a single treatment (monotherapy) on its own.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Response:

Cabozantinib will be taken by mouth once daily, as a single 20 mg, 40 mg or 60 mg tablet.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Response:

Study	Testing Cabozantinib in Patients With Advanced Pancreatic Neuroendocrine and Carcinoid Tumors (CABINET), NCT03375320
Study design	Chan, J.A. et al. Testing Cabozantinib in Patients With Advanced Pancreatic Neuroendocrine and Carcinoid Tumors. N Engl J Med (2024) doi: 10.1056/NEJMoa2403991 ³¹
Study design	Phase III, US based, multi-centre, randomised, double-blind, placebo-controlled.
Population	Adult patients with confirmed, locally advanced or metastatic well or moderately differentiated neuroendocrine tumours of extrapancreatic or pancreatic origin.
Settings and locations where the data were collected	US based trial with multiple study centres.
Completion Date	September 2024
Intervention(s)	Cabozantinib 60 mg once daily
Comparator(s)	Placebo (an inactive drug) once daily
Reported outcomes specified in the decision problem	The outcome measured include: • Overall survival • Progression-free survival

	• Response rates • Symptom control • Adverse effects of treatment • Health-related quality of life
All other reported outcomes	Pharmacokinetics
Key Inclusion Criteria	• Informed consent • Males or females over the age of 18 • Confirmed diagnosis of locally advanced or metastatic well or moderately differentiated neuroendocrine tumours of extrapancreatic or pancreatic origin • Experienced disease progression after receiving or intolerance leading to treatment discontinuation of at least one Food and Drug Administration (FDA)-approved line of therapy (except somatostatin analogues) • Females must be of non-childbearing potential

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Response:

The results of the CABINET study were positive, with the primary endpoint of progression free survival (PFS) being met. Cabozantinib demonstrated significant benefits over placebo as an anticancer therapy for people living with advanced pNETs and epNETs, who had progressed after a previous therapy. The adverse events reported for cabozantinib were consistent with the safety findings from previous studies.²⁴

pNET cohort:

Median PFS for people with pNETs was 9.4 months longer with cabozantinib versus with placebo (primary outcome) which was statistically significant. Median PFS for people with pNETs was 13.8 months with cabozantinib versus 4.4 months with placebo. The hazard ratio for PFS for cabozantinib versus placebo was 0.23, for people living with pNETs, meaning that people treated with cabozantinib had a 77% reduction in the risk of disease progression or death.²⁴

epNET Cohort:

Median PFS was 4.5 months longer in the cabozantinib arm vs the placebo arm which was statistically significant. Median PFS for people living with epNETs was 8.5 months with cabozantinib versus 4.0 months with placebo. The hazard ratio for PFS for cabozantinib versus placebo was 0.38, for people living with epNETs, meaning that people treated with cabozantinib had a 62% reduction in the risk of disease progression or death.²⁴

A feature of the trial design for CABINET was the permitting of crossover of patients in the placebo arm to the cabozantinib arm upon disease progression. Data was collected independently when these patients switched treatment, and therefore it is necessary to mitigate bias in the overall survival (OS) results. The ability of patients to switch from placebo to active treatment with cabozantinib on disease progression may also partly explain why no significant improvement in OS is found from the trial. But it is important to note that CABINET was not designed to capture improvement in OS therefore it is difficult to interpret OS results.²⁴

More key findings from the CABINET Phase III trial can be found in section B.2.12.1 of the company submission.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs)**.

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Response:

Patients with advanced NETs experience a substantial and persistent symptom burden that negatively impacts their quality of life (QoL) compared to the general population. A significant impact on QoL is also seen in patients with progressive disease compared to those with stable disease, and therefore treatments should delay progression to maintain QoL for as long as possible. This was demonstrated by the CLARINET randomised controlled trial (RCT), where a significant difference in utility values was identified when comparing patients with stable disease to those with progressive disease.²⁵

While delaying disease progression is the first priority treatment goal for most patients, a global experiment in 242 patients with advanced NETs revealed that avoiding treatment side effects and convenience in how the treatment is taken are also key priorities for patients.²⁶ The current treatment options for patients with advanced NETs impose a high impact on daily life of patients and caregivers (177Lu-dotatate) and are associated with considerable **tolerability burden** (177Lu-dotatate and chemotherapy).^{21, 27, 28, 29}

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Response:

Possible side effects that may require urgent medical treatment include:³⁰

- Symptoms including pain in the abdomen, nausea (feeling sick), vomiting, constipation, or fever.
- Severe or uncontrollable bleeding with symptoms such as: vomiting blood, black stools, bloody urine, headache, coughing up blood.
- Feeling drowsy, confused or loss of consciousness.
- Swelling, or shortness of breath
- A wound or cut that does not heal.

- Pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth.

Other very common side effects may include:

- Anaemia (low levels of red blood cells which carry oxygen), low levels of platelets (cells which help the blood to clot)
- Reduced thyroid activity; symptoms can include tiredness, weight gain, constipation, feeling cold and dry skin
- Decreased appetite, altered sense of taste
- Decreased amount of magnesium, potassium or calcium in the blood
- Decreased amount of protein albumin in blood (which carries substances such as hormones, medicines, and enzymes throughout your body)
- Headache, dizziness
- High blood pressure (hypertension)
- Bleeding
- Difficulty in speaking, hoarseness (dysphonia), cough and shortness of breath
- Stomach upset, including diarrhoea, nausea, vomiting, constipation, indigestion and abdominal pain
- Redness, swelling or pain in the mouth or throat (stomatitis)
- Skin rash sometimes with blisters, itching, pain of the hands or soles of the feet, rash
- Pain in the arms, hands, legs or feet, pain in joints
- Feeling tired or weak, inflammation of the oral and gastrointestinal mucosa, swelling in your legs and arms
- Weight loss
- Abnormal liver function tests (increased amounts of the liver enzymes aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase)

Cabozantinib can affect the way some other medicines work. Also, some medicines can affect the way Cabozantinib works. In particular these could include:

- Medicines that treat fungal infections, such as itraconazole, ketoconazole and posaconazole
- Medicines used to treat bacterial infections (antibiotics) such as erythromycin, clarithromycin, and rifampicin
- Allergy medicines such as fexofenadine
- Medicines to treat angina pectoris (chest pain owing to inadequate supply to the heart) such as ranolazine
- Medicines used to treat epilepsy or fits such as phenytoin, carbamazepine, and phenobarbital
- Herbal preparations containing St. John's Wort (*Hypericum perforatum*), sometimes used for treating depression or depression-related conditions such as anxiety
- Medicines used to thin the blood, such as warfarin and dabigatran etexilate
- Medicines to treat high blood pressure or other heart conditions, such as aliskiren, ambrisentan, digoxin, talinolol, and tolvaptan
- Medicines for diabetes, such as saxagliptin and sitagliptin
- Medicines used to treat gout, such as colchicine
- Medicines used to treat HIV or AIDS, such as efavirenz, ritonavir, maraviroc and emtricitabine
- Medicines used to prevent transplant rejection (ciclosporin) and ciclosporin-based regimens in rheumatoid arthritis and psoriasis

Information on other potential side effects is available in the Patient Information Leaflet.³⁰

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Response:

Cabozantinib offers several benefits for patients, caregivers, and communities. It effectively delays disease progression in NETs, linking to longer survival and better quality of life.²⁴ Patients maintain their daily activities longer and experience fewer side effects. As an oral medication, it reduces frequent hospital visits, lessening the burden on caregivers. Compared to treatments like radiotherapy and chemotherapy, cabozantinib is potentially a less invasive alternative. It addresses an unmet need for patients whose tumours progress despite initial treatments, particularly for lung NETs. Additionally, it may reduce healthcare costs by minimising hospital stays and the need for multiple therapies.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:

While cabozantinib offers significant benefits, it has some drawbacks:

- **Side Effects:** Common issues include fatigue, hypertension, diarrhea, and nausea, which may impact daily life and require dose adjustments.
- **Serious Risks:** Some patients may experience severe adverse events like embolic events, hypertension, or liver toxicity, requiring close monitoring.
- **Ongoing Monitoring:** Regular check-ups and blood tests are needed to manage side effects, adding to the treatment burden.
- **Drug Interactions:** Cabozantinib interacts with several medications, complicating treatment for those with other conditions.
- **Administration Challenges:** While taken orally, some patients may struggle with swallowing or gastrointestinal side effects.

Despite these drawbacks, cabozantinib remains a valuable option for patients with progressive NETs who have limited alternatives.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Response:

Healthcare services need to get the best value from their limited budgets. To do this, they want to know whether a new medicine provides 'good value for money' compared to existing medicines. They will look at the costs of the new medicine and how the health of people with NETs is likely to improve if they take it. The pharmaceutical company that develops the medicines provides this information to healthcare teams using a health economic model. The pharmaceutical company uses the health economic model to perform an analysis, which compares the benefits and costs of the new treatment (cabozantinib) with the existing treatment or comparator (best supportive care).

As part of the NICE submission, a **cost-effectiveness analysis** (CEA) was conducted to demonstrate the value for money of introducing cabozantinib as a treatment option for NETs patients. An **incremental cost-effectiveness ratio** (ICER) is determined in the CEA, and NICE has predetermined ICER thresholds to assess whether a medicine is cost-effective. The upper bound of the NICE cost effectiveness threshold is £30,000 per quality adjusted life year (QALY). It was found that the ICER for cabozantinib in the treatment of NETs falls below the threshold that the NHS considers to be cost effective. However, it should be noted that these results are based on company-preferred assumptions.

How the Model Reflects NETs

The model used to assess cabozantinib is designed to reflect how the disease typically progresses in patients with advanced NETs. It includes three health states: progression-free (when the cancer is stable), progressed disease (when the cancer has worsened), and death. These states are common in cancer models and help capture the different ways patients experience the disease over time. By tracking how patients move between these states, the model can estimate the benefits of cabozantinib compared to best supportive care (BSC).

Modelling How Much Cabozantinib Improves Survival

To understand how much cabozantinib extends life, the model used data from the CABINET trial.²⁴ This trial included patients with pancreatic (pNET) and extra-pancreatic (epNET) NETs who had already received other treatments, making it representative of patients seen in NHS practice. The trial measured two important outcomes: progression-free survival (PFS) – how long patients lived without their cancer worsening – and overall survival (OS) – how long patients lived in total. These

are widely accepted as key indicators of treatment success in NETs. However, because the CABINET trial only followed patients for just under two years (around 23 months),²⁴ the model estimates what might happen over the course of a patient's lifetime. This long-term prediction introduces some uncertainty but is necessary to understand the full value of the treatment.

Modelling How Cabozantinib Improves Quality of Life

In addition to survival, the model assessed quality of life using a measure called QALYs (quality-adjusted life years), which combines how long people live with how well they feel. The quality of life (or utility) data were taken from patients in the CABINET trial²⁴ for those who had not yet experienced disease progression. For patients whose disease had progressed, a reduction in quality of life was applied based on findings from a published study (Swinburn et al., 2012).³² This approach reflects what is seen in practice and has been used in previous NICE appraisals of other NET treatments such as everolimus, sunitinib, and PRRT.^{21, 22}

Modelling the Costs of Treatment

The model includes all the main costs that the NHS would expect to cover when treating patients with cabozantinib.³⁴ These include the cost of the medicine itself and how it is administered, as well as the costs of starting and monitoring treatment. It also accounts for the cost of managing side effects, using any additional supportive treatments, and providing care after disease progression or at the end of life. This comprehensive approach ensures that all relevant financial implications are captured in the model.³⁵

What the Results Showed

The analysis found that cabozantinib improves both survival and quality of life compared to best supportive care. Although the treatment is more expensive than BSC, the analysis aimed to determine whether the extra benefits it provides make it a cost-effective use of NHS resources. Specifically, the model showed that cabozantinib had an incremental cost-effectiveness ratio (ICER) of £24,815 per QALY for pNETs, which is below NICE's standard threshold of £30,000. For epNETs, the ICER was £15,419 per QALY, and dropped further to £12,849 when a severity modifier was applied. These results suggest that the treatment offers good value for money, especially for people with epNETs. These results are based on company-preferred assumptions, which will be considered by the NICE committee during this appraisal.

What's Still Uncertain

Like all models, this one includes some uncertainties. The data used in the model was sourced directly from the CABINET trial, with inputs corroborated by clinical experts to ensure the plausibility of predicting long-term benefits and outcomes of cabozantinib. In the CABINET trial, some patients who were originally on placebo later switched to cabozantinib, which may have affected the results. There are also limitations in how well the utility values used in the model represent the full patient experience, especially after disease progression.^{24, 33}

Because the trial data only covers a relatively short time, the model had to estimate long-term survival and quality of life, which can be difficult to predict accurately. To address these uncertainties, the company tested a range of alternative assumptions and scenarios, and sought validation from clinical experts to ensure that the model remained realistic and credible. The CEA of cabozantinib applies the model structure and key features from the NICE appraisal of everolimus, sunitinib, and PRRT, which have been accepted, thereby bolstering the model's validity.^{21, 22} Ipsen has incorporated additional clinical validation from current healthcare practitioners.

Areas of uncertainty within the CEA arise from the crossover in the CABINET trial where patients transitioned from the placebo arm to the treatment arm, the limitations of the utility values applied, and the inherent limitations in the extrapolation of the survival data. These uncertainties

can introduce challenges in accurately estimating treatment efficacy and cost-effectiveness. Emphasising clinical expert validation and alternative assumptions reinforces the robustness of the model.

Disease Severity

Disease severity can be measured as the future health that would be lost by people with NETs, compared with someone who does not have NETs. Benefits measured in terms of QALYs are valued more highly for severe diseases, and the epNET subgroup was deemed to meet NICE's threshold for a severe disease. When this severity modifier is applied, cabozantinib was associated with an ICER of £12,849 per QALY gained when compared with BSC.

Additional factors

Due to the structure of the CABINET trial, we have only analysed the two main subgroups of pancreatic and extra-pancreatic NETs. This approach was deemed appropriate as there is insufficient data to support further subgroups in the CEA. Highlighting the rationale for focusing on these subgroups provides clarity on the scope of the analysis.

*Utility: Health utility is a measure of the preference or value that an individual or society assigns to a particular health state, with 1 being perfect health and 0 being death.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Response:

The drug cabozantinib offers significant potential as a new treatment for NETs, which are often diagnosed late, leading to poorer outcomes. Current treatments for NETs, especially those in advanced stages, are limited and often their use is restricted to specific populations within NETs.^{21, 22}

Cabozantinib aims to extend the time patients live without the disease getting worse (progression-free survival) and could potentially improve overall survival. It is designed to be more convenient and has a manageable safety profile compared to existing options like chemotherapy, which is known for its high toxicity and inconvenience.

For patients who have already tried other treatments and need additional options, cabozantinib offers a new, effective, and convenient choice, providing hope for better management of their condition. This new therapy represents an advancement in treating NETs and addresses critical unmet needs in this patient group.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Response:

Cabozantinib does not present any issues to the NICE's commitment of promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Response:

Key clinical trial (CABINET) information:

- Published clinical trial data available at:
<https://www.nejm.org/doi/10.1056/NEJMoa2403991>
- Further information about the clinical trial available at:
<https://clinicaltrials.gov/study/NCT03375320>

Background information about neuroendocrine cancer:

- NHS information: <https://www.nhs.uk/conditions/neuroendocrine-tumours/>
- Neuroendocrine Cancer UK: <https://www.pbcfoundation.org.uk/what-is-pbc/about-pbc/>

Link to the NICE appraisal: <https://www.nice.org.uk/guidance/indevelopment/gid-ta11613>

Further information on NICE and the role of patients:

- Public Involvement at NICE [Public involvement](#) | [NICE and the public](#) | [NICE Communities](#) | [About](#) | [NICE](#)
- NICE's guides and templates for patient involvement in HTAs [Guides to developing our guidance](#) | [Help us develop guidance](#) | [Support for voluntary and community sector \(VCS\) organisations](#) | [Public involvement](#) | [NICE and the public](#) | [NICE Communities](#) | [About](#) | [NICE](#)
- EUPATI guidance on patient involvement in NICE: <https://www.eupati.eu/guidance-patient-involvement/>

- EFPIA – Working together with patient groups:
<https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative. <https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe:
http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Response:

Abbreviations:

- AE – Adverse Event
- ALP – Alkaline Phosphatase
- BSC – Best Supportive Care
- CABINET – Clinical trial titled "Testing Cabozantinib in Patients With Advanced Pancreatic Neuroendocrine and Carcinoid Tumors"
- CAPTEM – Capecitabine and Temozolomide (a chemotherapy drug combination)
- CEA – Cost-Effectiveness Analysis
- CT – Computed Tomography
- EQ-5D – EuroQoL 5-Dimension Questionnaire (used to measure quality of life)
- epNET – Extra-Pancreatic Neuroendocrine Tumour
- FDA – Food and Drug Administration (US regulatory agency)
- FOLFOX – Folinic Acid, Fluorouracil, and Oxaliplatin (a chemotherapy drug combination)
- G – Grade (used to describe how abnormal tumour cells look under a microscope)
- GEP – Gastroenteropancreatic
- GI – Gastrointestinal
- HRQoL – Health-Related Quality of Life
- HTA – Health Technology Assessment
- HTAi PCIG – Health Technology Assessment International – Patient and Citizens Involvement Group
- ICER – Incremental Cost-Effectiveness Ratio
- IJTAHC – International Journal of Technology Assessment in Health Care
- Lu-177 – Lutetium-177 (radioisotope used in radiotherapy)
- MHRA – Medicines and Healthcare Products Regulatory Agency (UK regulator)
- mTOR – Mammalian Target of Rapamycin (a protein involved in cancer cell growth)
- NET – Neuroendocrine Tumour
- NETs – Neuroendocrine Tumours
- NHS – National Health Service (UK)
- NICE – National Institute for Health and Care Excellence (UK)
- NCUK – Neuroendocrine Cancer UK
- OS – Overall Survival
- PBE – Patient-Based Evidence

- PFS – Progression-Free Survival
- PPI – Patient Preference Information
- pNET – Pancreatic Neuroendocrine Tumour
- pNETs – Pancreatic Neuroendocrine Tumours
- PRRT – Peptide Receptor Radionuclide Therapy
- PRO – Patient-Reported Outcomes
- QALY – Quality-Adjusted Life Year
- QoL – Quality of Life
- RCT – Randomised Controlled Trial
- SIP – Summary of Information for Patients
- SSA – Somatostatin Analogue
- SSTR – Somatostatin Receptor
- STZ – Streptozocin (a type of chemotherapy drug)
- TA – Technology Appraisal
- TKI – Tyrosine Kinase Inhibitor
- UKINETS – UK and Ireland Neuroendocrine Tumour Society

Definitions:

- **Adverse effects** – Unwanted or harmful effects that may happen after taking a medicine or undergoing treatment. These range from mild (like fatigue or nausea) to severe (like organ damage or bleeding).
- **ALP (Alkaline Phosphatase)** – A type of enzyme found in your body. High levels can indicate problems with the liver, bones, or bile ducts.
- **Anticipated approval date** – The expected date a regulatory body (like the MHRA) will give formal permission for a medicine to be used.
- **Best supportive care** – Care given to improve the quality of life of patients who have serious illnesses. This includes managing symptoms but does not treat the disease itself.
- **Biomarker testing** – Tests done to find specific biological markers in blood or tissue that can help diagnose a disease or predict how a disease will respond to treatment.
- **Biopsy** – A medical procedure that involves taking a small piece of tissue from the body to be examined under a microscope for signs of disease.
- **Cabozantinib** – A type of cancer drug that blocks certain proteins involved in the growth of tumours and blood vessels that supply them. It is used to treat certain types of neuroendocrine tumours.
- **Capecitabine** – A chemotherapy drug taken by mouth, often used in combination with other drugs to treat cancers.
- **CEA (Cost-effectiveness analysis)** – A method used to compare the costs and health benefits of a treatment to see if it offers good value for money.
- **Chemotherapy** – A type of cancer treatment that uses drugs to kill cancer cells or stop them from growing. It can affect the whole body and cause side effects.
- **Clinical trial** – A study involving patients to test how well a new treatment works and how safe it is.
- **Comparator** – A treatment or placebo used as a point of comparison in clinical trials to evaluate the effects of a new medicine.
- **Disease progression** – When a disease gets worse or spreads in the body.
- **Dosing** – How much of a medicine a patient takes and how often they take it.
- **Double-blind** – A type of clinical trial where neither the participants nor the researchers know who is receiving the treatment or the placebo to avoid bias.

- **Drug interaction** – When one medicine affects how another medicine works. This can make one medicine stronger, weaker, or cause unexpected side effects. Doctors need to carefully check for interactions to keep treatments safe.
- **Endoscopic procedures** – Medical exams that use a flexible tube with a camera to look inside the body, often used to find and diagnose tumours.
- **Enzyme inhibitors** – Medicines that block certain enzymes in the body. Some cancer drugs, like cabozantinib, work this way to stop cancer cells from growing.
- **epNETs (Extra-pancreatic neuroendocrine tumours)** – A type of neuroendocrine tumour that starts outside of the pancreas, such as in the lungs or digestive system.
- **Everolimus** – A targeted cancer therapy that blocks certain signals in cancer cells to stop them from growing.
- **Exclusion criteria** – Factors that prevent a person from participating in a clinical trial.
- **First-line treatment** – The initial and often standard treatment given for a disease.
- **Functional tumours** – Tumours that produce hormones and cause symptoms due to excess hormone production.
- **Grading** – A way to describe how quickly cancer cells are likely to grow and spread. Grade 1 = slow-growing, Grade 3 = fast-growing.
- **Health economic model** – A tool used to compare the costs and benefits of different treatments. It helps decision-makers understand whether a new treatment is worth the money.
- **Histopathology** – The study of tissues under a microscope to look for signs of disease, especially cancer.
- **HRQoL (Health-related quality of life)** – A measure of how well someone feels in terms of physical, emotional, and social well-being while living with a health condition.
- **ICER (Incremental cost-effectiveness ratio)** – A calculation that shows whether a treatment gives good value by comparing how much it costs and how much it improves health.
- **Imaging scans** – Tests that take pictures of the inside of the body (e.g., CT scans, MRIs) to detect abnormalities like tumours.
- **Incidence** – The number of new cases of a disease diagnosed in a specific period.
- **Incremental cost-effectiveness ratio** – See ICER above.
- **Informed consent** – A process by which a patient voluntarily confirms their willingness to participate in a particular procedure or clinical trial, after being informed of all the potential risks and benefits.
- **Intervention** – The treatment or action taken to improve a health condition in a clinical trial.
- **Lanreotide** – A type of somatostatin analogue drug used to control symptoms and slow tumour growth in people with NETs.
- **Liver enzymes** – Substances in the liver that help break down drugs. Some medicines can raise or lower these enzyme levels, affecting how drugs are processed.
- **Locally advanced** – Describes cancer that has spread beyond the original site but not to distant parts of the body.
- **Lutetium oxodotreotide (177Lu-dotatate)** – A targeted cancer treatment that uses radioactive material to kill neuroendocrine tumour cells that have specific receptors.
- **Marketing authorisation** – Official approval granted by a regulatory body (like MHRA) allowing a medicine to be sold and prescribed for specific conditions.
- **Metastatic** – Cancer that has spread from where it started to other parts of the body.
- **Misdiagnosis** – When a patient is wrongly diagnosed with a condition they do not have, delaying appropriate treatment.
- **Monotherapy** – A treatment using a single drug rather than a combination of drugs.

- **Multi-centre trial** – A clinical trial conducted at more than one medical institution or clinic.
- **NETs (Neuroendocrine tumours)** – A rare type of cancer that affects neuroendocrine cells, which are found throughout the body and help regulate hormones.
- **NICE (National Institute for Health and Care Excellence)** – A public organisation in the UK that provides national guidance and advice to improve health and social care.
- **Non-functional** – A term for tumours that do not release hormones or do not cause symptoms related to hormone release.
- **Octreotide** – A somatostatin analogue used to reduce hormone-related symptoms and tumour progression in people with certain types of NETs.
- **Off-label use** – When a medicine is used in a way that is different from what it was officially approved for (e.g., different disease, age group, or dosage).
- **Opportunity cost** – In healthcare, this refers to what is given up when money is spent on one treatment instead of another. Choosing one option means the money can't be used elsewhere.
- **Oral administration** – Taking a medicine by mouth, usually as a pill or tablet.
- **Overall survival** – The length of time from either the date of diagnosis or the start of treatment that patients are still alive.
- **pNETs (Pancreatic neuroendocrine tumours)** – Neuroendocrine tumours that originate in the pancreas.
- **Patient-based evidence (PBE)** – Research that includes patients' experiences, preferences, and feedback to better understand how a condition and its treatments affect their lives.
- **PPI (Patient preference information)** – Research that shows what matters most to patients, such as avoiding side effects or choosing convenient treatment methods.
- **Pharmacodynamics** – The study of what a drug does to the body, including how it affects cells, organs, or overall health.
- **Pharmacokinetics** – How the body absorbs, distributes, breaks down, and gets rid of a drug.
- **Placebo** – A substance with no active ingredient, used as a control in clinical trials.
- **Population bioequivalence** – A statistical method to compare drug performance in a population, ensuring consistency across groups.
- **Poorly differentiated** – Cancer cells that look very abnormal and tend to grow and spread faster than well-differentiated cells.
- **Prevalence** – The total number of people who have a disease at a given time.
- **Primary tumour site** – The place in the body where cancer first started growing.
- **Progression-free survival (PFS)** – The length of time during and after treatment that the disease does not get worse.
- **Progressive disease** – A disease that is worsening or spreading despite treatment.
- **Progressive** – A term to describe cancer that is growing or spreading.
- **Protein binding** – How a drug attaches to proteins in the blood. Only unbound (free) drug can work in the body. This affects how strong or long-lasting a drug is.
- **QALY (Quality-adjusted life year)** – A way to measure the value of health outcomes by combining how long people live and how well they feel.
- **Qualitative** – Information or data described in words rather than numbers, often about people's experiences or feelings.
- **Quantitative** – Information or data that is measured and described in numbers.
- **Radiotherapy** – A cancer treatment that uses high-energy radiation to kill or damage cancer cells.

- **Randomised trial** – A study where participants are randomly assigned to different treatment groups to avoid bias.
- **Re-treatment** – Giving the same treatment again after it was previously used, which may not always be reimbursed or recommended.
- **Response rates** – The percentage of patients whose cancer shrinks or disappears after treatment.
- **Severity modifier** – A factor used in economic analysis that gives extra weight to treatments for more serious or life-threatening conditions.
- **Sunitinib** – A cancer drug that blocks the growth of blood vessels that feed tumours and stops cancer cells from growing.
- **Streptozocin (STZ)** – A chemotherapy drug that is used to treat certain types of pancreatic neuroendocrine tumours.
- **Staging** – A way of describing the size of a tumour and how far it has spread in the body.
- **Subgroup** – A smaller, defined group of patients within a clinical trial population, often sharing specific characteristics.
- **Systematic therapy** – Treatment that works throughout the whole body, such as pills or injections that affect all cancer cells, not just one area.
- **TA (Technology Appraisal)** – A formal process by which NICE assesses the clinical and cost-effectiveness of medicines.
- **Therapeutic window** – The range between the smallest dose of a medicine that works and the largest dose that is safe. It helps guide safe prescribing.
- **TKI (Tyrosine Kinase Inhibitor)** – A type of drug that blocks signals needed for tumours to grow.
- **Tolerability burden** – The difficulty or discomfort a patient experiences in managing side effects of a treatment.
- **Treatment pathway** – The step-by-step plan for how a patient is treated over time, including the order and types of treatments given.
- **Tumour grade** – A measure of how fast a tumour is likely to grow, based on how abnormal the cells look under a microscope.
- **Unmet need** – A medical condition for which there are limited or no effective treatment options available.
- **Unresectable** – A tumour that cannot be removed through surgery.
- **Utility** – A score that reflects the preference for a certain health state, where 1 = perfect health and 0 = death.
- **Value for money** – A judgment about whether the benefits of a treatment are worth its cost, often considered by healthcare systems like the NHS.
- **Well-differentiated tumour** – A tumour in which the cancer cells look more like normal cells and tend to grow and spread more slowly than poorly differentiated tumours.
- **Well-tolerated** – A term used when a medicine does not cause severe side effects and is generally easy for patients to take.
- **Xenobiotics** – Chemical substances not naturally produced by the body, like medicines. The body must process and eliminate these safely.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

Clarification questions

June 2025

File name	Version	Contains confidential information	Date
ID6474 cabozantinib (NETs) EAG clarification letter	2.0	Yes	04 June 2025

Section A: Clarification on effectiveness data

The EAG considers that the company's proposed positioning of cabozantinib as a second-line systemic treatment is not reflected by the population in the CABINET trial. Patients in the CABINET trial were heavily pre-treated, having exhausted all other active systemic treatment options, leaving BSC as the only remaining option. These patients were, therefore, at a later stage in the treatment pathway than patients who would be eligible for cabozantinib based on its full marketing authorisation (i.e. for patients with disease progression after at least one prior systemic therapy).

Comparators

A1. Priority. Based on feedback from the EAG's clinical experts, and the company's proposed positioning of cabozantinib (progression after at least one prior systemic therapy), the EAG considers that the choice of best supportive care (BSC) as the only comparator is an inadequate oversimplification of the treatment pathway.

The EAG considers that further comparators need to be included in the company's analysis, and considers that the relevant comparators for the majority of patients in each population are:

- The pNET population: Everolimus, sunitinib and PRRT, respectively;
 - The epNET population (without lung NETs): Everolimus, PRRT, and BSC respectively;
 - The epNET population (lung): Everolimus and BSC, respectively.
- a) Please estimate the treatment effectiveness for overall survival (OS), progression-free survival (PFS) and time to treatment discontinuation (where possible) between cabozantinib and its relevant comparators, listed in the bullet points above.

As an example, the EAG notes that TA449 and TA539 included different methods for indirect treatment comparisons to estimate the relative

effectiveness of relevant treatments. While the EAG appreciates that the number of previous systemic treatments received in RADIANT-3, RADIANT-4 and A6181111 might differ from those in the population anticipated to be eligible for cabozantinib, the CS for cabozantinib indicates that the number of previous systemic treatments received does not affect the relative treatment effect of cabozantinib for PFS (Figure 16). TA449 also provided subgroup analyses based on the number of prior systemic treatments in A6181111. This method would provide an analysis more closely aligned to the population proposed for cabozantinib. The EAG also notes that other trials reported in the CS which were excluded “on the basis that less than 70% of patients had received a relevant prior line of therapy” could also be relevant for this analysis.

If the company conducts an ITC relying on a relative treatment effect, please ensure that proportional hazards exist in the comparator trial. Please note that the EAG considers that PHs do not hold for PFS in the CABINET study. If proportional hazards do not hold, please use a method to estimate treatment effectiveness that does not rely on proportional hazards.

BSC is the only relevant comparator in this appraisal

The marketing authorisation for cabozantinib is for the treatment of [REDACTED]

[REDACTED] This does not represent a second-line systemic treatment, but third-line or later use after an SSA and at least one prior systemic therapy such as everolimus, sunitinib or peptide receptor radionuclide therapy (PRRT).

The marketing authorisation for cabozantinib is broad, and does not restrict by primary tumour site, grade, somatostatin receptor (SSTR) expression status and functional status, in line with the eligibility criteria for the CABINET trial. The company acknowledge that the patient population in the CABINET trial included heavily pre-treated patients, but is not appropriate to characterise these patients as “having exhausted all other active systemic treatment options”, given this was not a requirement of the trial eligibility criteria. Given the restriction of systemic therapies to specific subgroups, there may be circumstances where patients would be eligible for cabozantinib and where the only treatment option remaining at 3L is BSC. For example, in patients with lung NETs, the only systemic treatment that is reimbursed after SSAs is everolimus; given patients must have received at least one prior systemic therapy other than an SSA to be eligible for cabozantinib, cabozantinib would represent an option after progression on everolimus, where the only remaining option is BSC. The EAG have requested a comparison to everolimus in lung NETs, but there are no circumstances under which cabozantinib could be positioned as an

alternative to everolimus in this population. Similarly, in patients with functional gastrointestinal (GI) NETs, the only systemic treatment that is reimbursed after SSAs is PRRT; cabozantinib would represent an option after progression on PRRT, where the only remaining option is BSC. Furthermore, if patients are contraindicated to any existing systemic therapies, BSC may be the only remaining option in a 3L setting. Given the requirement for "*at least one*" prior systemic therapy in addition to an SSA, this population may include patients who have received only one prior systemic treatment (as described above), but does not reflect an exclusively 3L positioning, and feedback from clinical experts suggested that the number of prior systemic treatments before considering treatment with cabozantinib would differ depending on individual patient characteristics due to the highly individualised treatment pathway. Given the marketing authorisation of cabozantinib, the restricted use of other systemic therapies, and the evidence from the CABINET trial, five clinical experts unanimously considered BSC to be the appropriate comparator for the broad population expected to be treated with cabozantinib in UK clinical practice.¹

Therefore, the only relevant comparator in the current appraisal is BSC.

The company conducted a comprehensive feasibility assessment for an ITC versus other systemic therapies which indicated a robust ITC was not feasible

No relevant randomised controlled trials (RCTs) investigating other systemic therapy were identified in the SLR (with the exception of two small studies based in China investigating surufatinib versus everolimus or sunitinib); RCTs investigating other systemic treatments used in UK clinical practice were excluded on the basis that less than 70% of patients had received a relevant prior line of therapy, and thus the enrolled population could not be considered comparable to CABINET. However, for completeness and to address the EAG's request, the company explored the feasibility of conducting an indirect treatment comparison (ITC) versus sunitinib, ¹⁷⁷Lu-dotatate and everolimus.

The feasibility assessment, as presented in the Appendix, compared CABINET to pivotal studies of other systemic therapies: A6181111, NETTER-1, NETTER-2, RADIANT-3 and RADIANT-4.²⁻⁷ Treatment effect modifiers (TEMs) were identified from published literature, clinical expert opinion and consideration of subgroup analyses from the CABINET trial. There was varying availability of reported outcomes for the pivotal trials, including OS, PFS and time to treatment discontinuation (TTD). Median OS was not reached in some of the pivotal trials which would restrict comparisons, and comparative analyses of TTD were considered infeasible due to lack of reporting for other studies. In the epNET cohort, heterogeneity was identified between the trials due to differences in patient populations and trial designs, such as uncertainties in prior therapy lines, variations in tumour grade and sex, and discrepancies in concurrent SSA usage, which would not be feasible to adjust for within potential analyses. Heterogeneity was also identified in the pNET cohort, where A6181111 had limited overlap with CABINET in prior therapies and missing tumour grade data, and subgroup baseline data were insufficient for matching; RADIANT-3 lacked key baseline characteristics such as tumour grade, and NETTER-2 comparisons were constrained by differences in lines of therapy, reducing the robustness of potential indirect comparisons. The results of the feasibility assessment suggest that no robust ITC can be conducted to compare the efficacy of cabozantinib with other systemic therapies.

As noted above, the company considers that BSC is the primary comparator for this appraisal and that everolimus, sunitinib and PRRT do not reflect relevant comparators. However, despite this, comparisons with other systemic treatments were explored for completeness and an indirect treatment comparison was ultimately not considered feasible.

b) Please conduct a comparison of the safety profile of cabozantinib vs the relevant comparator listed in the bullet points above.

As noted in the company response to A1, BSC is the appropriate comparator for cabozantinib. Furthermore, it was not feasible to perform a robust ITC between cabozantinib and the other systemic therapies listed above. However, whilst sunitinib, everolimus or PRRT do not represent relevant comparators, for completeness, a naïve comparison of the adverse events (AEs) reported in the CABINET trial for cabozantinib and key pivotal trials for other systemic treatments has been presented below; any comparisons should be interpreted with caution given the considerable differences in trial design and patient populations outlined above.

Whilst the CABINET safety results showed that cabozantinib is associated with a predictable and manageable safety profile with no notable safety findings across trial patients in both the pNET cohort and epNET cohort, there are differences in safety profiles across systemic treatments; this is one of the factors that influences individualised treatment decisions in clinical practice.

Table 1. Overall frequency of Grade 3/4 TRAEs in greater than 5% of pNET patients

Adverse event, n (%)	Cabozantinib (n=63) CABINET ⁸	Placebo (n=31) CABINET ⁸	Sunitinib (n=83) A6181111 ^{2,a}	Everolimus (n=204) RADIANT-4 ⁶	PRRT (Lu-177) (n=111) NETTER-1 ^{9, a}
Mean follow-up (months)	25.68	27.62	11.40	17.00	14.00
Fatigue	7 (11.11%)	1 (3.23%)	4 (4.82%)	17 (8.33%)	2 (1.80%)
Diarrhoea	4 (6.35%)	0 (0.00%)	4 (4.82%)	7 (3.43%)	3 (2.70%)
Hypertension	12 (19.05%)	3 (9.68%)	8 (9.64%)	0 (0.00%)	0 (0.00%)
Stomatitis	4 (6.35%)	0 (0.00%)	3 (3.61%)	14 (6.86%)	0 (0.00%)
PPE syndrome	6 (9.52%)	0 (0.00%)	5 (6.02%)	0 (0.00%)	0 (0.00%)
Nausea	5 (7.94%)	1 (3.23%)	1 (1.20%)	5 (2.45%)	4 (3.60%)
Vomiting	4 (6.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	8 (7.21%)
Blood result abnormality	0 (0.00%)	0 (0.00%)	10 (12.05%)	0 (0.00%)	11 (9.91%)
Embolism	4 (6.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Small Intestinal obstruction	0 (0.00%)	2 (6.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hyperglycaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	11 (5.39%)	0 (0.00%)

^aTRAEs were not reported in A6181111 and NETTER-1 so drug-related AEs are presented here.

Abbreviations: BSC: best supportive care; Lu-177: Lutetium-177-DOTATATE; PPE: palmar-plantar erythrodysesthesia; pNET: pancreatic neuroendocrine tumour; PRRT: peptide receptor radionuclide therapy; SSA: somatostatin analogue; TRAE: treatment-related adverse events.

Source: Ipsen Data on File. CABINET Trial CSR (Table 52). 21 May 2024. AEs are reported for the most severe event only per patient;⁸ Raymond *et al.* (2011);² Yao *et al.* (2016);⁶ Strosberg *et al.* (2017).⁹

Table 2. Overall frequency of Grade 3/4 TRAEs in greater than 5% of epNET patients

Adverse event, n (%)	Cabozantinib (n=132) CABINET ⁸	Placebo (n=67) CABINET ⁸	Everolimus (n=204) RADIANT-4 ⁶	PRRT (Lu-177) (n=111) NETTER-1 ^{9,a}
Mean follow-up (months)	24.40	24.21	21.00	14.00
Fatigue	17 (12.88%)	5 (7.46%)	7 (3.47%)	2 (1.80%)
Diarrhoea	14 (10.61%)	3 (4.48%)	15 (7.43%)	3 (2.70%)
Hypertension	27 (20.45%)	2 (2.99%)	0 (0.00%)	0 (0.00%)

Stomatitis	0 (0.00%)	0 (0.00%)	18 (8.91%)	0 (0.00%)
Vomiting	0 (0.00%)	0 (0.00%)	0 (0.00%)	8 (7.21%)
Blood result abnormality	5 (3.79%)	0 (0.00%)	0 (0.00%)	10 (9.01%)
Infections	0 (0.00%)	0 (0.00%)	14 (6.93%)	0 (0.00%)

^aTRAEs were not reported in NETTER-1 so all drug related AEs are presented here.

Abbreviations: AE: adverse event; BSC: best supportive care; epNET: extra-pancreatic neuroendocrine tumour; Lu-177: Lutetium-177-DOTATATE; PRRT: peptide receptor radionuclide therapy; TRAE: treatment-related adverse events; SSA: somatostatin analogue.

Source: Ipsen Data on File. CABINET Trial CSR (Table 52). 21 May 2024. AEs are reported for the most severe event only per patient;⁸ Yao *et al.* (2016);⁶ Strosberg *et al.* (2017).⁹

Methods

A2. Table 14.1.4.1.b.2 provides the stratification factors for the epNET carcinoid tumour cohort based on concurrent SSA use and primary tumour site. The EAG notes that the percentage of patients in each group differs between the use of the OPEN enrolment form and EDC. Please:

- a) clarify whether the OPEN enrolment form or the EDC were used for stratification in the trial;

The company can confirm that the Oncology Patient Enrollment Network (OPEN) enrolment form was used for stratification within the CABINET trial.

- b) provide an explanation for the choice of stratification method.

Efficacy analyses were performed primarily based on the disease cohort and stratification factors at randomisation per the OPEN registration system. Sensitivity analyses were performed using the actual disease cohort and stratification factors collected per electronic data capture (EDC).

Data related to stratification factors and patient eligibility was captured in the OPEN registration dataset only and not in case report forms (CRFs)/electronic data capture (EDC).

Randomisation stratification factors were generally balanced between treatment arms. Stratification factors were entered into the OPEN registration system prior to randomisation. For the epNET population, using EDC data as reference, differences were noted with the OPEN system with a greater percentage stratified as using a concurrent SSA (68% cabozantinib and 70% placebo per the OPEN registration system vs 54% cabozantinib and 63% placebo per EDC) and midgut/unknown as the primary site (55% in the cabozantinib arm and 54% in the placebo arm per the OPEN system vs 48% cabozantinib and 43% placebo per EDC).

Of note, although differences in cohort allocation and stratification existed between the OPEN registration system and EDC, sensitivity analysis using disease allocation and stratification factors per EDC (PFS-EP4) showed consistent results with the primary analysis.

A3. Table 12 of the CS states that “other than for partial dates, missing data was not imputed and data was treated as missing”. For each relevant outcome, please provide details on the number (and percentage) of observations missing in:

- a) the cabozantinib arm for the pNET subgroup;
- b) the placebo arm for the pNET subgroup;
- c) the cabozantinib arm for the epNET subgroup;
- d) the placebo arm for the epNET subgroup.

Available data on missing observations in CABINET for PFS and ORR endpoints is summarised in Table 3. Completion rates for the HRQoL endpoints in the CABINET trial are summarised in Appendix J.4 of the company submission.

Table 3: Missing data in CABINET (PFS and ORR)

	pNET cohort		epNET cohort	
	Cabozantinib (n=64)	Placebo (n=31)	Cabozantinib (n=134)	Placebo (n=69)
PFS censors due to missing assessments				
2 or more missing ATA prior to event	1 (1.6%)	0	1 (0.7%)	5 (7.2%)
No post baseline ATA	4 (6.3%)	1 (3.2%)	15 (11%)	2 (2.9%)
ORR missing data				
Missing	8 (13%)	2 (6.5%)	24 (18%)	9 (13%)
No qualifying post-baseline assessments on or before PFS censoring or event date ^a	8 (13%)	2 (6.5%)	23 (17%)	6 (8.7%)
SD or non-CR/non-PD not meeting minimum criteria (>42 days) from randomisation	0	0	2 (1.5%)	1 (1.4%)

^aNo qualifying post-baseline assessments on or before PFS censoring or event date included the following: In the cabozantinib arm: first scheduled imaging timepoint after the clinical cutoff date (7 patients), adverse event (6 patients), death (4 patients), withdrawal (3 patients), no study treatment given (2 patients), and other complicating disease (1 patients).

Abbreviations: ATA: adequate tumour assessment; CR: complete response; epNET: extra-pancreatic neuroendocrine tumour; ORR: objective response rate; PFS: progression free survival; PD: progressive disease; SD: stable disease; pNET: pancreatic neuroendocrine tumour.

Source: Ipsen Data on File. CABINET Trial CSR (Table 18, Table 23, Table 35, Table 40). 21 May 2024.⁸

A4. Appendix J.3 provides the results of sensitivity analyses for patients who were misallocated to the incorrect pNET or epNET cohort (ITT population). Table 35 in Appendix J reports the results of the sensitivity analyses for PFS. Please provide the same information for overall survival.

There were some differences in cohort allocation and stratification between the OPEN registration system used for cohort allocation and stratification and electronic data capture (EDC). In the CABINET trial, three patients in the pNET cohort (two in the cabozantinib arm and one in the placebo arm) and seven patients in the epNET cohort (four in the cabozantinib arm and three in the placebo arm) were misallocated to the alternative cohort.⁸

An analysis to adjust for this misallocation was conducted post-hoc given there was no pre-specified analysis by EDC for OS in the CABINET clinical study report (CSR). The misallocation was well balanced across treatment arms with small numbers of patients allocated to the wrong cohorts. Therefore, the sensitivity analysis was consistent with the primary analysis, as presented in Table 4. This provided a stratified HR for OS of 0.95 and ■■■ observed for cabozantinib versus placebo in pNETs across the primary and sensitivity analyses, respectively. For epNETs the stratified HRs for OS were ■■■■.

OS results should be interpreted with caution, given CABINET was not powered to test for statistical significance in OS, and due to the crossover trial design of CABINET and the high rate of subsequent therapy usage in both trial arms, OS was likely confounded (crossover and subsequent therapy usage could cause a potential inflation of OS in the placebo arm).

Table 4: Sensitivity analyses of OS for disease allocation in pNET cohort and epNET cohort (ITT population)

Cohort	Analysis	Treatment arm	Events, n (%)	Stratified HR (95% CI) ^a
pNETs	Primary analysis	Cabozantinib: (N=64) Placebo: (N=31)	Cabozantinib: 20 (31%) Placebo: 12 (39%)	0.95 (0.45, 2.00)
	Corrected cohort	██████████ ██████████	██████████ ██████████	██████████ ██████████
epNETs	Primary analysis	Cabozantinib: (N=134); Placebo: (N=69)	Cabozantinib: 77 (57%) Placebo: 20 (29%)	0.86 (0.56, 1.31)
	Corrected cohort	██████████ ██████████	██████████ ██████████	██████████ ██████████

^a Hazard ratios were calculated from the Cox proportional hazards model.

Abbreviations: CI: confidence interval; ITT: intention-to-treat; epNET: extra-pancreatic neuroendocrine tumour; HR: hazard ratio; OS: overall survival; pNET: pancreatic neuroendocrine tumour.

Population

A5. Priority. Figure 4 in the CS states that “The NHS does not reimburse re-treatment with the same treatment class”. Table 10 of the CS reports that 28% of patients in the cabozantinib arm of the pNET cohort had treatment with a prior anti-VEGF TKI (sunitinib), which is in the same treatment class as cabozantinib. Randomisation in the pNET cohort was also stratified for prior sunitinib use.

- a) Please confirm if treatment with cabozantinib would not be permitted in the NHS for patients who have had prior sunitinib;**

Cabozantinib would be permitted for use in patients in the NHS who had received prior sunitinib. This was validated by UK clinical experts in NETs that suggested the proposed treatment pathway including cabozantinib for the specified population was aligned with expected clinical practice. It was noted that cabozantinib would provide a valuable treatment option for patients who have progressed through multiple prior lines of therapy, none of which noted that prior sunitinib would not be appropriate.

It should be noted that NHS reimbursement of re-treatment with the same treatment class is specific to each therapy. Although under the current criteria for the treatment of NETs, NHS England does not reimburse treatment with sunitinib if a prior treatment has been received of the same treatment class.¹⁰ However, the reimbursement recommendation (TA449) for the use of sunitinib in NETs does not specify this.¹¹ Given that the anticipated marketing authorisation of cabozantinib does not restrict on the basis of prior sunitinib (the same treatment class), cabozantinib should be permitted following sunitinib.¹²

We note that during the EAG during the clarification call with the Company on 21 May 2025, NHS England (██) confirmed that cabozantinib could be prescribed after sunitinib.

b) If patients cannot be retreated with a TKI in the NHS, please provide the following subgroup analysis of the pNET cohort of the CABINET trial:

- i) For patients who had prior treatment with sunitinib, please provide:**
 - 1) Kaplan-Meier (KM) data, including curves and median survival estimates for OS; PFS; and time to treatment discontinuation (TTD);**
 - 2) Hazard ratios (HRs) with 95% confidence intervals for OS and PFS, and respective p-values.**
 - 3) Baseline characteristics for these patients.**
- ii) For patients who did not have prior treatment with sunitinib, please provide:**
 - 1) Kaplan-Meier (KM) data, including curves and median survival estimates for OS; PFS; and time to treatment discontinuation (TTD);**
 - 2) Hazard ratios (HRs) with 95% confidence intervals for OS and PFS, and respective p-values.**
 - 3) Baseline characteristics for these patients.**

N/A – no response required.

A6. Priority (also see B1 in the cost-effectiveness section). The EAG's clinical experts indicated that the prognosis and treatment for lung NETs differs significantly from the other epNETs in the midgut subgroup. Where data is available, please provide a separate analysis for patients with lung NETs for the following outcomes:

- Kaplan-Meier (KM) data, including curves and median survival estimates for OS; PFS; and time to treatment discontinuation (TTD);**
- Hazard ratios (HRs) with 95% confidence intervals for OS and PFS, and respective p-values.**
- Baseline characteristics for these patients (as provided for the full population in Tables 9 and 10 of the CS).**

As reported in Section 2.8 of the company submission, a post-hoc analysis of the epNET cohort was conducted to determine PFS by primary tumour site (GI NETs, lung [including thymic] NETs

and other/unknown NETs), with details presented in Appendix C.

Randomisation was not stratified according to this classification of subgroups by primary tumour type (instead, randomisation was stratified by midgut GI/unknown versus non-midgut GI/lung/other); results of these subgroup analyses are likely to be subject to bias due to imbalances in patient characteristics across treatment arms and associated confounding. The post-hoc subgroups also have very small sample sizes and should therefore be interpreted with considerable caution. Furthermore, whilst remaining limited by small sample sizes, pre-specified subgroup analysis by primary tumour location in the stratified subgroups (where randomisation is maintained) of midgut GI/unknown versus non-midgut GI/lung/other demonstrated a broadly consistent PFS benefit, with HRs of 0.33 (95% CIs: 0.19, 0.57) and 0.57 (95% CIs: 0.24, 1.29), respectively, as shown in Section 2.8 of the company submission. Given the limitations of the post-hoc subgroup analyses, the full epNETs cohort provides the most robust data to inform the comparative efficacy of cabozantinib versus BSC in all epNETs patients.

However, to address the EAG's request, subgroup analysis results for PFS, OS and TTD results are presented in full below. Stratified randomisation was done at the cohort level for pNETs and epNETs, where stratified hazard ratios were a pre-specific outcome measure. However, for these post-hoc analyses where randomisation is not maintained, unstratified hazard ratios have been reported.

Baseline characteristics

The subgroups were based on very small sample sizes, with differences in baseline characteristics observed across treatment arms, as outlined in Table 5. A greater proportion of White patients were allocated to cabozantinib and a greater proportion of Black and Hispanic patients to placebo compared with cabozantinib. Additionally, patients in the cabozantinib arm had a shorter mean disease duration from diagnosis prior to randomisation, a higher proportion of Grade 1 tumours compared with patients in the placebo arm, and lower proportion of patients with functional disease.

Table 5: Patient disease and treatment characteristics by treatment arm in epNET lung subgroup

Patient characteristic		Treatment arm	
		Cabozantinib	Placebo
Sample Size		33	16
Age (in years)		██████	██████
Sex	Female	████	████
	Male	████	████
Race	White	████	████
	Asian	████	████
	Black or African American	████	████
	Not reported	████	████
	Unknown	████	████
Ethnicity	Hispanic/ Latino	████	████
	Not Hispanic/ Latino	████	████
	Not Reported	████	████
	Unknown	████	████

ECOG status	0		
	1		
	2		
Number of prior therapies	1		
	2		
	≥3		
Con. SSA use	Yes		
	No		
Disease duration to randomisation (mean, months)			
Tumour grade	Grade 1		
	Grade 2		
	Grade 3		
	Unknown		
Histological differentiation	Well differentiated		
	Moderately differentiated		
	Not specified		
Carcinoid tumour histological type	pNET		
	Carcinoid tumour		
	Atypical carcinoid tumour		
	Not specified		
Functional status	Functional		
	Non-functional		
	Unknown		

Abbreviations: BMI: body mass index; Con.: concurrent; ECOG: Eastern Co-operative Oncology Group; epNET: extra-pancreatic neuroendocrine tumours; GI: gastrointestinal; pNET : pancreatic neuroendocrine tumours; SSA: somatostatin analogue.

Progression-free survival

The post-hoc PFS HR and median PFS for cabozantinib versus placebo for the lung subgroup are presented in Table 6, respectively. The KM plot by treatment arm is provided in Figure 1. Given stratified randomisation was conducted at the cohort level and not with subgroups by primary tumour subtype, unstratified HRs have been presented for all outcomes.

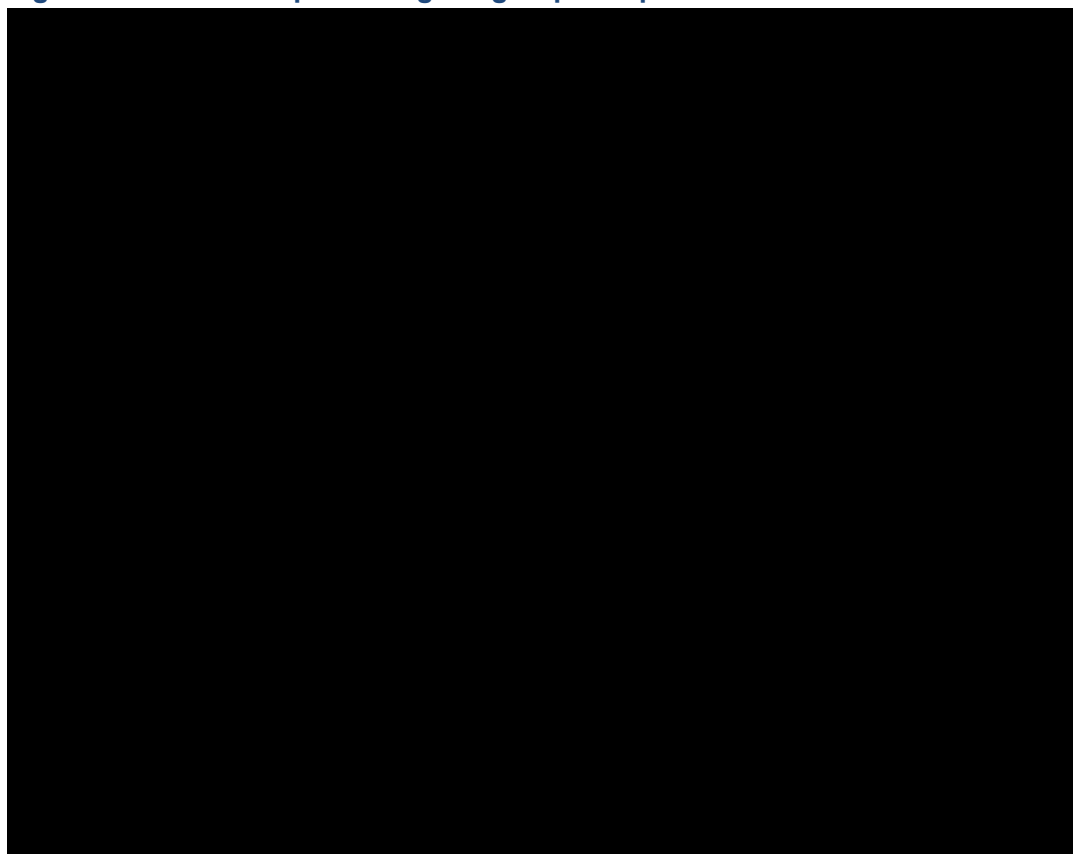
Table 6: PFS in the epNET lung subgroup: ITT population

Analysis	Cabozantinib N/Evt/Med	Placebo N/Evt/Med	Unstratified HR (95% CI) Cabozantinib vs Placebo
ITT			

DCO: 24th August 2023.

Abbreviations: CI: confidence interval; epNET: extra-pancreatic neuroendocrine tumour; Evt: number of patients with events; HR: hazard ratio; ITT: intent-to-treat; Med: median; N: number of patients; PFS: progression-free survival.

Figure 1: PFS in the epNET lung subgroup: KM plot



Abbreviations: epNET, extra-pancreatic neuroendocrine tumour; KM, Kaplan-Meier; PFS: progression-free survival.

Overall survival

The IPCW-adjusted HRs of OS and median OS for cabozantinib versus placebo are presented in Table 7 and Table 8, respectively. An IPCW-adjusted KM plot of OS by treatment arm only (i.e., not accounting for baseline covariates) is provided in Figure 2.

Table 7: IPCW-adjusted OS in the epNET lung subgroup: unstratified HRs

Analysis	Unstratified HR (95% CI) Cabozantinib vs Placebo
ITT	
IPCW (untruncated weights)	
IPCW (truncated weights)	

IPCW HRs are adjusted HRs from a Cox model which includes all baseline prognostic factors used as part of the weight estimation procedure as covariates. Cut-off for weight truncation was the most extreme percentile of observations ($p < 0.01$).

Abbreviations: CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; IPCW, inverse probability of censoring weights; ITT, intention to treat.

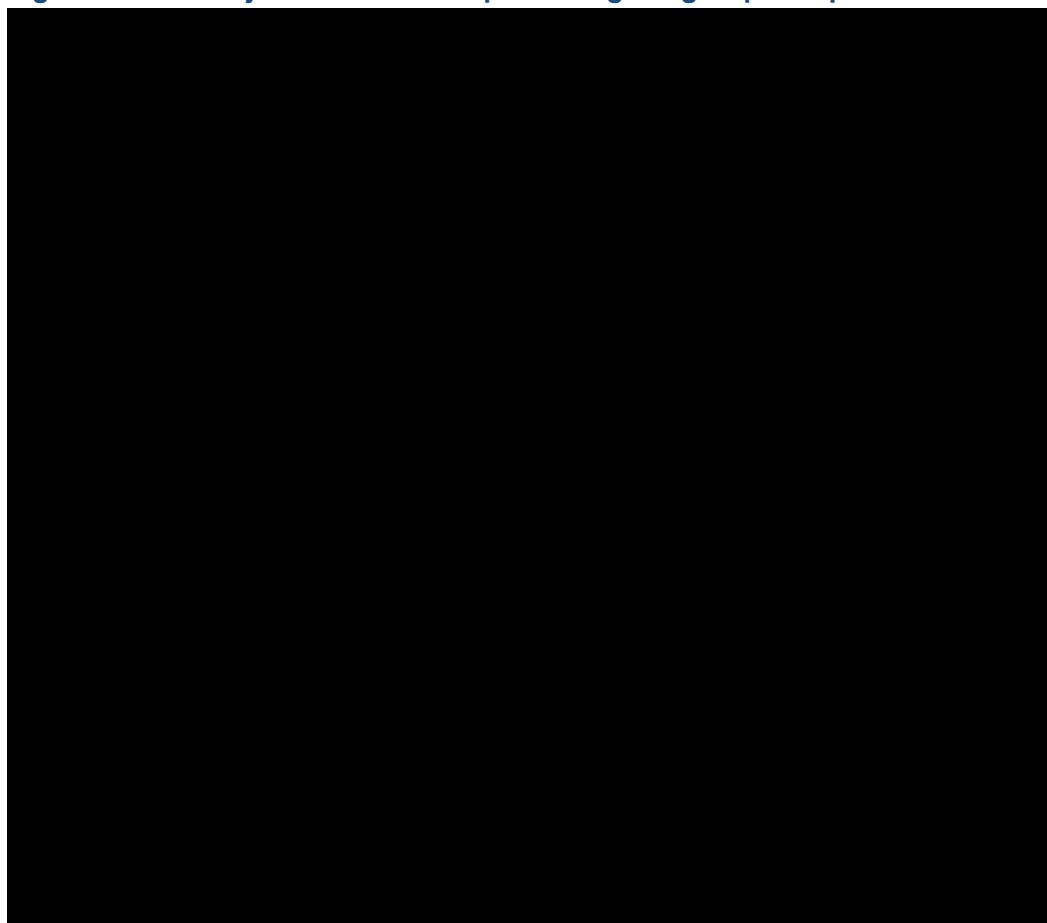
Table 8: Median OS in the epNET lung subgroup: ITT population

Analysis	Cabozantinib	Placebo
Median survival (months)		

DCO: 24th August 2023.

Abbreviations: epNET: extra-pancreatic neuroendocrine tumour; ITT: intent-to-treat; OS: overall survival.

Figure 2. IPCW-adjusted OS in the epNET lung subgroup: KM plot



Patients have been censored upon switching from placebo to cabozantinib, and placebo patients who have not switched are re-weighted based on stabilised IPCW weights. Note that the IPCW-adjusted KM curves, unlike the adjusted HRs obtained from the weighted outcomes models, do not account for variation in baseline covariates. Thus, they do not align with the adjusted HRs and should not be interpreted in conjunction with them. Rather, these plots should be inspected in conjunction with the ITT KM curves to illustrate the impact of artificial censoring and re-weighting without adjusting for baseline covariates in the estimation of treatment differences.

Abbreviations: epNET, extra-pancreatic neuroendocrine tumour; IPCW, inverse probability of censoring weights; KM, Kaplan-Meier; OS: overall survival.

TTD

The HRs of TTD and median TTD for cabozantinib versus placebo are presented in Table 9. A KM plot of TTD is provided in Figure 3.

Table 9: TTD in the epNET lung subgroup: unstratified HRs

Analysis	Unstratified HR (95% CI) Cabozantinib vs Placebo
ITT	

IPCW HRs are adjusted HRs from a Cox model which includes all baseline prognostic factors used as part of the weight estimation procedure as covariates. Cut-off for weight truncation was the most extreme percentile of observations ($p < 0.01$).

Abbreviations: CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; IPCW, inverse probability of censoring weights; ITT, intention to treat; TTD: time to treatment discontinuation.

Table 10: Median TTD in the epNET lung subgroup: ITT population

Analysis	Cabozantinib	Placebo
Median (months)		

DCO: 24th August 2023.

Abbreviations: epNET: extra-pancreatic neuroendocrine tumour; ITT: intent-to-treat; TTD: time to treatment discontinuation.

Figure 3: TTD in the epNET lung subgroup: KM plot



Abbreviations: epNET, extra-pancreatic neuroendocrine tumour; KM, Kaplan-Meier; TTD, time to treatment discontinuation.

A7. Priority. The EAG notes that the primary tumour site in the epNET population was classified as ‘Other’ for 18% of patients in the cabozantinib arm and 16% in the placebo arm. Please provide a breakdown of the tumour locations, and the percentage of patients for each location for:

- a) the cabozantinib arm;
- b) the placebo arm.

The CABINET trial CSR outlines that primary tumour locations categorised under ‘Other’ for both arms included: small bowel, mesenteric, ampullary, midgut, hindgut, biliary tract, larynx, pre-sacral, kidney and ethmoid sinus. Table 11 shows that the number of patients with each of these was very low, with the overall proportion being well balanced across treatment arms.

Table 11: Baseline characteristics – other primary tumour locations within the epNET cohort

Primary tumour location (N, %)	Cabozantinib (n=134)	Placebo (n=69)
Other primary tumour locations	24 (17.9%)	11 (15.9%)
Small bowel	13 (9.7%)	4 (5.8%)
Small intestine	3 (2.2%)	3 (4.3%)
Ampullary	1 (0.7%)	0 (0.0%)
Mesenteric	1 (0.7%)	0 (0.0%)
Kidney	2 (1.5%)	0 (0.0%)
Pre-sacral	1 (0.7%)	1 (1.4%)
Larynx	1 (0.7%)	0 (0.0%)
Hindgut	1 (0.7%)	0 (0.0%)
Midgut	1 (0.7%)	1 (1.4%)
Right ethmoid sinus	0 (0.0%)	1 (1.4%)
Biliary tract	0 (0.0%)	1 (1.4%)

Abbreviations: epNET: extra-pancreatic neuroendocrine tumour.

A8. The EAG notes that none of the primary tumour sites included hormonal-dependent cancer (such as ovarian or prostate). Please provide an explanation of why these patients were not recruited as part of the CABINET trial.

Neuroendocrine cancer of the prostate is rare (less than 2% of all prostate cancers) and is usually associated with aggressive disease: more likely to be a neuroendocrine carcinoma (NEC) than a neuroendocrine tumour (NET).¹³

Neuroendocrine cancers of the gynaecological organs range from the uncommon to incredibly rare, depending on site of origin. Neuroendocrine cancer of the ovary affects approximately 30 women a year in the UK. They are usually secondary deposits from the bowel or appendix, but primary disease can occur. Primary neuroendocrine cancers of the cervix and uterus are even rarer, with vaginal and vulval neuroendocrine neoplasms (NENs) the most rare – with only a handful of women, across the world, diagnosed each year.¹⁴

Feedback from a clinical expert aligns with the above information stating that most prostate NENs are initially treated as a prostate cancer and then further down the line, when it is discovered they are a NEN, they are more likely to be a NEC instead of a NET, so these patients would not be eligible for the CABINET trial. Although ovarian NETs are not explicitly listed as exclusion criteria, their extreme rarity in hormonal-dependent sites makes it statistically unlikely for such patients to be identified and recruited into the trial. Consequently, the majority of recruited patients are expected to have more prevalent tumour types, such as those in the GI tract, pancreas, or lungs.¹⁵

A9. The EAG notes that the primary tumour site in the epNET population was classified as 'Unknown' for between 2.9% to 3.7% of patients in the cabozantinib and placebo arms. Please provide an explanation of why a tumour location may be unknown for these patients.

Although, it is usually possible to determine where a cancer has started by assessing symptoms and reviewing tests and scans, sometimes confirmation of the primary site is not always possible.¹⁶

NETs often originate in the gastrointestinal tract or pancreas, but the primary tumour can be tiny, slow-growing, or even spontaneously regress, making it difficult to detect with imaging or biopsies.¹⁶ In some cases, the immune system may suppress or eliminate the primary tumour while metastases continue to grow.¹⁶

As they are slow-growing by the time they are discovered (often due to symptoms from metastases), the primary tumour may be too small or hidden (e.g., in the small intestine, pancreas, or lung) to detect.¹⁶ Even advanced imaging techniques like CT, MRI, PET scans (especially Gallium-68 DOTATATE PET/CT) may fail to locate the primary.¹⁶ Small bowel NETs, in particular, are difficult to see without specialised imaging or surgical exploration. Some biopsy samples may be too non-specific, especially if taken from metastases, to trace back to a primary location.¹⁶ When NETs are diagnosed at a metastatic stage, the cancer has already spread to the liver, lymph nodes, or bone and the spread may obscure or even destroy the original tumour, making it unidentifiable.¹⁷

This is therefore the likely reason why in the CABINET trial patients have their cancer classified as being of unknown origin – or Cancer of Unknown Primary (CUP).

Feedback from a clinical expert to Ipsen also corroborates this interpretation that there are a group of NETs patients where they are unable to classify the primary tumour site, therefore treated under the bracket of "NET of unknown primary". This is often due to slow growing disease which isn't picked up on a scan but can still metastasise. Often, whilst they may have an unknown primary, if the clinician gets the impression from immunohistochemistry that it may be a pNET or small intestine (SI) NET, they will treat per those pathways. However, if they are not certain of the primary, this rules out certain licensed treatments. The expert stated that around

1/3 of poorly differentiated NETs are of unknown primary which is not relevant for cabozantinib's indication. For well-differentiated NETs which is in scope of the cabozantinib indication the expert was unable to provide a number but estimated the percentage of patients with NETs of unknown primary would be much lower.

HRQoL

A10. Priority. The EAG notes that HRQoL data were derived from a sub study (A021602-HO1), and not all patients in the CABINET trial were included in this sub study.

a) Please describe the methods used to determine which patients were enrolled into this sub study;

The CABINET protocol specified that patients were enrolled into the HRQoL sub study if they opted to participate. There were not any specific eligibility criteria other than those already specified for the trial overall.¹⁸ The majority of patients (85%) were enrolled into the sub study.

b) Please provide the baseline characteristics for the pNET and epNET populations for the HRQoL sub study, separated by treatment arm.

Baseline characteristics for participants in the HRQoL sub study, separated by treatment arm are provided in Table 12. These have been provided for any patients providing European Organisation for Research and Treatment of Cancer (EORTC) quality of life (QoL) data. Available QoL data do not necessarily imply availability at baseline, but rather at least one response during the course of the CABINET trial. Two patients included in the HRQoL sub study were randomised after the 24th August 2023 data cutoff (DCO) and are not included in the summary of available data above.

Table 12: Baseline characteristics for patients providing EORTC QoL data (pNET cohort and epNET cohort; ITT population)

Characteristic	pNET cohort		epNET cohort	
	Cabozantinib (n=55)	Placebo (n=28)	Cabozantinib (n=113)	Placebo (n=58)
Age				
Median	████	████	████	████
Sex				
Male	██████	██████	██████	██████
Female	██████	██████	██████	██████
Race, n (%)				
White	██████	██████	██████	██████
Black or African American	██████	██████	██████	██████
Asian	██████	██████	██████	██████
American Indian or Alaska Native	██████	██████	██████	██████

Native Hawaiian or Other Pacific Islander	████	████	████	████
Not reported	████	████	████	████
Unknown	████	████	████	████
Ethnicity, n (%)				
Hispanic or Latino	████	████	████	████
Not Hispanic or Latino	████	████	████	████
Not reported	████	████	████	████
Unknown	████	████	████	████
ECOG performance status (as reported on the OPEN registration system)				
0	████	████	████	████
1	████	████	████	████
2	████	████	████	████
Functional (hormone secretion) status, n (%)				
Functional tumour	████	████	████	████
Non-functional tumour	████	████	████	████
Unknown	████	████	████	████
Tumour grade, n (%)				
G1	████	████	████	████
G2	████	████	████	████
G3	████	████	████	████
Unknown	████	████	████	████
Histologic differentiation, n (%)				
Well differentiated	████	████	████	████
Moderately differentiated	████	████	████	████
Not specified	████	████	████	████
Number of prior systemic anticancer regimens^a				
1	████	████	████	████
2	████	████	████	████
≥3	████	████	████	████

^a A regimen was defined as a unique systemic anticancer therapy, excluding SSAs.

Results

A11. Priority. The EAG notes that the interim analysis of PFS led to early termination of the CABINET trial in August 2023.

- a) Please clarify if overall survival was monitored beyond this point, or if all follow-up of participants was stopped;**
- b) If further data is available beyond the data cut-off reported for August 2023, please provide the results for overall survival for the pNET and epNET (and epNET lung) subgroups;**
- c) If the company anticipates that a more recent OS data cut will be available soon, please specify when.**

An additional descriptive OS analysis of the CABINET trial was conducted using a data cutoff (DCO) of 4th September 2024, derived from an unplanned OS sweep requested during marketing authorisation assessment, providing an additional 12 months of survival follow-up compared to the previous cut-off date.

This analysis was conducted on the pNET and epNET cohorts using the ITT population and includes updated disposition data and information on subsequent non-protocol anticancer therapy (NPACT). All patients who were known to be alive at their last known visit before the DCO of 4th September 2024, were censored at their last known alive date. Patients who were known to have died or be alive after the DCO of 4th September 2024, were censored on 4th September 2024. Patients initially assigned to the placebo arm who later crossed over to cabozantinib were not censored at the time of crossover. Instead, these patients were analysed under the randomized placebo arm for OS according to the ITT principles.

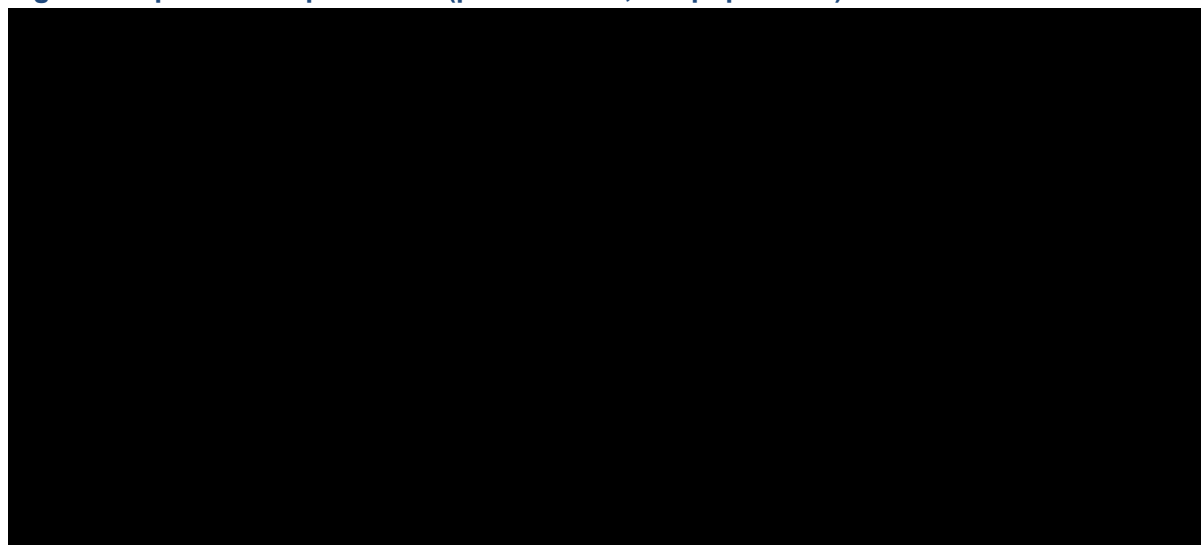
As with the OS results presented in the company submission, interpretation of OS data is limited due to the crossover design of the CABINET trial, and the extensive use of other NPACT, as outlined below. All economic analyses presented in this response are based on the original data cut (24th August 2023), given the constraints of the clarification response timelines.

pNET cohort

In the pNET cohort, [REDACTED] of patients (n=[REDACTED]) in the cabozantinib arm and [REDACTED] of patients (n=[REDACTED]) in the placebo arm had died at the time of DCO of 4th September 2024.

At the time of DCO of 24th August 2023, the KM estimates of median OS were 40.08 months in the cabozantinib arm and 31.11 months in the placebo arm (stratified HR: 0.95; 95% CI: 0.45, 2.00; p=0.8852). At the time of DCO of 4th September 2024, the KM estimates of median OS were [REDACTED] months in the cabozantinib arm and [REDACTED] months in the placebo arm ([REDACTED]). A KM plot for OS is presented in Figure 4.⁸

Figure 4: Updated KM plot of OS (pNET cohort; ITT population)



DCO: 4th September 2024. Stratification factors for pNET: 1. Concurrent SSA Use (Yes, No) and 2. Prior sunitinib therapy (Yes, No). Stratification was per OPEN criteria.

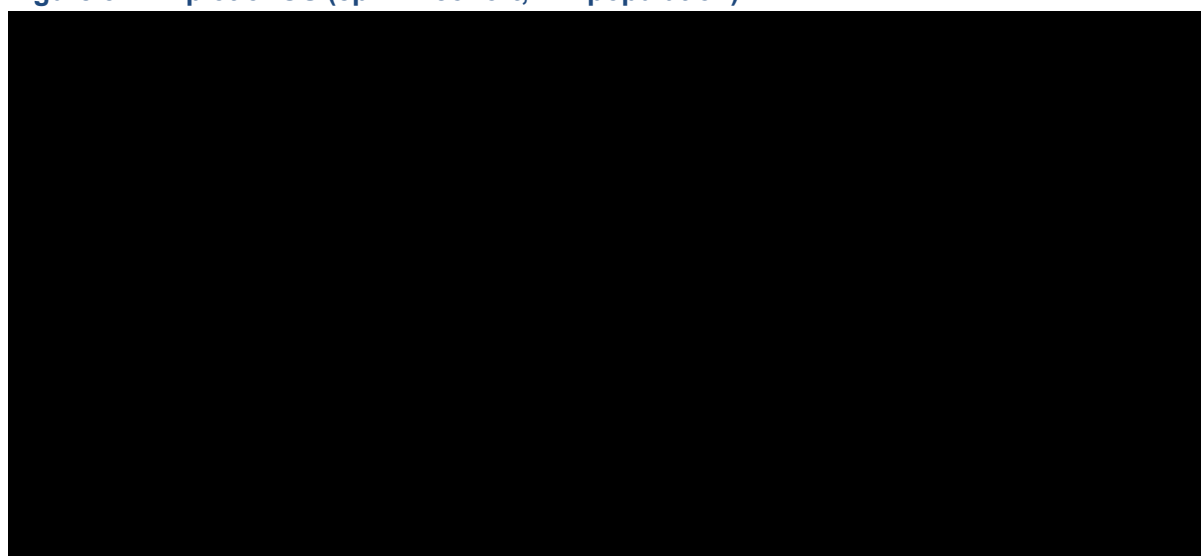
Abbreviations: CI: confidence interval; DCO: data cut-off; HR: hazard ratio; ITT: intent-to-treat; LR: log-rank test; OPEN: Oncology Patient Enrollment Network; OS: overall survival; pNET: pancreatic neuroendocrine tumour.

epNET cohort

In the epNET cohort, ■ of patients (n=■) in the cabozantinib arm and ■ of patients (n=■) in the placebo arm had died at the time of DCO of 4th September 2024.

At the time of DCO of 24th August 2023, the KM estimates of median OS were 21.95 months in the cabozantinib arm and 19.71 months in the placebo arm (HR: 0.86; 95% CI: 0.56, 1.31; p=0.4871). At the time of DCO of 4th September 2024, the KM estimates of median OS were ■ months in the cabozantinib arm (■) and ■ months in the placebo arm (■). A KM plot for OS is provided in Figure 5.⁸

Figure 5: KM plot of OS (epNET cohort; ITT population)



DCO: 4th September 2024. Stratification factors for epNET: 1. Concurrent Somatostatin Analogue Use (Yes, No) and 2. Primary Site [Midgut/Unknown versus Non-midgut GI/Lung/Other]. Stratification was per OPEN criteria.

Abbreviations: CI: confidence interval; DCO: data cut-off; epNET: extra-pancreatic neuroendocrine tumour; HR: hazard ratio; ITT: intent-to-treat; KM: Kaplan-Meier; LR: log-rank test; OPEN: Oncology Patient Enrollment Network; OS: overall survival.

Subsequent treatments

As of the 4th September 2024 cutoff date, in the cabozantinib arm, subsequent systemic NPACT were received by [REDACTED] and [REDACTED] patients in the pNET and epNET cohorts, respectively.⁸ This represents an increase the proportion receiving subsequent treatments compared with the DCO of 24th August 2023, where subsequent systemic treatments were received by 25 (39%) and 45 (34%) patients in the cabozantinib arms of the pNET and epNET cohorts respectively.⁸ This was predominantly cytotoxic chemotherapy and PRRT as outlined in Table 13.⁸

In the placebo arm, [REDACTED] and [REDACTED] of patients initiated systemic NPACT or crossed over to cabozantinib in the pNET and epNET cohorts, respectively. This represents an increase the proportion receiving subsequent systemic treatments compared with the DCO of 24th August 2023, where 18 (58%) and 38 (55%) of patients initiated systemic NPACT or crossed over to cabozantinib in the pNET and epNET cohorts respectively. Subsequent treatments received in the placebo arm were predominantly open-label cabozantinib, PRRT and anti-VEGFR TKIs in the pNET cohort and open-label cabozantinib or cytotoxic chemotherapy in the epNET cohort (Table 13).⁸

- In the pNET cohort, a total of [REDACTED] of patients in the placebo arm ([REDACTED]) crossed over to receive cabozantinib (compared with 12 [39%] at the DCO of 24th August 2023); in the analyses presented above, these patients were not censored at the time of crossover and were analysed under the arm to which they were randomised (i.e., placebo) for OS under ITT principles.⁸ Of the [REDACTED] placebo patients who crossed over [REDACTED] had died as compared to [REDACTED] in the [REDACTED] placebo patients who had not crossed over.
- In the epNET cohort, [REDACTED] of patients ([REDACTED]) in the placebo arm crossed over to receive cabozantinib (compared with 20 [29%] at the DCO of 24th August 2023); in the analyses presented above, these patients were not censored at the time of crossover and were analysed under the arm to which they were randomised (i.e. placebo) for OS under ITT principles.⁸ Of the [REDACTED] placebo patients who crossed over [REDACTED] had died as compared with [REDACTED] in the [REDACTED] placebo patients who had not crossed over.

Table 13: Summary of the subsequent treatments received in CABINET (pNET cohort)

	pNET cohort		epNET cohort	
	Cabozantinib (N=64)	Placebo (N=31)	Cabozantinib (N=134)	Placebo (N=69)
Proportion of patients receiving subsequent treatment	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Cabozantinib (crossover)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
PRRT	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Everolimus	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Anti-VEGFR TKI	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Cytotoxic chemotherapy regimens	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Other anticancer therapies	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Percentages are expressed as a proportion of the total pNET or epNET cohorts.

Abbreviations: ITT: intention-to-treat; NPACT: non-protocol anticancer therapy; pNET: pancreatic neuroendocrine tumour; PRRT: peptide receptor radionuclide therapy; SD: standard deviation; VEGFR TKI: vascular endothelial growth factor receptor tyrosine kinase inhibitor.

OS analyses adjusted for crossover

The substantial proportion of patients receiving subsequent treatment in both arms, as well as crossover to cabozantinib, makes it challenging to assess the effect of cabozantinib in improving OS compared to placebo. Therefore, the post-hoc inverse-probability-of-censoring weighting (IPCW) analysis was repeated for the data from the 4th September 2024 cutoff date to adjust for crossover, as per the approach taken in the company submission. Details of the methodology of the IPCW analysis are presented in Section 3.3.4 of the company submission.

The IPCW approach was considered the most appropriate approach to adjust for crossover, given Latimer *et al.* (2024) suggested that RPSFTM may perform relatively poorly compared with other crossover adjustment methods when ITT analyses provided HRs close to 1,¹⁹ which is the case for the epNET and pNET cohorts in CABINET; IPCW does not suffer from the same limitation. However, when switching proportions are high, IPCW results can be prone to bias, especially when sample sizes are small, primarily because in these cases extreme weights are common (as noted in TSD24);²⁰ it should be noted that the switching proportions have increased since the DCO of 24th August 2023, and thus this repeat analysis may be prone to a higher degree of bias. Furthermore, it should be noted that the modelling inherent in the IPCW method is significantly impacted by influential observations at the tail end of the curve in the placebo arms of the epNET and pNET cohorts.

Table 14. OS hazard ratios (cabozantinib vs BSC)

Population	Measure	ITT Analysis (95% CI)	IPCW (95% CI)
pNET	Stratified HR		
epNET	Stratified HR		

Stratified HRs were based on the relevant stratification factors for each population (pNET: concomitant SSA use and prior sunitinib use; epNET: concomitant SSA use and primary site [midgut/unknown vs non-midgut GI/lung/other]).

Abbreviations: BSC: best supportive care; epNET: extra pancreatic neuroendocrine tumour; GI: gastrointestinal; HR: hazard ratio; IPCW: inverse probability coefficient weighting; ITT: intention-to-treat; NET: neuroendocrine tumour; OS: overall survival; pNET: pancreatic neuroendocrine tumour; SSA: somatostatin analogue.

Source: Ipsen Data on File, 2024 (CABINET CSR).⁸

Subgroup analysis

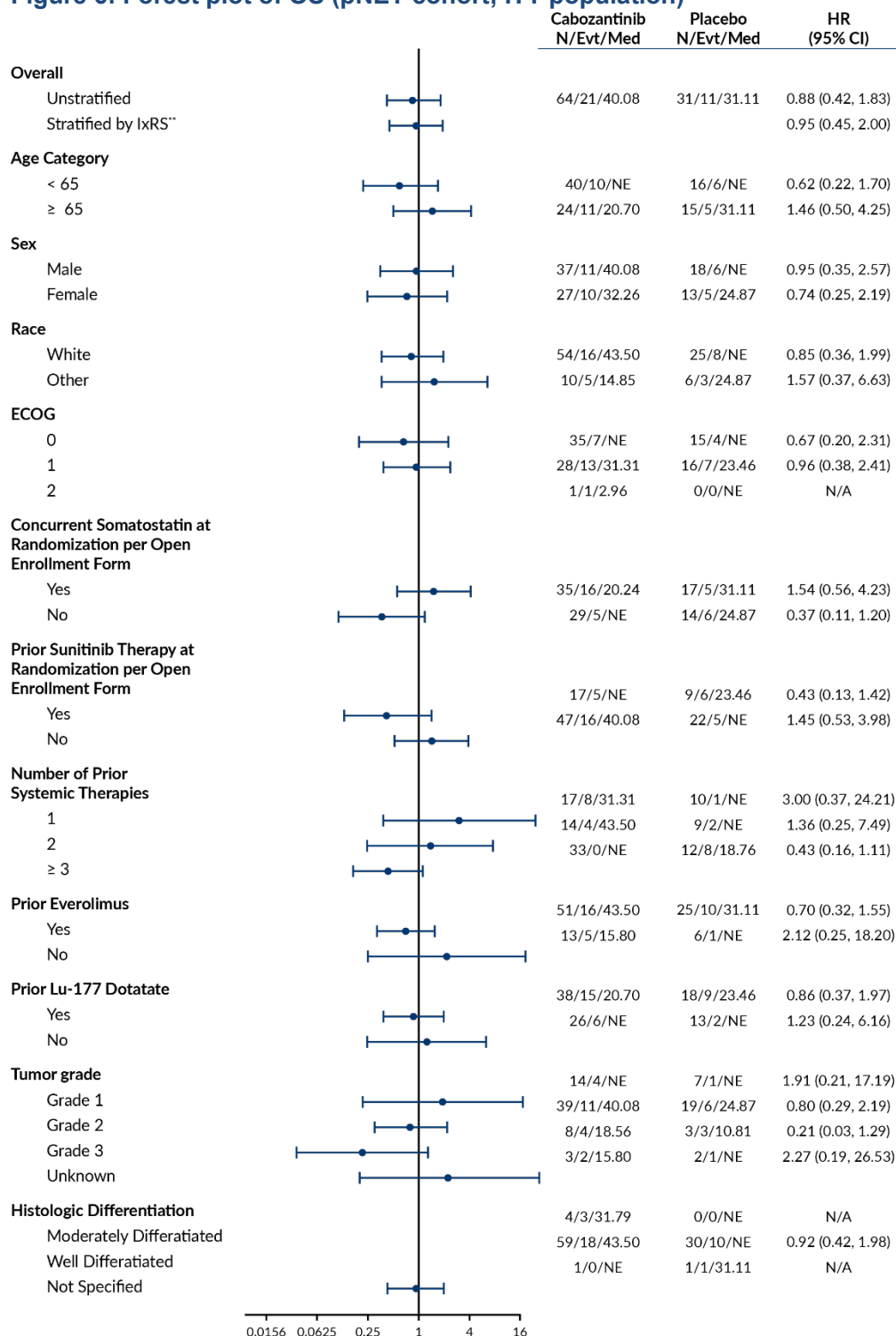
A12. Priority. The EAG notes that the results of subgroup analyses are only provided for the primary endpoint (PFS in Figures 16 and 17). For the pNET and epNET subgroups, please also provide the results for overall survival.

CABINET was not powered to test for statistical significance in OS, and interpretation of OS data is limited due to the crossover design of the CABINET trial and the immaturity of OS data at the time of clinical trial termination. Regardless, results have been provided below for completeness, given the limitations, these should be interpreted with caution.

Subgroup analyses for OS are presented below. The results of these analyses, as shown by the forest plots in Figure 6 and Figure 7, were consistent with the entire population and suggested a consistent numerical OS benefit across the subgroups. Due to small sample sizes, a HR above

one was observed in some subgroups, but all lower bounds of the confidence intervals were below one for all subgroups. Treatment benefits were observed irrespective of age, sex, performance status, and number of prior therapies, demonstrating the potential for cabozantinib to provide an effective treatment option for the broad NETs population.

Figure 6: Forest plot of OS (pNET cohort; ITT population)

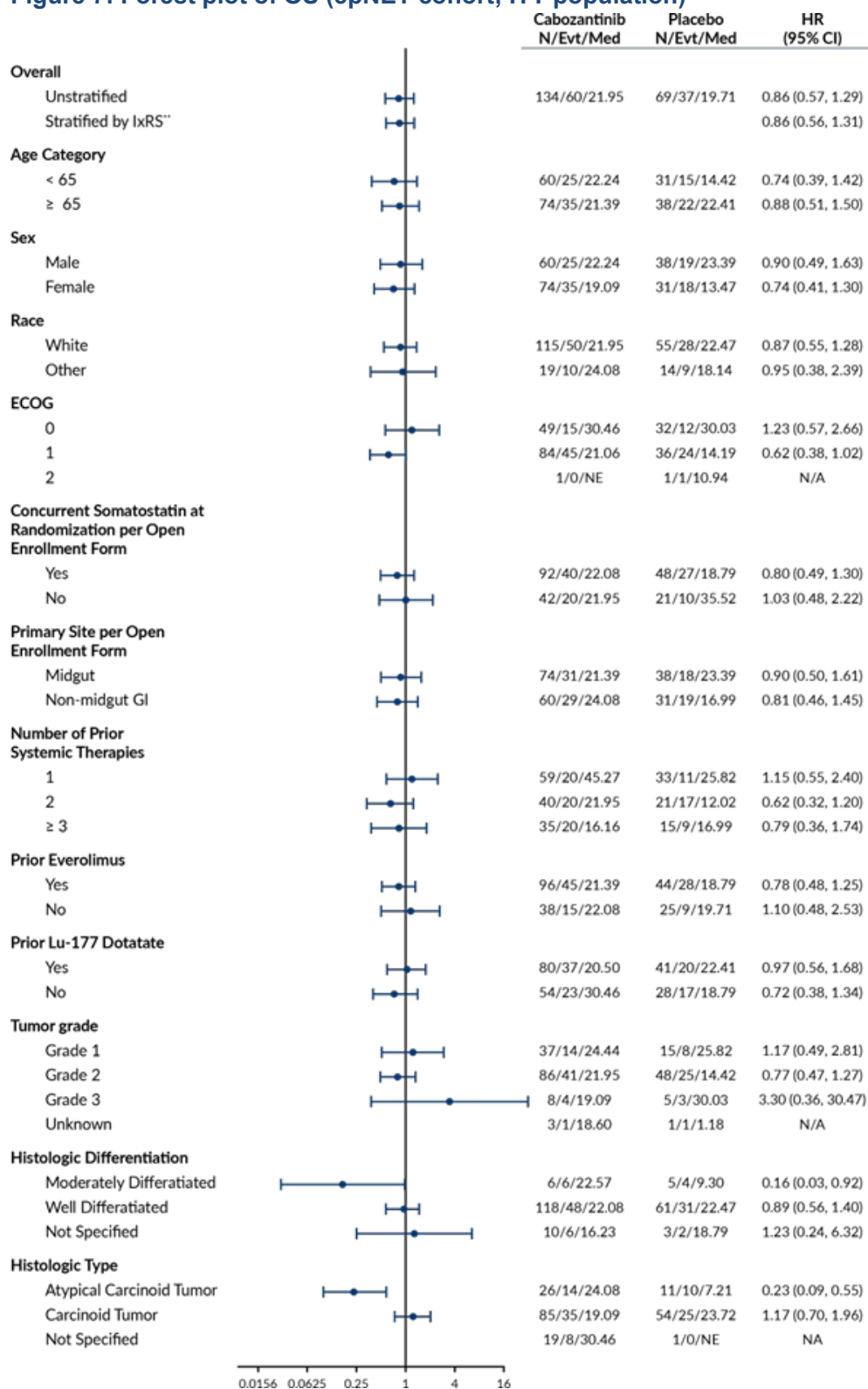


Stratification factors are as follows: (1) concurrent somatostatin analogue use (yes, no) and (2) prior sunitinib therapy (yes, no).

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; Evt, number of patients with events; ITT, intent-to-treat; IxRS, interactive voice/web response system; Med, median; N, number of patients; NA, not applicable; NE, not estimable; OPEN, Oncology Patient Enrollment Network; pNET, pancreatic neuroendocrine tumour.

Source: Ipsen Data on File. CABINET Trial CSR (Figure 17, Table 14.2.6.1a). 21 May 2024.⁸

Figure 7: Forest plot of OS (epNET cohort; ITT population)



Stratification factors are as follows: (1) concurrent somatostatin analogue use (yes, no) and (2) primary site

(midgut/unknown vs non-midgut GI/lung/other). Hazard ratio and 95% CI estimates from unstratified Cox proportional hazards model are presented for all subgroups.

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; epNET, extra-pancreatic neuroendocrine tumour; Evt, number of patients with events; GI, gastrointestinal; HR, hazard ratio; ITT, intent-to-treat; IxRS, interactive voice/web response system; Med, median; N, number of patients; NA, not applicable; OPEN, Oncology Patient Enrollment Network.

Source: Ipsen Data on File. CABINET Trial CSR (Figure 9, Table 14.2.6.1b). 21 May 2024.⁸

A13. Priority. The EAG notes that hazard ratios for the *post-hoc* subgroup analysis by primary site are only provided for PFS (Table 11 of Appendix C). Please also provide the hazard ratios for overall survival.

A post-hoc subgroup analysis for OS has been conducted for subgroups of the epNET cohort with GI NETs, lung NETs and other/unknown NETs, in line with the approach presented for PFS in Appendix C.

However, randomisation in the subgroups for this post-hoc analysis was not maintained because these subgroups do not align with protocol-specified stratification factors at randomization for the epNET cohort by primary tumour site (midgut/unknown vs non-midgut/lung/other known primary site). Therefore, these results are likely subject to considerable bias due to imbalances across treatment arms (baseline characteristics and imbalances are discussed in Appendix C of the company submission).

Furthermore, CABINET was not powered to test for statistical significance in OS, and interpretation of OS data is limited due to the crossover design of the CABINET trial and the immaturity of OS data at the time of clinical trial termination. The full epNETs cohort provides the most robust data to inform the benefit of cabozantinib versus BSC in epNETs patients. The post-hoc OS hazard ratios (HRs) for the epNET subgroups are presented in Table 15.

Table 15: OS post-hoc analysis (epNET cohort; ITT population)

Primary site (per OPEN enrolment form)	ITT; HR (95% CI)
epNET	
GI	
Lung/thymus	
Unknown/other	

DCO: 24th August 2023.

Abbreviations: CI: confidence interval; epNET: extra-pancreatic neuroendocrine tumour; GI: gastrointestinal; HR: hazard ratio; ITT: intent-to-treat; Med: median; N: number of patients; OPEN: Oncology Patient Enrollment Network; PFS: progression-free survival.

Source: Based on internal analyses of individual patient data from CABINET. Note: these data are not reported in the CSR.

ACQ1. Section 2.10 of the CS reports that RCTs investigating other systemic treatments used in UK clinical practice were excluded on the basis that less than 70% of patients had received a relevant prior line of therapy. Please provide the references for these excluded studies.

The SLR excluded studies on the basis of having “no relevant outcomes reported” which included either of the following:

- Studies with fewer than 70% of patients treated with a relevant prior line of therapy where results were not stratified for patients of interest (as per the EAG’s request)
- Studies including stratified results for patients of interest, but with no reported outcomes of interest

Table 16 below is an adapted version of Table 7 in the company submission appendices, which presented all studies excluded from the SLR, showing only studies excluded on the basis of the above criteria.

There was no systematic recording of the reason for exclusion between either (or both) of these criteria. Determining this would require re-sifting of those studies which would be challenging within the timeframe of the response to clarification. However, it is expected that the majority of these studies were excluded on the basis that fewer than 70% of patients treated with a relevant prior line of therapy, given it is unlikely for interventional studies to not report an outcome of interest.

Table 16: Studies excluded from the SLR on the basis of "no relevant outcomes reported"

#	Reference	Reason for Exclusion
Original SLR		
28	Aggarwal R, Thomas S, Pawlowska N, et al. Inhibiting histone deacetylase as a means to reverse resistance to angiogenesis inhibitors: Phase i study of abexinostat plus pazopanib in advanced solid tumor malignancies. Journal of Clinical Oncology 2017;35(11):1231-1238.	No relevant outcomes reported
32	Al-Toubah T, Schell MJ, Cives M, et al. A Phase II Study of Ibrutinib in Advanced Neuroendocrine Neoplasms. Neuroendocrinology 2020;110(5):377-383.	No relevant outcomes reported
40	Bajetta E, Zilembo N, Di Bartolomeo M, et al. Treatment of metastatic carcinoids and other neuroendocrine tumors with recombinant interferon-alpha-2a: A study by the Italian trials in Medical Oncology Group. Cancer 1993;72(10):3099-3105.	No relevant outcomes reported
42	Baudin E, Goichot B, Berruti A, et al. Sunitinib for metastatic progressive pheochromocytomas and paragangliomas: results from FIRSTMAPPP, an academic, multicentre, international, randomised, placebo-controlled, double-blind, phase 2 trial. The Lancet 2024;403(10431):1061-1070.	No relevant outcomes reported

#	Reference	Reason for Exclusion
51	Bongiovanni A, Nicolini S, Ibrahim T, et al. 177Lu-DOTATATE Efficacy and Safety in Functioning Neuroendocrine Tumors: A Joint Analysis of Phase II Prospective Clinical Trials. <i>Cancers</i> 2022;14(24) (no pagination).	No relevant outcomes reported
53	Braat A, Bruijnen RCG, van Rooij R, et al. Additional holmium-166 radioembolisation after lutetium-177-dotatate in patients with neuroendocrine tumour liver metastases (HEPAR PLuS): a single-centre, single-arm, open-label, phase 2 study. <i>Lancet Oncology</i> 2020;21:561-570.	No relevant outcomes reported
54	Braat A, Kwekkeboom DJ, Kam BLR, et al. Additional hepatic 166Ho-radioembolization in patients with neuroendocrine tumours treated with 177Lu-DOTATATE; a single center, interventional, non-randomized, non-comparative, open label, phase II study (HEPAR PLUS trial). <i>BMC Gastroenterology</i> 2018;18:84.	No relevant outcomes reported
59	Capdevila J, Teule A, Barriuso J, et al. Phase II Study of Everolimus and Octreotide LAR in Patients with Nonfunctioning Gastrointestinal Neuroendocrine Tumors: The GETNE1003_EVERLAR Study. <i>Oncologist</i> 2019;24(1):38-46.	No relevant outcomes reported
66	Chan JA, Blaszkowsky L, Stuart K, et al. A prospective, phase 1/2 study of everolimus and temozolomide in patients with advanced pancreatic neuroendocrine tumor. <i>Cancer</i> 2013;119(17):3212-3218.	No relevant outcomes reported
68	Chan JA, Ryan DP, Zhu AX, et al. Phase I study of pasireotide (SOM 230) and everolimus (RAD001) in advanced neuroendocrine tumors. <i>Endocrine-Related Cancer</i> 2012;19(5):615-623.	No relevant outcomes reported
80	Claringbold PG, Turner JH. NeuroEndocrine tumor therapy with lutetium-177-octreotate and everolimus (NETTLE): A Phase I study. <i>Cancer Biotherapy and Radiopharmaceuticals</i> 2015;30(6):261-269.	No relevant outcomes reported
81	Claringbold PG, Turner JH. Pancreatic neuroendocrine tumor control: Durable objective response to combination 177Lu-octreotate-capecitabine-temozolomide radiopeptide chemotherapy. <i>Neuroendocrinology</i> 2016;103(5):432-439.	No relevant outcomes reported
88	Creutzfeldt W, Bartsch HH, Jacubaschke U, et al. Treatment of gastrointestinal endocrine tumours with interferon-alpha and octreotide. <i>Acta Oncologica</i> 1991;30:529-35.	No relevant outcomes reported
93	Dasari A, Phan A, Gupta S, et al. Phase i study of the anti-IGF1R antibody cixutumumab with everolimus and octreotide in advanced well-differentiated neuroendocrine tumors. <i>Endocrine-Related Cancer</i> 2015;22(3):431-441.	No relevant outcomes reported
121	Fazio N, Buzzoni R, Delle Fave G, et al. Efficacy and safety of everolimus in advanced, progressive, nonfunctional neuroendocrine tumors (NET) of the lung: a subgroup analysis of the phase 3 radiant-4 study. <i>Neuroendocrinology</i> 2016;103:2016-03.	No relevant outcomes reported
126	Ferolla P, Berruti A, Spada F, et al. Efficacy and Safety of Lanreotide Autogel and Temozolomide Combination Therapy in Progressive Thoracic Neuroendocrine Tumors (Carcinoid): Results from the Phase 2 ATLANT Study. <i>Neuroendocrinology</i> 2023;113(3):332-342.	No relevant outcomes reported
131	Fjallskog ML, Sundin A, Westlin JE, et al. Treatment of malignant endocrine pancreatic tumors with a combination of alpha-interferon and somatostatin analogs. <i>Medical Oncology</i> 2002;19(1):35-42.	No relevant outcomes reported

#	Reference	Reason for Exclusion
132	Fjallskog MLH, Janson ET, Falkmer UG, et al. Treatment with combined streptozotocin and liposomal doxorubicin in metastatic endocrine pancreatic tumors. <i>Neuroendocrinology</i> 2008;88(1):53-58.	No relevant outcomes reported
138	Glasberg J, Talans A, Giollo TR, et al. METNET: a phase II trial of metformin in patients with well-differentiated neuroendocrine tumours. <i>ecancermedicallscience</i> 2022;16(no pagination).	No relevant outcomes reported
145	Halperin DM, Liu S, Dasari A, et al. Assessment of Clinical Response Following Atezolizumab and Bevacizumab Treatment in Patients With Neuroendocrine Tumors A Nonrandomized Clinical Trial. <i>JAMA Oncology</i> 2022;8(6):904-909.	No relevant outcomes reported
151	Hudson JM, Singh S, Milot L, et al. Dynamic Contrast-enhanced CT to Evaluate Early Response in Neuroendocrine Liver Metastases Treated With Everolimus and Radiation. <i>Anticancer Research</i> 2022;42(7):3523-3527.	No relevant outcomes reported
153	Ianniello A, Sansovini M, Severi S, et al. Peptide receptor radionuclide therapy with (177)Lu-DOTATATE in advanced bronchial carcinoids: prognostic role of thyroid transcription factor 1 and (18)F-FDG PET. <i>European Journal of Nuclear Medicine & Molecular Imaging</i> 2016;43:1040-6.	No relevant outcomes reported
160	Jeong H, Shin J, Jeong JH, et al. Capecitabine plus temozolomide in patients with grade 3 unresectable or metastatic gastroenteropancreatic neuroendocrine neoplasms with Ki-67 index <55%: single-arm phase II study. <i>ESMO Open</i> 2021;6(3) (no pagination).	No relevant outcomes reported
164	Kesavan M, Claringbold PG, Turner JH. Hematological toxicity of combined 177Lu-octreotate radiopeptide chemotherapy of gastroenteropancreatic neuroendocrine tumors in long-term follow-up. <i>Neuroendocrinology</i> 2014;99(2):108-117.	No relevant outcomes reported
165	Kesavan M, Grover P, Lam WS, et al. Long-term hematologic toxicity of 177Lu-octreotate-capecitabine-temozolomide therapy of GEPNET. <i>Endocrine-Related Cancer</i> 2021;28(7):521-527.	No relevant outcomes reported
174	Kong G, Callahan J, Hofman MS, et al. High clinical and morphologic response using 90Y-DOTA-octreotate sequenced with 177Lu-DOTA-octreotate induction peptide receptor chemoradionuclide therapy (PRCRT) for bulky neuroendocrine tumours. <i>European Journal of Nuclear Medicine & Molecular Imaging</i> 2017;44:476-489.	No relevant outcomes reported
177	Kulke MH, Kim H, Stuart K, et al. A phase II study of docetaxel in patients with metastatic carcinoid tumors. <i>Cancer Investigation</i> 2004;22(3):353-359.	No relevant outcomes reported
179	Kulke MH, Ou FS, Niedzwiecki D, et al. Everolimus with or without bevacizumab in advanced pNET: CALGB 80701 (Alliance). <i>Endocrine-Related Cancer</i> 2022;29(6):335-344.	No relevant outcomes reported
183	Kunz PL, Graham NT, Catalano PJ, et al. Randomized Study of Temozolomide or Temozolomide and Capecitabine in Patients With Advanced Pancreatic Neuroendocrine Tumors (ECOG-ACRIN E2211). <i>Journal of Clinical Oncology</i> 2023;41(7):1359-1369.	No relevant outcomes reported

#	Reference	Reason for Exclusion
193	Lepage C, Phelip JM, Lievre A, et al. Lanreotide as maintenance therapy after first-line treatment in patients with non-resectable duodeno-pancreatic neuroendocrine tumours: An international double-blind, placebo-controlled randomised phase II trial - Prodiges 31 REMINET: An FFCD study. <i>European Journal of Cancer</i> 2022;175:31-40.	No relevant outcomes reported
197	Liu Q, Cheng Y, Zang J, et al. Dose escalation of an Evans blue-modified radiolabeled somatostatin analog 177Lu-DOTA-EB-TATE in the treatment of metastatic neuroendocrine tumors. <i>European Journal of Nuclear Medicine and Molecular Imaging</i> 2020;47(4):947-957.	No relevant outcomes reported
205	McStay MKG, Maudgil D, Williams M, et al. Large-volume liver metastases from neuroendocrine tumors: Hepatic intraarterial 90Y-DOTA-lanreotide as effective palliative therapy. <i>Radiology</i> 2005;237(2):718-726.	No relevant outcomes reported
206	Mehnert JM, Bergsland E, O'Neil BH, et al. Pembrolizumab for the treatment of programmed death-ligand 1-positive advanced carcinoid or pancreatic neuroendocrine tumors: Results from the KEYNOTE-028 study. <i>Cancer</i> 2020;126(13):3021-3030.	No relevant outcomes reported
207	Meyer T, Qian W, Caplin ME, et al. Capecitabine and streptozocin +/- cisplatin in advanced gastroenteropancreatic neuroendocrine tumours. <i>European Journal of Cancer</i> 2014;50(5):902-911.	No relevant outcomes reported
208	Mileva M, Marin G, Levillain H, et al. Prediction of 177Lu-DOTATATE PRRT Outcome Using Multimodality Imaging in Patients with Gastroenteropancreatic Neuroendocrine Tumors: Results from a Prospective Phase II LUMEN Study. <i>Journal of Nuclear Medicine</i> 2024;65(2):236-244.	No relevant outcomes reported
219	Nicolini S, Bodei L, Bongiovanni A, et al. Combined use of 177Lu-DOTATATE and metronomic capecitabine (Lu-X) in FDG-positive gastro-entero-pancreatic neuroendocrine tumors. <i>European Journal of Nuclear Medicine and Molecular Imaging</i> 2021;48(10):3260-3267.	No relevant outcomes reported
220	Nicolini S, Severi S, Ianniello A, et al. Investigation of receptor radionuclide therapy with 177Lu-DOTATATE in patients with GEP-NEN and a high Ki-67 proliferation index. <i>European Journal of Nuclear Medicine and Molecular Imaging</i> 2018;45(6):923-930.	No relevant outcomes reported
232	Owen DH, Benner B, Wei L, et al. A Phase II Clinical Trial of Nivolumab and Temozolomide for Neuroendocrine Neoplasms A Phase II Clinical Trial of Nivolumab and Temozolomide for Neuroendocrine Neoplasms. <i>Clinical Cancer Research</i> 2023;29(4):731-741.	No relevant outcomes reported
246	Pavel ME, Baum U, Hahn EG, et al. Doxorubicin and streptozotocin after failed biotherapy of neuroendocrine tumors. <i>International Journal of Gastrointestinal Cancer</i> 2005;35:179-85.	No relevant outcomes reported
258	Pisegna JR, Slimak GG, Doppman JL, et al. An evaluation of human recombinant alpha interferon in patients with metastatic gastrinoma. <i>Gastroenterology</i> 1993;105:1179-83.	No relevant outcomes reported
284	Ryoo HG, Suh M, Kang KW, et al. Phase 1 Study of No-Carrier Added 177Lu-DOTATATE (SNU-KB-01) in Patients with Somatostatin Receptor-Positive Neuroendocrine Tumors: The First Clinical Trial of Peptide Receptor Radionuclide Therapy in Korea. <i>Cancer Research and Treatment</i> 2023;55(1):334-343.	No relevant outcomes reported

#	Reference	Reason for Exclusion
288	Salazar R, Tafuto S, Krogh M, et al. LBA45 Randomized open label phase III study comparing the efficacy and safety of everolimus followed by chemotherapy (CT) with streptozotocin (STZ)-5FU upon progression or the reverse sequence, in advanced progressive panNETs: The SEQTOR study (GETNE 1206). Annals of Oncology 2022;33(Supplement 7):S1412.	No relevant outcomes reported
293	Schneider TC, De Wit D, Links TP, et al. Beneficial effects of the mTOR inhibitor everolimus in patients with advanced medullary thyroid carcinoma: Subgroup results of a phase II trial. International Journal of Endocrinology 2015;2015(no pagination).	No relevant outcomes reported
301	Signorovitch J, Swallow E, Kantor E, et al. Everolimus and sunitinib for advanced pancreatic neuroendocrine tumors: a matching-adjusted indirect comparison. Experimental hematology and oncology 2013;2.	No relevant outcomes reported
326	Strosberg JR, Weber JM, Choi J, et al. A phase ii clinical trial of sunitinib following hepatic transarterial embolization for metastatic neuroendocrine tumors. Annals of Oncology 2012;23(9):2335-2341.	No relevant outcomes reported
334	Sun W, Lipsitz S, Catalano P, et al. Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. Journal of Clinical Oncology 2005;23(22):4897-4904.	No relevant outcomes reported
335	Sundlov A, Gleisner KS, Tennvall J, et al. Phase II trial demonstrates the efficacy and safety of individualized, dosimetry-based 177Lu-DOTATATE treatment of NET patients. European Journal of Nuclear Medicine and Molecular Imaging 2022;49(11):3830-3840.	No relevant outcomes reported
340	Swiha MM, Sutherland DEK, Sistani G, et al. Survival predictors of 177Lu-Dotatate peptide receptor radionuclide therapy (PRRT) in patients with progressive well-differentiated neuroendocrine tumors (NETS). Journal of Cancer Research & Clinical Oncology 2022;148:225-236.	No relevant outcomes reported
361	Walter T, Lepage C, Coriat R, et al. Everolimus after hepatic arterial embolisation therapy of metastases from gastrointestinal neuroendocrine tumours: The FFCD 1104-EVACEL-GTE phase II study. European Journal of Cancer 2019;123:92-100.	No relevant outcomes reported
387	Yao JC, Phan AT, Chang DZ, et al. Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: Results of a phase II study. Journal of Clinical Oncology 2008;26(26):4311-4318.	No relevant outcomes reported
SLR Update		
12	Baudin E, Capdevila J, Horsch D, et al. Treatment of advanced BP-NETS with lanreotide autogel/depot vs placebo: the phase III SPINET study. Endocrine-Related Cancer 2024;31:e230337.	No relevant outcomes reported

#	Reference	Reason for Exclusion
13	Capdevila Castillon J, Tafuto S, Krogh M, et al. 1142O Multivariable analysis of streptozotocin plus 5-fluorouracil and everolimus sequences in advanced pancreatic neuroendocrine tumor patients: The SEQTOR trial (GETNE-1206). Annals of Oncology 2024;35:S750.	No relevant outcomes reported

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user selectable options in the economic model (“Settings” tab), so that these can be combined for the same analysis. If scenarios cannot be implemented as user selectable options, please supply instructions on how to replicate the scenario. Furthermore, if the company chooses to update its base case analysis, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base case assumptions are provided with the response along with a log of changes made to the company base case.

As discussed in questions A1 and A6, the EAG considers that the company should conduct further analysis to include additional comparators to cabozantinib; and to separately consider the lung NET population from the other epNET patients in the analysis. Therefore, the clarification questions in Section B are based on the assumption that any individual scenario requested, can be conducted in combination as to generate cost-effectiveness measures for the relevant comparators, in the pNET; epNET and lung NET groups.

B1. Priority. Please update the model to incorporate the relevant comparators requested in question A1, in order to generate incremental cost-effectiveness ratios for cabozantinib against all relevant comparators.

- a) Please do so for the three relevant populations: pNETs; epNETs; lung NETs.

The company maintains, as explained in company response to A1.a, that BSC is the appropriate comparator for cabozantinib. Furthermore, no appropriate comparator efficacy data was available to inform a robust ITC between cabozantinib and the comparators listed above other than BSC.

- b) Please assess the need of having independently fitted survival curves in this scenario, for all treatments.

N/A – no further analyses have been explored.

B2. Priority. As mentioned in question A6, the EAG’s clinical experts consider lung epNETs to have a considerably different treatment pathway and

prognosis from the other epNETs included in the company's analysis. Please include an option in the model to estimate the cost-effectiveness of cabozantinib against BSC and everolimus for lung NETs, separately from the other epNETs.

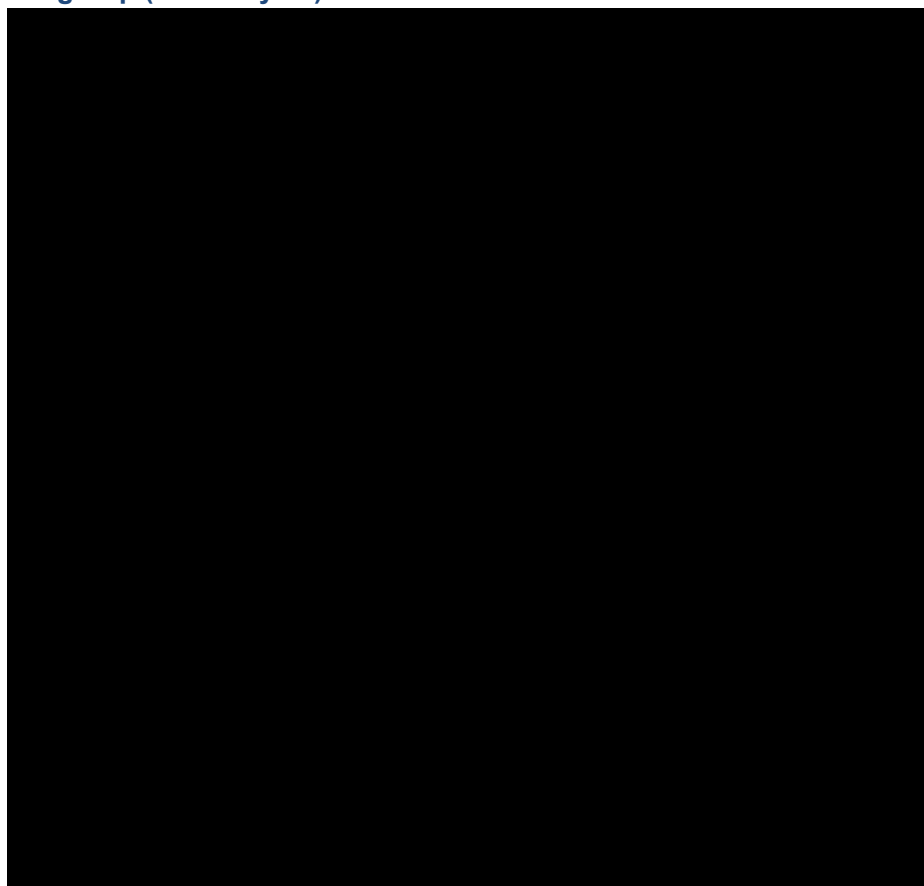
As explained in the company response to question A1, the appropriate comparator for cabozantinib in patients with lung NETs is BSC. Cabozantinib would not be considered as an alternative to everolimus based on the license, given patients must have received at least one prior systemic therapy other than an SSA to be eligible for cabozantinib, and everolimus is the only other systemic therapy reimbursed for patients with lung NETs.

Furthermore, as outlined in the response to question A6, the lung epNETs post-hoc analysis of the CABINET data is subject to limitations given the breaking of randomisation and imbalances in baseline characteristics across treatment arms, as well as very small patient numbers. The analyses presented for the overall epNETs cohort are therefore the most robust for to inform comparisons between cabozantinib and BSC in epNETs patients, and any subgroup analysis should be interpreted with considerable caution. However, to address the EAG's request, an analysis of the lung NETs subgroup has been conducted and included within the model.

In the lung NETs scenario within the model, cabozantinib efficacy (i.e. OS, PFS, and TTD) has been informed by the lung subgroup analysis of the CABINET trial. The KM data for cabozantinib CABINET has been extrapolated to inform this scenario. Extrapolation choices were based on a combination of statistical fit and similarity to underlying hazard functions. Specifically:

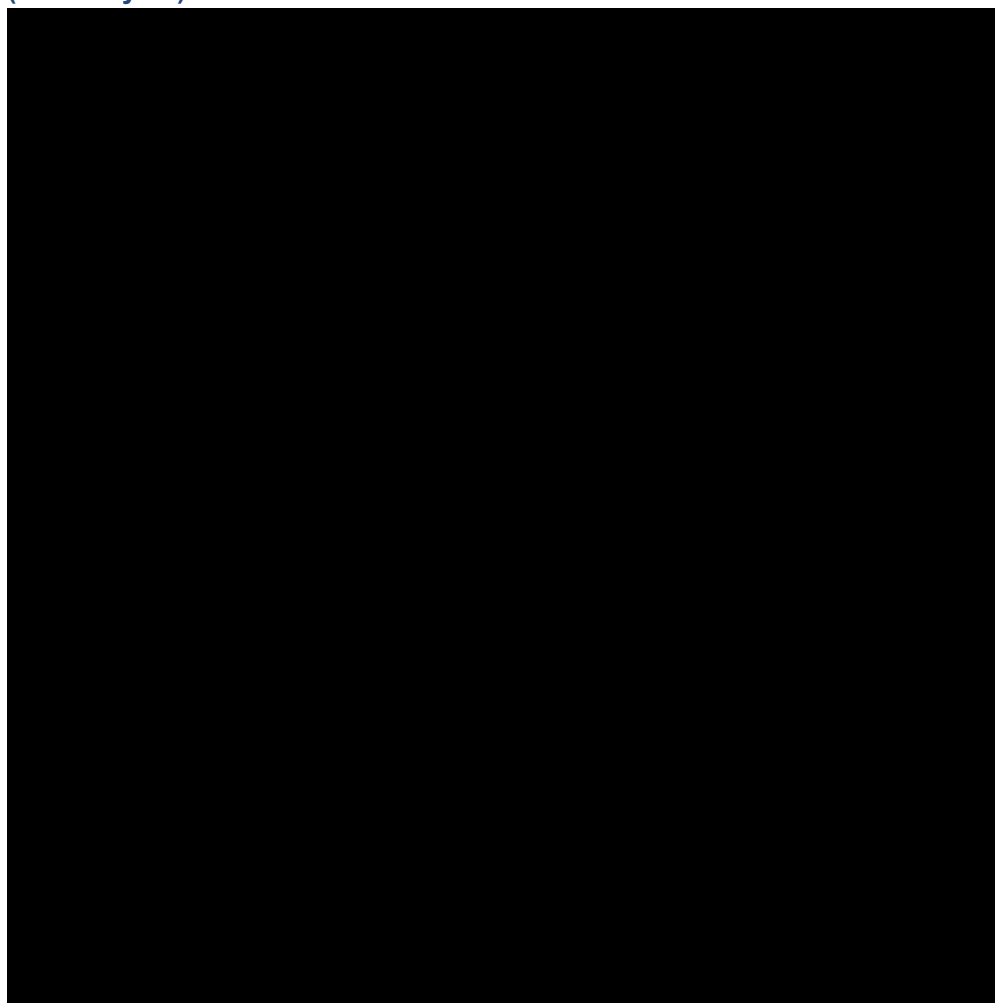
- The lognormal extrapolation was selected for PFS as it is the statistically best fitting extrapolation based on Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) (see Figure 8), and has a suitable hazard profile to match the underlying patient data.
- Weibull was selected as the OS extrapolation as this had the best statistical fit (best AIC and 2nd best BIC, see Figure 8), a good visual fit with the KM data, and a plausible long-term survival estimate of <5% survival after 15 years.
- Exponential was selected as the TTD extrapolation as this had the best statistical fit (see Figure 9), modelled a suitable hazard profile compared to the underlying patient data and showed a good visual fit.

Figure 8: Parametric OS and PFS extrapolation for the cabozantinib arm: epNET lung subgroup (ITT analysis)



Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; epNETs: extra-pancreatic neuroendocrine tumours; ITT: intention-to-treat; OS: overall survival; PFS: progression-free survival.

Figure 9: Parametric TTD extrapolation for the cabozantinib arm: epNET lung subgroup (ITT analysis)



Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; epNETs: extra-pancreatic neuroendocrine tumours; ITT: intention-to-treat; TTD: time to treatment discontinuation.

In line with the base case approach taken in the company submission, a HR was applied to the cabozantinib extrapolation to derive BSC efficacy in lung NETs. As per the response to A6, the full epNETs cohort provides the most robust data to inform the comparative efficacy of cabozantinib versus BSC in all epNETs patients, and thus the HR derived from the overall epNETs cohort was applied to the cabozantinib extrapolation for the lung epNETs subgroup to estimate BSC efficacy. This approach allows for differences in prognosis to be reflected in the model (as per the feedback from the EAG's clinical experts), whilst ensuring the modelled treatment effect is robust. This also represents a conservative approach, given the HRs from the lung epNETs subgroup are more favourable than the HRs derived from the overall epNETs cohort. Nevertheless, the results of this analysis results should be interpreted with caution, given the extrapolated data for cabozantinib in the lung subgroup are based on small patient numbers. All other model inputs were assumed to align to the overall epNET data. PRRT was not modelled as a subsequent treatment in this scenario as it is not reimbursed in the UK for lung NETs, and subsequent treatments were reweighted accordingly.

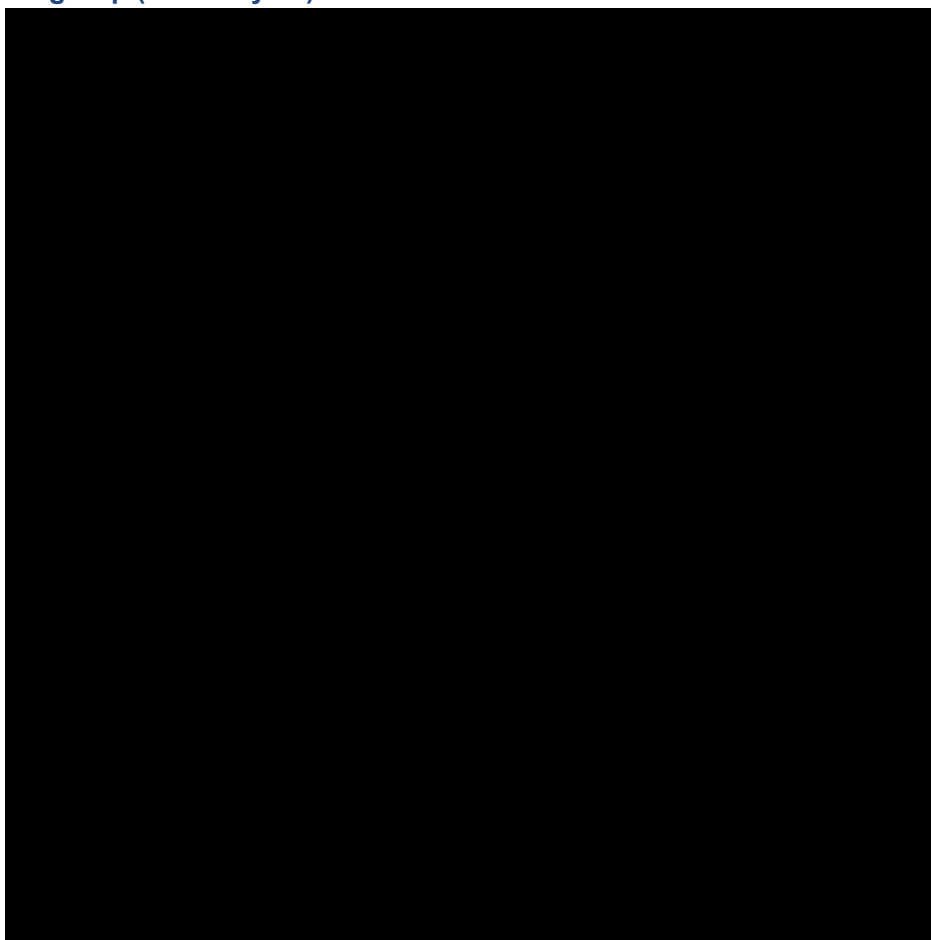
Given that the epNET lung subgroup has been split out from the overall epNET analyses in response to this question, the equivalent analyses have also been provided for an "epNET without lung" subgroup. As the same limitations apply for this post-hoc analysis (breaking of randomisation and imbalances in baseline characteristics across treatment arms, as well as

small patient numbers), this subgroup analysis should also be interpreted with caution. The efficacy for cabozantinib in the epNET without lung subgroup is derived from the subgroup-specific KM data and BSC efficacy has been derived using the overall epNET HR. All other model inputs are assumed to align to the overall epNET cohort.

Extrapolations for the cabozantinib epNET without lung subgroup data are presented in Figure 10, Figure 11, and Figure 12 below for OS, PFS and TTD respectively. The extrapolations chosen for each endpoint include:

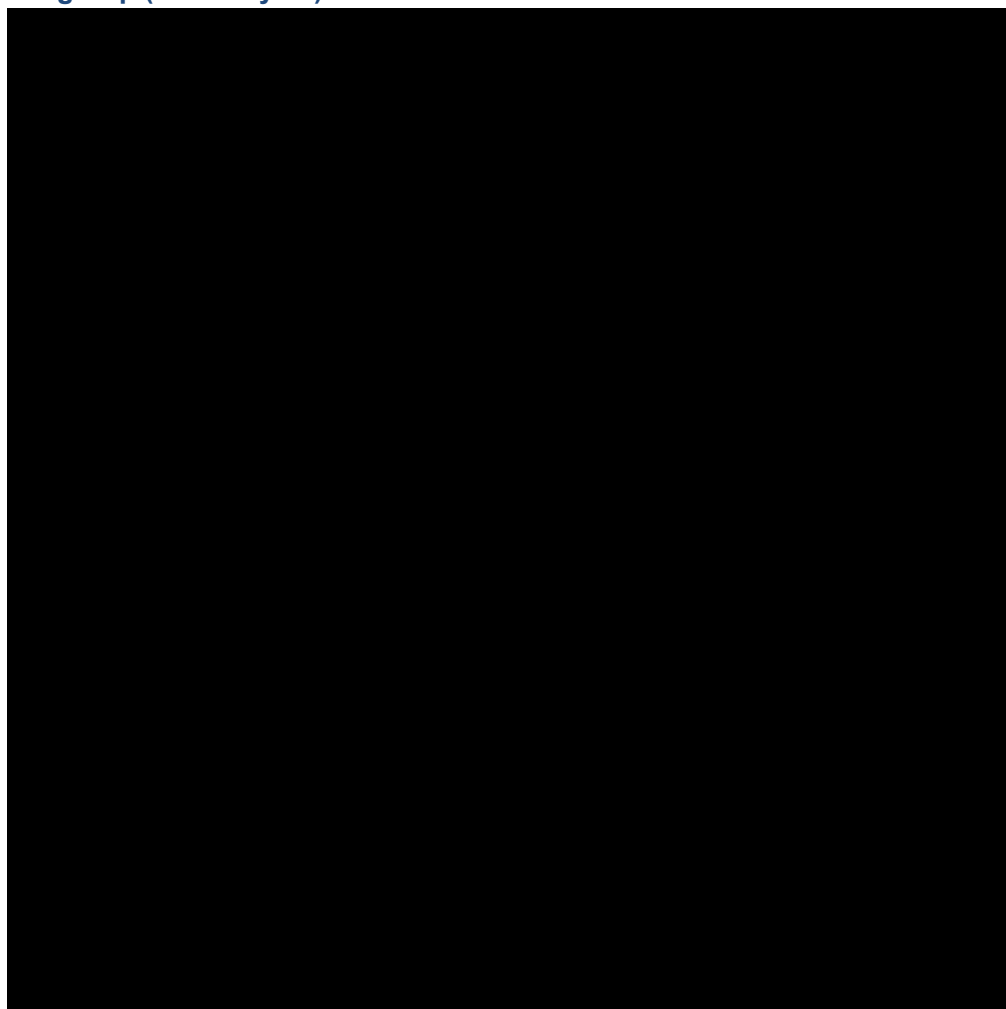
- Loglogistic was chosen for OS as this was the best statistically fitting curve and estimated similar long-term survival at 10 and 15 years to that predicted by clinicians for overall epNETs as described in Section 3.3.4 of the original submission.
- Lognormal was chosen for PFS as it was the best statistically fitting curve, it aligns with the PFS extrapolation choices for the other subgroups (given similar underlying hazards) and predicts similar long-term survival as described in Section 3.3.3 of the original submission for overall epNETs.
- Exponential was chosen for TTD as it had both good visual and statistical fit to the data, and aligned with the extrapolations chosen for the other subgroups (given similar underlying hazards). Gompertz also had a good statistical and visual fit to the data, however was deemed to estimate too low TTD for cabozantinib.

Figure 10: Parametric OS extrapolation for the cabozantinib arm: epNET without lung subgroup (ITT analysis)



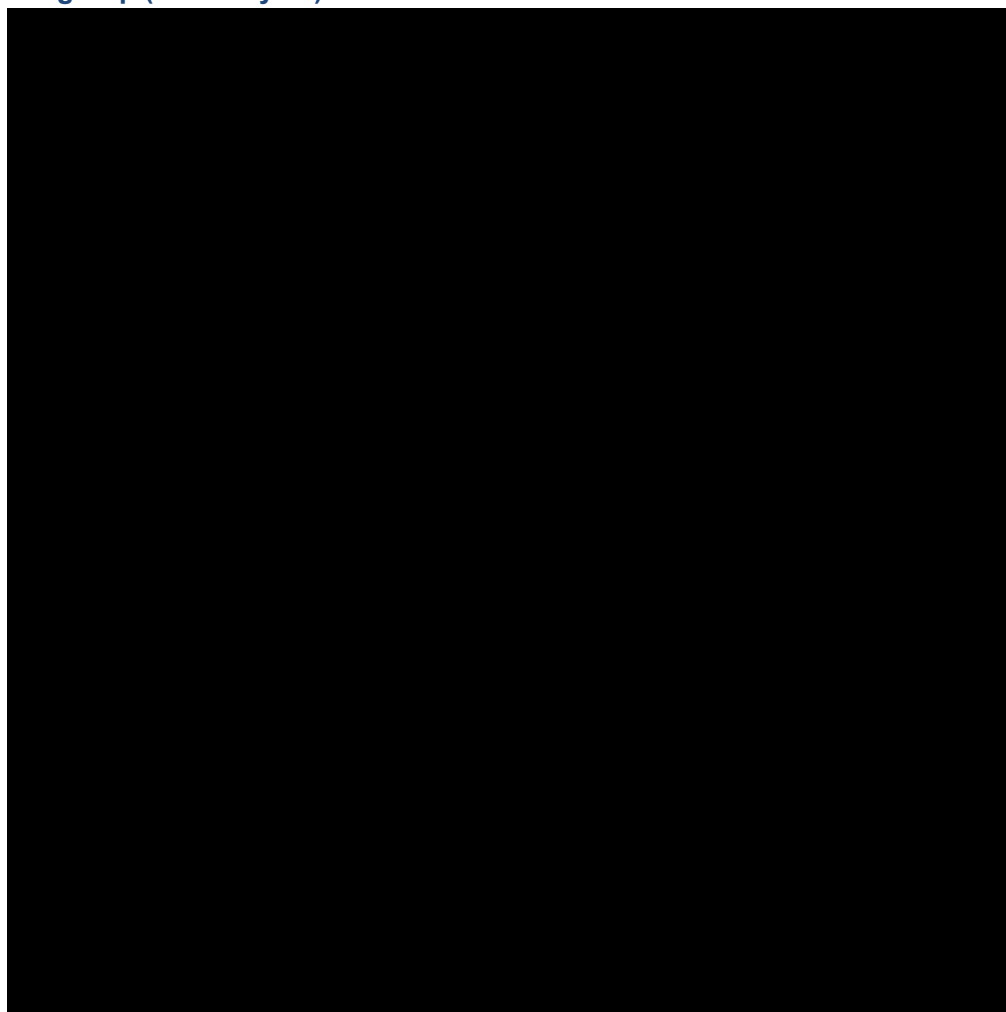
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; epNETs: extra-pancreatic neuroendocrine tumours; ITT: intention-to-treat; OS: overall survival.

Figure 11: Parametric PFS extrapolation for the cabozantinib arm: epNET without lung subgroup (ITT analysis)



Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; epNETs: extra-pancreatic neuroendocrine tumours; ITT: intention-to-treat; PFS: progression-free survival.

Figure 12: Parametric TTD extrapolation for the cabozantinib arm: epNET without lung subgroup (ITT analysis)



Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; epNETs: extra-pancreatic neuroendocrine tumours; ITT: intention-to-treat; TTD: time to treatment discontinuation.

B3. Priority. As described in question A5, the CS implies that the relevant population from CABINET eligible to receive cabozantinib consists of patients who have not been pre-treated with sunitinib. If retreatment with TKIs is not possible in the NHS, please include an option in the economic model to allow the estimation of the cost-effectiveness of cabozantinib against all relevant comparators (as per Question B1), using the population from CABINET who did not receive prior sunitinib.

N/A – no response required.

Survival

B4. Priority. For PFS, OS and TTD, the company used an HR stratified for prior sunitinib use, concomitant SSA and primary site to model the best supportive care arm (BSC) in the analysis. Please justify the use of this stratified HR.

Stratified HRs as per OPEN registration system were used within the model as these were the prespecified primary outcome measures for OS and PFS within the CABINET trial. Use of the stratified HR reflects the stratified randomisation into treatment arms based on primary tumour site (stratified by midgut GI/unknown versus non-midgut GI/lung/other), prior sunitinib use (pNETs) and concomitant SSA use (both). These stratification factors were all prespecified in the CABINET protocol. However, unstratified HRs were also generated and showed similar results.

Progression free survival

B5. Priority. The figures 14-19 from the CS appendix show evidence that the proportional hazards assumption is violated in PFS in both epNET and pNET. Schoenfeld residuals appear to show consistent decline up to 12 months (where the KM data for BSC ends). Given this, the EAG considers that the company's modelling approach of using HRs to derive BSC curves is fundamentally flawed. If the company decides to include an analysis in the model where cabozantinib and BSC (only) are compared using CABINET data (i.e., without modelling other comparators), please:

a) use independently fitted curves in the model for cabozantinib and BSC.

While figures 14–19 from the CS appendix show *some* evidence of PH violation for pNETs and epNETs, ultimately all Schoenfeld tests had p-values higher than 0.1 suggesting that there was not enough evidence to reject the null hypothesis of PH in either pNET or epNET cohorts. Furthermore, the number at risk in the placebo arm of the CABINET trial from 6 months onwards was limited (n=6) and therefore there is inherent uncertainty in latter half of the BSC arm's KM data; assessment of PHs after this timepoint is therefore not reliable. Considering the pNETs smoothed hazard plot in the original company appendix K (Figure 16), very similar hazard profiles in the first 6 months of PFS follow-up are seen. This further highlights that it cannot be said with confidence that PH is violated and so the company maintains that a PH assumption is appropriate.

Nonetheless, the model already includes the ability to model independently fitted curves for PFS and TTD. This was discussed in Appendix K1.1 and K3.1 of the original submission, with results of a scenario analysis presented in Table 74 and Table 75 in Section 3.11.3 of the Company submission. As demonstrated in the original scenario analysis, using direct extrapolations for BSC PFS and TTD (Lognormal and Weibull, respectively) results in incremental cost-effectiveness ratio (ICER) changes of only £56 in the pNETs population and £424 in the epNET population, so this has limited impact on results, and shouldn't be considered a key source of uncertainty.

- b) provide this analysis for the separate populations requested in B1 and B3; i.e., using the population from CABINET separated into pNET, epNET (without lung NET) and epNET (lung), restricted to patients who were not pre-treated with sunitinib, if the latter is appropriate.**

As discussed in the response to question A6, randomisation was not stratified according to this classification of subgroups by primary tumour type; results of subgroup analyses for epNET (without lung) and epNET (lung) patients are subject to bias due to imbalances in patient characteristics across treatment arms and associated confounding, and limited by small patient numbers. Functionality to select independent extrapolations of cabozantinib and BSC subgroup data has been included in the economic model, but analyses based on independent extrapolation of cabozantinib and BSC curves within these subgroups are not appropriate.

Analyses have been explored in epNET (without lung NET) and epNET (lung) as part of the response to question B2, with BSC efficacy derived using robust comparative efficacy estimates from the overall epNETs cohort.

B6. Priority. PFS in the pNET population appears to be considerably overestimated for cabozantinib, by all curves, from 18 to 28 months (figure 20 of CS). Furthermore, the EAG does not consider that any of the provided parametric curves is adequate to reflect the change in hazard in the PFS KM curve from month 18. Therefore, when independently fitting the PFS curves for cabozantinib, please consider fitting more flexible models to the PFS KM data (such as splines or piecewise models, following the guidance in TSD 14.

Please provide this analysis for:

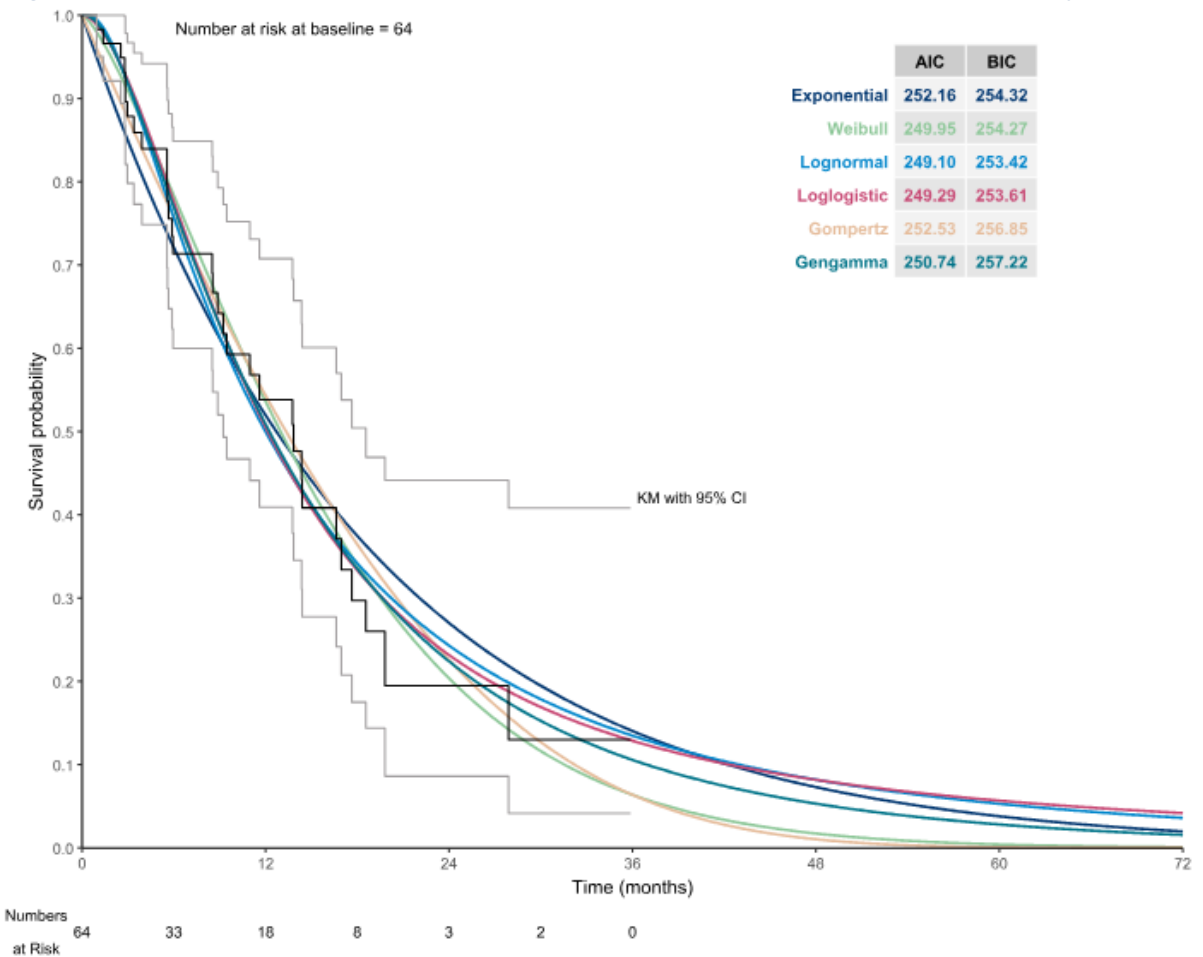
- a) The pNET, epNET (without lung NET) and epNET (lung) populations, respectively**
- b) If appropriate, patients who were not pre-treated with sunitinib in CABINET**
- c) Please consider this when fitting curves for the comparison of cabozantinib with the treatments included in question B1.**

Given the uncertainty of long-term extrapolations in oncology, the fit of the tail ends of the standard parametric extrapolations to the KM curves should not be overinterpreted. These can often be biased due to low numbers at risk for later timepoints, particularly for extrapolations already based on small patient numbers.

The standard extrapolations for pNETs offer good visual fit the KM curves, sitting well within the 95% CIs of the KM curves at all later timepoints, as shown in Figure 13. There are very few patients at risk at the tail end of the curve, with only 8 and 3 patients at risk at 18 and 24 months,

respectively, and thus the tail of the KM curve should not be overinterpreted. The use of flexible spline models is not justified and would likely result in overfitting of the data; more parsimonious models are preferred. Accordingly, prior appraisals in NETs have not explored flexible models (standard parametric models were accepted in TA449 and TA539).^{11, 21} Nevertheless, to address the EAG's request, flexible spline models have been generated and parameters provided in the reference pack.

Figure 13: Parametric PFS extrapolation for cabozantinib: pNET cohort (ITT analysis)



Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: intention to treat; KM: Kaplan-Meier; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour.

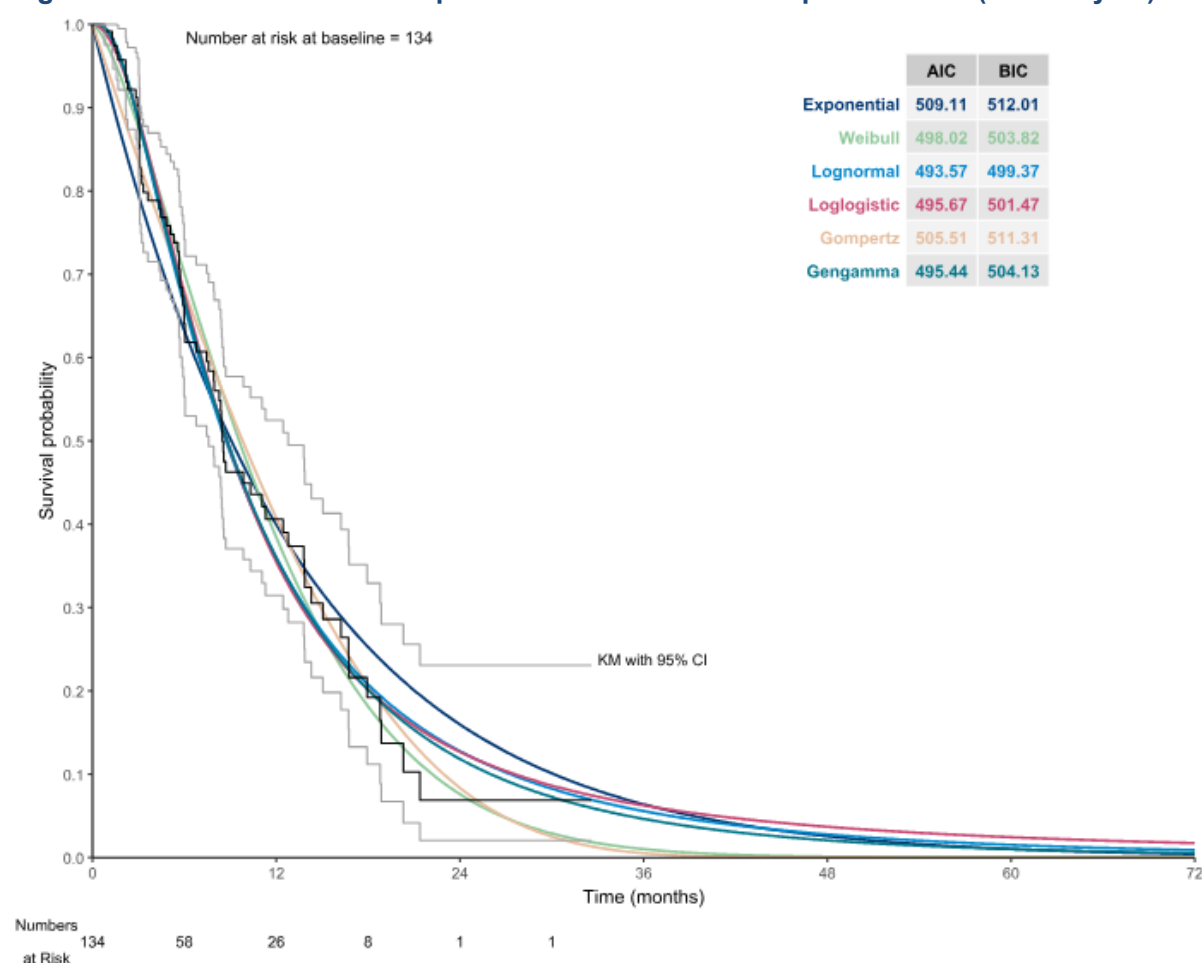
B7. PFS in the epNET population appears to be overestimated, by the selected Lognormal curves, from 18 to 28 months (figure 21 of CS). Furthermore, the curves that do reflect the change in hazard from month 18, gompertz and weibull, have lower AIC and BIC rankings. Therefore, when independently fitting the PFS curves, please consider fitting more flexible models to the PFS KM data (such as splines or piecewise models, following the guidance in TSD 14).

- a) Please provide this analysis for the separate populations requested in B1, B2 and B3; i.e., using the appropriate comparators; the population from CABINET separated into pNET, epNET (without lung NET) and epNET (lung),

and, if appropriate, restricted to patients who were not pre-treated with sunitinib.

As noted in the company response to B6, the use of flexible models such as splines is not justified and would likely result in overfitting the data. Figure 14 demonstrates the standard extrapolations for epNETs provide good visual fit to the KM curves, sitting well within the 95% CIs of the KM curves at all later timepoints. There are very few patients at risk at the tail end of the curve, with only 8 and 1 patient(s) at risk at 18 and 24 months, respectively, and thus the tail of the KM curve should not be overinterpreted. Nevertheless, to address the EAG's request, flexible spline models have been generated and parameters provided in the reference pack.

Figure 14: Parametric PFS extrapolation for cabozantinib: epNET cohort (ITT analysis)



Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; epNET: extra-pancreatic neuroendocrine tumour; ITT: intention to treat; KM: Kaplan-Meier; PFS: progression-free survival.

B8. The company has provided clinical expert and parametric landmark estimates for overall survival (OS) in table 33 and 34 of the CS. Please provide the same clinical expert and parametric landmark estimates for progression-free survival (PFS). Given the rate of progression for NETs, please provide only 1, 2 and 5 year PFS%. Please

prioritise estimates for BSC, where clinicians have direct experience of using it in clinical practice.

The parametric landmark estimates for PFS are presented in Table 17 and Table 18 for pNETs and epNETs, respectively. Due to the scope of the clarification response timelines, it is not possible to gain clinician estimates for PFS. However, given the PFS data are very mature (with PFS events at the DCO occurring in 50% and 81% of patients in the cabozantinib and placebo arms, respectively), this does not represent a key source of uncertainty in the model. KM data reported in the CSR for years 1 and 2 has been presented for comparison. These data, as shown in Table 17 and Table 18, show that all the modelled extrapolations produce survival predictions that fall well within the 95% confidence intervals of the KM estimates and are closely aligned with the point estimates of the landmark survival at the relevant timepoints.

Table 17: KM and parametric survival landmark estimates for PFS for cabozantinib and BSC (pNETs)

PFS (pNETs)				
Category	Curve	PFS %		
		1	2	5
Cabozantinib				
KM data (95% CI)	Cabozantinib	53.8% (38.1%, 67.1%)	19.5% (6.7%, 37.1%)	NR (NR, NR)
Extrapolations	Exponential	52.1%	27.1%	3.8%
	Weibull	53.8%	20.5%	0.4%
	Log-logistic	50.7%	23.3%	5.7%
	Lognormal	50.1%	24.4%	5.3%
	Generalised gamma	51.0%	22.5%	2.8%
	Gompertz	54.5%	22.7%	0.1%
BSC				
KM data (95% CI)	Placebo	0.0% (NE, NE)	0.0% (NE, NE)	NR (NR, NR)
Cabozantinib curve + HRs	Exponential	5.6%	0.3%	<0.1%
	Weibull	6.4%	0.1%	<0.1%
	Log-logistic	5.0%	0.2%	<0.1%
	Lognormal	4.7%	0.2%	<0.1%
	Generalised gamma	5.1%	0.1%	<0.1%
	Gompertz	6.8%	0.1%	<0.1%

Abbreviations: BSC: best supportive care; NE: not estimable; NR: not reported; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour.

Source: Ipsen Data on File. CABINET Trial CSR (Table 35). 21 May 2024.⁸

Table 18: KM and parametric survival landmark estimates for PFS for cabozantinib and BSC (epNETs)

Category	Curve	PFS %		
		1	2	5
Cabozantinib				
KM data	Cabozantinib	40.6% (30.2%, 50.8%)	6.9% (1.5%, 18.2%)	NR (NR, NR)
	Exponential	40.1%	16.1%	1.0%

Extrapolations	Weibull	38.6%	7.7%	<0.1%
	Log-logistic	35.7%	12.7%	2.4%
	Lognormal	36.1%	12.8%	1.5%
	Generalised gamma	36.2%	11.9%	1.01%
	Gompertz	40.9%	8.5%	<0.1%
BSC				
KM data	Placebo	10.3% (2.1%, 26.1%)	NE (NE, NE)	NR (NR, NR)
Cabozantinib curve + HRs	Exponential	9.0%	0.8%	<0.1%
	Weibull	8.2%	0.1%	<0.1%
	Log-logistic	6.6%	0.4%	<0.1%
	Lognormal	6.8%	0.4%	<0.1%
	Generalised gamma	6.9%	0.4%	<0.1%
	Gompertz	9.5%	0.2%	<0.1%

Abbreviations: BSC: best supportive care; epNET: extra-pancreatic neuroendocrine tumour; NE: not estimable; NR: not reported; PFS: progression-free survival.

Source: Ipsen Data on File. CABINET Trial CSR (Table 18). 21 May 2024.⁸

Overall survival

B9. Priority. The company states in the appendix with regards to testing the RPSFTM assumption “Sensitivity analyses were conducted to test the common treatment effect assumption based on a range of values applied to the acceleration factor, ranging from 0.5 to 1, in increments of 0.1”. Please explain where the results of this sensitivity analysis are located and provide these if it is not included. The EAG notes that in figure 16 of the company submission, assessing the relative treatment effect of cabozantinib compared to BSC, that no significant difference was identified when assessed by number of prior lines of treatment.

Results from the sensitivity analyses conducted to test the common treatment effect assumption are presented in Table 19, noting that a factor of 1 corresponds to analyses assuming a common treatment effect. These were conducted without recensoring. For each of the subgroups, the hazard ratios were similar across the different factors applied to psi, suggesting that violations of the common treatment effect assumption would have a relatively small effect on results. Therefore, only results assuming a common treatment effect were presented.

Table 19: Sensitivity analyses conducted to test the common treatment effect

Population	Factor applied to Psi	Unstratified HR (95% CI)	Stratified HR (95% CI)
pNET	■	■	■
	■	■	■
	■	■	■
	■	■	■

epNET			

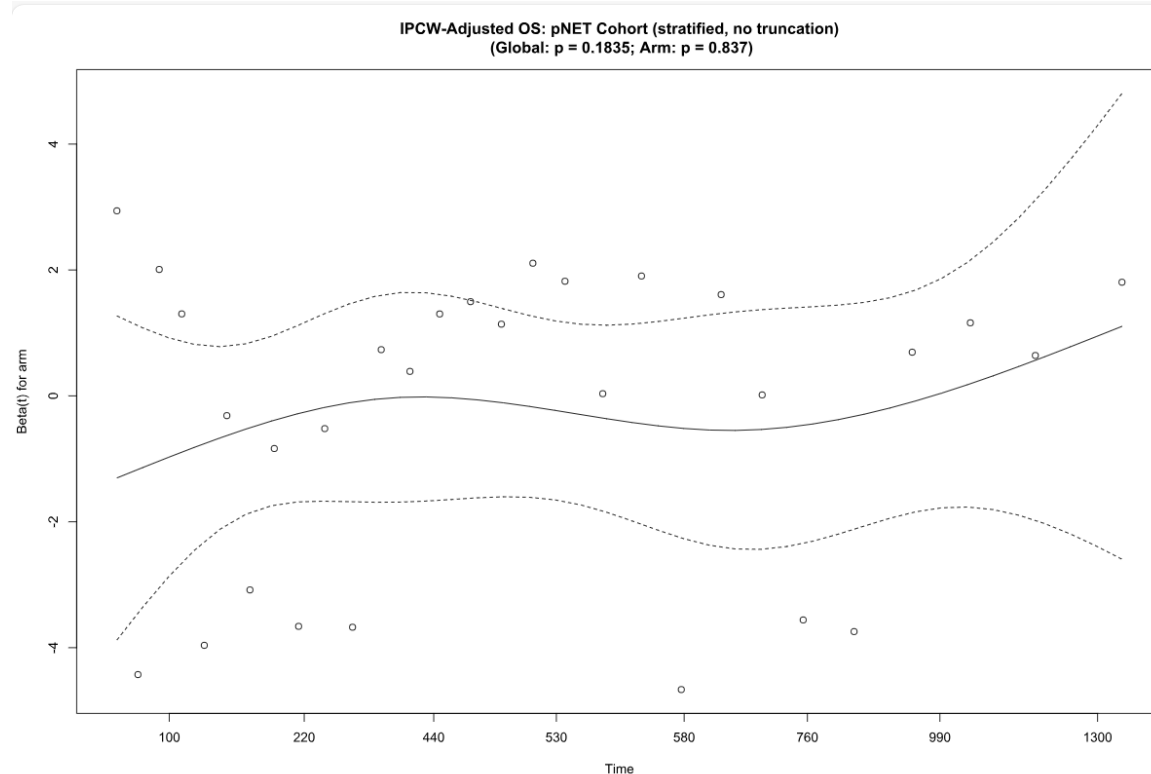
Abbreviations: CI: confidence interval; epNET: extra-pancreatic neuroendocrine tumour; HR: hazard ratio; pNET: pancreatic neuroendocrine tumour.

B10. Priority. Please clarify whether figures 20-25 in the appendix assessing proportional hazards in the OS data use the crossover adjusted data. If not, please provide this analysis.

Plots presented in Figures 20–25 in Appendix K of the submission were based on the OS ITT data.

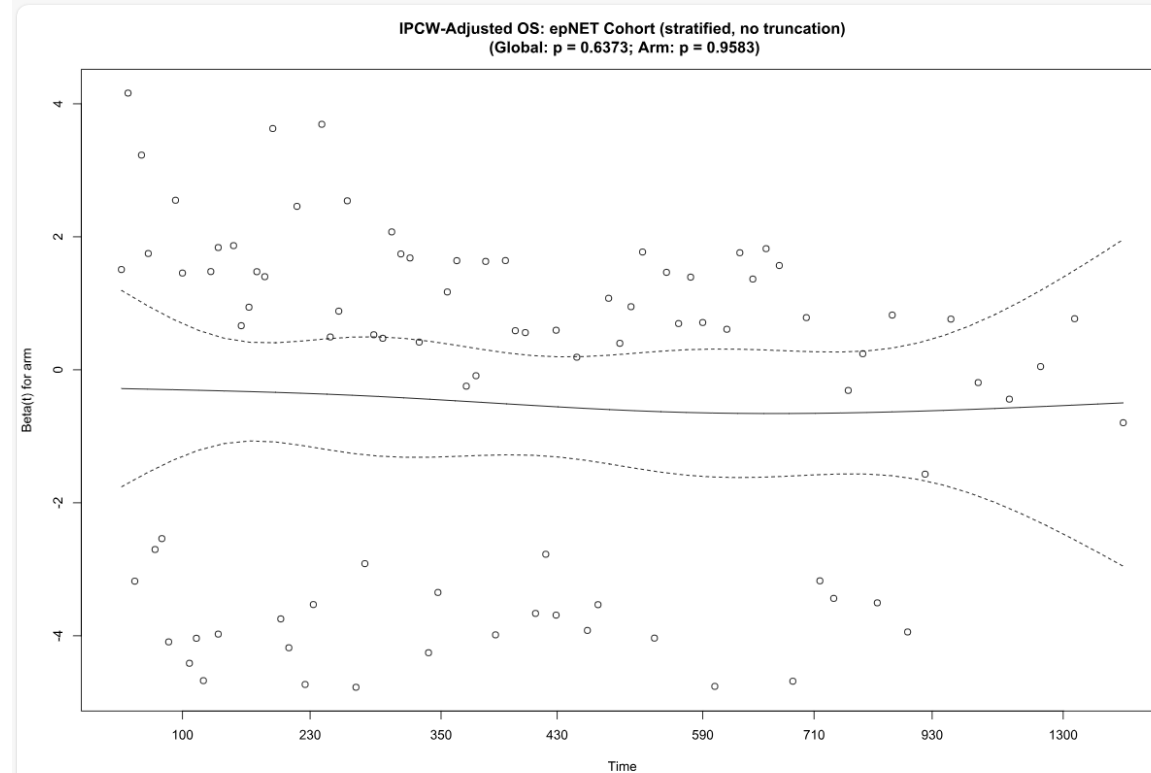
Schoenfeld residuals of the IPCW weighted outcomes model, which included baseline prognostic factors as covariates, were inspected, and are presented in Figure 15 for pNETs and Figure 16 for epNETs, respectively. The plots show the Schoenfeld residuals for the treatment covariate alongside p-values from the global Schoenfeld test and the Schoenfeld test for treatment. Neither the residual plots nor the Schoenfeld tests showed any evidence of non-proportional hazards for treatment arms in the pNET and epNET cohorts, with all p-values higher than 0.1. As such, it was deemed appropriate to model the relative treatment effect based on the IPCW-adjusted OS HR. Log cumulative and smoothed hazard plots were not produced because they do not account for the effect of other covariates and are thus less reliable for assessing the proportional hazards assumption for a Cox model with multiple covariates.

Figure 15: OS pNET: Schoenfeld residual plot (crossover-adjusted analysis)



Abbreviations: IPCW: inverse probability of censoring weights; OS: overall survival; pNET: pancreatic neuroendocrine tumour.

Figure 16: OS epNET: Schoenfeld residual plot (crossover-adjusted analysis)



Abbreviations: epNET; extra-pancreatic neuroendocrine tumour; IPCW: inverse probability of censoring weights; OS: overall survival.

B11. Priority. For both epNETs and pNETs, please include the weighted Kaplan-Meier (KM) curve produced through the IPCW crossover adjustment for BSC OS in the model, and provide plots showing these KM curves on the same axes as the relevant extrapolations.

Please provide this analysis for the separate populations requested in B1 and B3; i.e., using the population from CABINET separated into pNET, epNET (without lung NET) and epNET (lung), restricted to patients who were not pre-treated with sunitinib, if appropriate.

To determine the true impact of cabozantinib on OS, a post-hoc IPCW analysis was conducted to adjust for crossover, following the methods outlined in TSD 16 and TSD 24.^{22, 23} HRs estimated from the IPCW analysis were lower than the ITT HRs, due to adjustment for crossover in both the pNET and epNET cohorts, demonstrating a reduced hazard of death with cabozantinib. By accounting for prognostic factors in the estimation of weights and treatment effects, IPCW results correct bias induced by crossover but also potential bias resulting from imbalances in prognostic factors between treatment arms. Following the estimation of IPCW stabilised weights (following the default approach of the *ipcwswitch* package [CRAN]), IPCW HRs were estimated as adjusted HRs from a Cox model which was weighted using time-varying IPCW weights and which included the same baseline prognostic factors used as part of the weight estimation procedure as covariates. Including the baseline prognostic factors used for weight stabilisation in the weighted outcomes model is essential as the treatment effect estimated with stabilised weights is conditional on these prognostic factors. However, the resulting adjusted HR robustly captures the relative effect of each treatment having adjusted for crossover. The HRs being applied in the model therefore represent a robust comparative estimate that adjusts for crossover and, as demonstrated in the response to B10, is suitable given that the proportional hazards assumption holds.

Since standard KM curves are non-parametric, there are challenges in producing a weighted KM curve for OS that fully reflects IPCW adjustment with stabilised weights. While it is possible to supply the stabilised weights to produce KM curves, these KMs would not account for the fact that treatment effects using stabilised weights are conditional on the baseline prognostic factors. Instead, it is necessary to include the baseline prognostic factors in the weighted outcomes model in the stabilised IPCW approach as outlined in TSD 24.²³ In other words, KMs only weighted by IPCW weights do not reflect the comparative estimate obtained by IPCW. Thus, these KMs would not be expected to align with the adjusted HRs and should not be interpreted in conjunction with them.

The company notes that there is a lack of specific guidance on the generation of “IPCW-adjusted KMs” and independent extrapolations based on these, particularly when using widely recommended stabilised weights. Prior appraisals presenting extrapolations based on IPCW-adjusted OS against an “IPCW-adjusted KM” have not provided sufficient detail on the approach taken in order to enable replication, and many have used IPCW to adjust for receipt of subsequent treatment rather than crossover specifically, which means that the applicability of the selected approach may not be suitable here.²³

Nevertheless, the company investigated the feasibility of an approach to produce KMs using

stabilised weights and conduct independent extrapolation. This aimed to estimate survival probabilities by fitting separate weighted Cox models for OS to both cabozantinib and placebo treatment arms in order to incorporate stabilised weights. However, as these weighted outcomes models included coefficients for each baseline prognostic factor adjusted for, a survival probability can only be estimated at a specified level for each covariate. It was deemed that no single combination of levels for the covariates could reliably be applied to obtain a survival probability that reflected the patient population under analysis. In addition, while survival probabilities could technically be obtained using covariate levels determined by each patient's baseline characteristics, no appropriate approach to obtain an average of the survival probabilities for use in the model was identified. For pNETs, this approach is also complicated by small sample sizes (n=31 in the BSC arm), which increases the risk of overfitting from adjustment for eight covariates and thus also the risk of spurious survival probabilities for some covariate levels.

The company therefore maintains that the application of the adjusted HR obtained using IPCW with stabilised weights, as recommended in TSD 16, represents the most accurate estimate of comparative efficacy of cabozantinib and BSC with crossover adjustment.²²

B12. Priority. The EAG notes that the total number of patients eligible for crossover included in the crossover analyses for OS is relatively small for both pNETs and epNETs.

a) Please comment on the appropriateness of using IPCW, RPSFTM or two-stage crossover adjustments in light of the small patient numbers; in particular, please comment on the extent to which prior validation of these approaches is applicable to the CABINET trial.

As reported in Section 3.3.4 of the company submission and Appendix L, the IPCW method was considered the most robust method to adjust for crossover observed within the CABINET trial:

- Unlike the RPSFTM and IPCW methods, the two-stage approach separately models post-progression survival in patients eligible to switch (i.e., patients in the placebo arm who progressed). As there were very small numbers of patients eligible for crossover, and OS events among these patients were few, it was not possible to robustly adjust for a sufficient number of prognostic factors to balance differences between patients who did and did not switch and thus it was concluded that the two-stage method was not feasible.
- The RPSFTM approach aims to adjust the survival of placebo switchers by making two key assumptions. Firstly, it assumes that patients are comparable across randomised treatment arms, and so no adjustment of prognostic factors are required. Secondly, that the effect of cabozantinib is the same for participants switching onto treatment as for those randomised to it initially, relative to time on treatment; the extent to which this key common treatment effect assumption of RPSFTM holds is unclear. Notably, Latimer *et al.* (2024) suggested that RPSFTM may perform relatively poorly compared with other crossover adjustment methods when ITT analyses provided HRs close to 1, which is the case for the pNET and epNET cohorts in CABINET.¹⁹
- In contrast, by accounting for prognostic factors in the estimation of weights and treatment effects, IPCW results do not only correct bias induced by crossover but also potential bias

resulting from imbalances in prognostic factors between treatment arms in the epNET subgroups. In contrast to the two-stage method, analyses are not restricted to only including patients eligible to switch, hence allowing for an increased number of prognostic factors to be adjusted for. Additionally, IPCW does not suffer from the same limitation as RPSFTM in being able to adequately adjust a HR close to 1. Thus, the IPCW results provide the most robust estimate of the true treatment effect of cabozantinib for OS. Whilst the IPCW method is prone to error when a very large proportion of control patients switch onto the experimental treatment, this is not the case for the CABINET trial, where a minority of patients switched treatment arms.

- The IPCW method performs better when sample sizes are large and with or moderate proportions of switchers; sample sizes for the pNET (n=95) and epNET (n=193) cohorts in the IPCW analysis and the proportion of patients switching to cabozantinib in the pNET (38.7%) and epNET cohorts (29.0%) were deemed appropriate for the IPCW method to perform well.²⁵

b) Please provide scenario analysis for both the pNETs and epNETs populations using the ITT OS without crossover adjustment, using independent extrapolations for the cabozantinib and comparator arms.

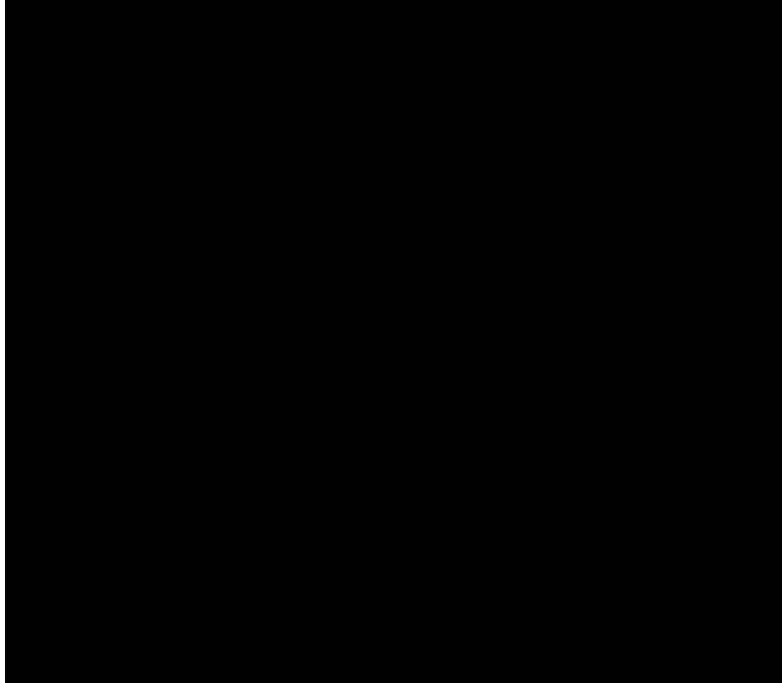
The independent extrapolations for the placebo arm from CABINET have been added as a scenario to model OS for BSC. As stated in Section 3.3.4 of the company submission and reiterated in the above response, ITT analysis results have considerably overestimated the OS of placebo patients and underestimated the relative benefits in OS for patients receiving cabozantinib resulting from unblinding and crossover which was permitted in CABINET after confirmation of progressed disease. Further, as presented in Appendix L of the company submission and the plots below, the KM of OS by treatment arm and switching status shows that for all populations patients who did not switch treatment were associated with poorer OS than patients who switched to cabozantinib. Thus, crossover-adjusted analyses to account for the impact of patients switching from placebo to cabozantinib after disease progression on OS were required and results based on the ITT OS that do not adjust for crossover are not appropriate for decision making.

When using direct extrapolations for BSC, an exponential distribution was selected for both pNETs and epNETs. Both distributions had good statistical fit for their population (first AIC and BIC for pNETs and first BIC for epNETs) with limited deviation from the hazard profiles. However, none of the generated extrapolations for pNETs provided plausible long term OS rates, with consistent overestimation compared to clinical estimates, exceeding the upper plausible value provided by clinicians at all timepoints. For epNETs, the exponential curve overestimates survival at 5 years relative to clinician's average estimates, but may underestimate survival at later timepoints; it was selected on the basis of producing estimates that fall in the middle of the range of models explored, and given the best statistical fit for BIC. As detailed in section 3.3.2 of the company submission, feedback from five UK NET clinicians was obtained via a pre-read questionnaire and teleconference, where they provided lower, upper, and most likely estimates for patient survival at 5, 10, and 15 years under BSC or cabozantinib. Their feedback for BSC for both epNETs and pNETs was provided in the original company submission and is repeated below in Table 20, alongside the long-term estimates from all extrapolation curves based on the ITT population not adjusted for cross-over.

Nonetheless, results of the scenario analysis are presented in Table 21. However, given the lack of clinical plausibility of the BSC OS extrapolations, it is advised that these results are interpreted

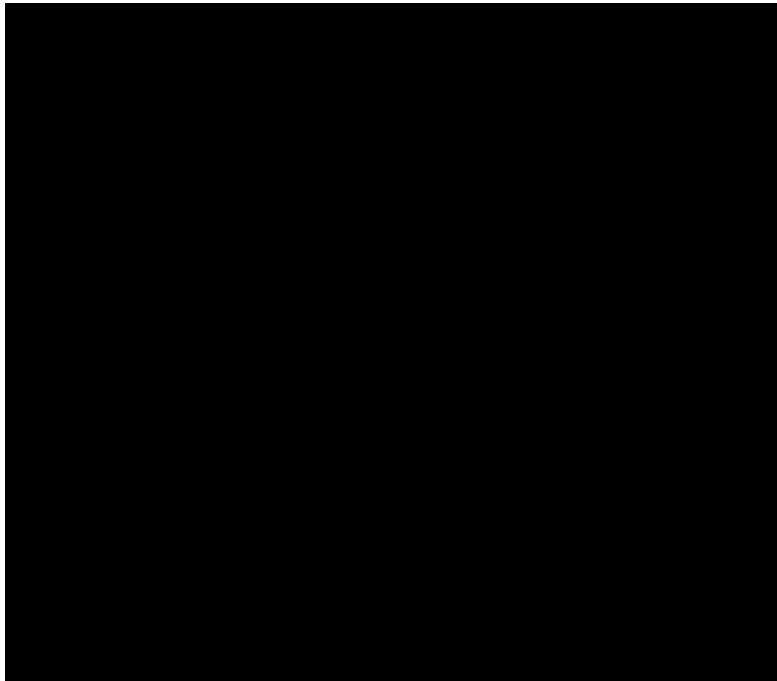
with caution and not relied upon for decision-making. It should also be noted that in this scenario, while patients in the BSC arm received cabozantinib, this has not been costed and is therefore a conservative estimate of cost-effectiveness both due to overestimating efficacy of BSC and underestimating the subsequent treatment costs.

Figure 17: KM plot for OS by treatment arm and switching status (pNETs)



Abbreviations: KM: Kaplan-Meier; OS: overall survival; pNETs: pancreatic neuroendocrine tumours

Figure 18: KM plot of OS by treatment arm and switching status (epNETs)



Abbreviations: epNETs: extra-pancreatic neuroendocrine tumours; KM: Kaplan-Meier; OS: overall survival

Table 20: Clinician and parametric survival landmark estimates for OS for BSC based on independent models fitted to ITT data (pNETs and epNETs)

Category	Curve	OS %		
		5	10	15
pNETs				
Average clinician estimates	Lower plausible limit	11.0%	2.8%	0.5%
	Most likely	20.0%	6.0%	2.0%
	Upper plausible limit	27.8%	9.8%	2.8%
Extrapolations	Exponential	34.6%	12.0%	4.1%
	Weibull	33.6%	10.8%	3.3%
	Loglogistic	36.6%	19.8%	13.0%
	Lognormal	39.3%	22.9%	15.3%
	Generalised gamma	40.7%	25.5%	18.3%
	Gompertz	39.6%	23.8%	17.9%
epNETs				
Average clinician estimates	Lower plausible limit	5.8%	2.0%	0.5%
	Most likely	10.8%	3.8%	1.5%
	Upper plausible limit	15.5%	6.8%	2.3%
Extrapolations	Exponential	12.6%	1.6%	0.2%
	Weibull	6.5%	0.1%	<0.1%
	Loglogistic	13.2%	4.6%	2.4%
	Lognormal	14.5%	4.5%	1.9%
	Generalised gamma	10.3%	1.4%	0.3%
	Gompertz	7.1%	<0.1%	<0.1%

Light orange shading indicates that the predicted survival of the selected curve falls below the lower plausible limit of the clinician's estimate of overall survival. Light blue shading indicates that the curves predict survival that exceeds the clinician's upper estimate of overall survival.

Abbreviations: BSC: best supportive care; epNET: extrapancreatic neuroendocrine tumour; HR: hazard ratio; NET: neuroendocrine tumour; OS: overall survival.

Table 21: BSC independent extrapolations results

Scenario	pNETs			epNETs		
	Inc costs	Inc QALYs	ICER	Inc costs	Inc QALYs	ICER
Base case: IPCW HR	████	██	£24,815	████	██	£12,849
ITT OS independent extrapolations	████	██	£41,413	████	██	£12,102

All epNET results qualify for a 1.2x severity modifier, which is applied here.

Abbreviations: epNETs: extra-pancreatic neuroendocrine tumours; ICER: incremental cost-effectiveness ratio; IPCW: inverse probability of censoring weights; ITT: intention to treat; OS: overall survival; pNETs: pancreatic neuroendocrine tumours; QALYs: quality adjusted life years.

B13. Priority. Please include an option in the economic model that allows the user to change between the IPCW, RPSFTM, and the two-stage approach to adjust OS for crossover.

- a) Please provide this analysis for the separate populations requested in B2 and B3; i.e., using the population from CABINET separated into pNET, epNET (without lung NET) and epNET (lung), restricted to patients who were not pre-treated with sunitinib, if appropriate.**
- b) Please provide scenario analysis for both the pNETs and epNETs populations using the RPSFTM and two-stage OS crossover adjustment, including the additional relevant comparators requested in B1.**

As per the response to question B12, as there were very small numbers of patients eligible for crossover, and OS events among these patients were few, it was not possible to robustly adjust for a sufficient number of prognostic factors to balance differences between patients who did and did not switch and thus it was concluded that the two-stage method was not feasible.

As noted in the company submission, HRs derived using the RPSFTM have considerable limitations compared to the IPCW method, and are not recommended for decision making. Specifically, Latimer *et al.* (2024) indicated that RPSFTM may perform poorly compared to other crossover adjustment methods when the ITT HRs are close to 1, as is the case for the epNET and pNET cohorts in CABINET.¹⁹ IPCW HR was selected as the base case option because it accounts for prognostic factors in weighting and treatment effect estimation, thereby correcting for bias from crossover and imbalances in prognostic factors between treatment groups in the epNET subgroups. Additionally, IPCW is less affected than RPSFTM when adjusting HRs near 1.

However, to address the EAG’s request, the RPSFTM HRs and 95% CIs are presented in Table 22 for each population for pNETs and epNETs. RPSFTM HRs have been included as a scenario in the model for pNETs, epNETs, epNETs (without lung) and lung NETs (using otherwise the same methodology as outlined in the response to question B2). As noted in B2, the HRs generated post-hoc for the lung epNET subgroup are not included given the data is subject to significant limitations in the breaking of randomisation and imbalances in baseline characteristics across treatment arms, as well as very small patient numbers. Therefore, the HRs for the full epNET cohort have been applied given these are the most robust to inform comparisons between cabozantinib and BSC, with corresponding results are presented in

Table 22.

Table 22: RPSTFM-Adjusted OS HRs with 95% CI

Population	Stratified RPSFTM HRs for cabozantinib vs placebo without recensoring (95% CI)
pNETs	
epNETs	

Abbreviations: CI: confidence interval; epNETs: extra-pancreatic neuroendocrine tumours; HR: hazard ratio; OS: overall survival; pNETs: pancreatic neuroendocrine tumours; RPSFTM: rank preserving structural failure time model.

Table 23: OS Adjusted HRs

Scenario	pNETs			epNETs			Lung NETs			epNETs (without lung NETs)		
	Inc costs	Inc QALYs	ICER	Inc costs	Inc QALYs	ICER	Inc costs	Inc QALYs	ICER	Inc costs	Inc QALYs	ICER
<i>Base case: IPCW HR</i>	████	██	£24,815	████	██	£12,849	████	██	£20,904	████	██	£13,718
RPSTFM	████	██	£43,974	████	██	£20,588	████	██	£35,950	████	██	£22,305

All epNET results (including lung NETs and epNETs [without lung NETs]) qualify for a 1.2x severity modifier, which is applied here.

Abbreviations: epNETs: extra-pancreatic neuroendocrine tumours; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; IPCW: inverse probability of censoring weights; OS: overall survival; pNETs: pancreatic neuroendocrine tumours; QALY: quality-adjusted life year; RPSFTM: rank preserving structural failure time model.

B14. Priority. The EAG considers that proportional hazards assumption being met does not justify excluding independently modelled BSC curves, and that use of independent extrapolations gives more flexibility in obtaining a good fit to KM curves. Therefore, please update the model as per the following requests:

- a) When including the other relevant comparators described in question A1 and B1, please assess the viability of having independently fitted curves using the weighted KM curve produced by the IPCW crossover adjustment, and allowing for alternative cross-over methods to be used to estimate the BSC curve) for both pNETs, epNETs (excluding lung) and lung NETs. If appropriate, also conduct this analysis for the population who did not receive prior sunitinib in CABINET,
- b) If the company decides to include an analysis in the model where cabozantinib and BSC (only) are compared using CABINET data (i.e., without modelling other comparators), please include an option to use independent extrapolations of OS for cabozantinib, BSC (using the weighted KM curve produced by the IPCW crossover adjustment, and allowing for alternative cross-over methods to be used to estimate the BSC curve)
- c) For whichever option the company decides to follow (a or b), please include:
 - I. Model-fit statistics;
 - II. Plots showing KM curves alongside OS extrapolations;
 - III. Probabilistic scenario results using these independent model fits.

As per the response in B11, the company investigated the feasibility of independently fitting curves using the weighted KM curve produced by the IPCW crossover adjustment, but no robust analyses were feasible. The company maintains that the application of the adjusted HR obtained using IPCW with stabilised weights, as outlined in TSD 16, represents the most accurate estimate of comparative efficacy of cabozantinib and BSC with crossover adjustment.²²

B15. Priority. The company appears to be missing the OS KM data for “pNETs Extrapolations” in columns DO and DP and “epNETs Extrapolations” in columns DL and DM. Please add these into the model.

OS KM data adjusted for crossover are not available nor appropriate to produce and so are not provided in the model.

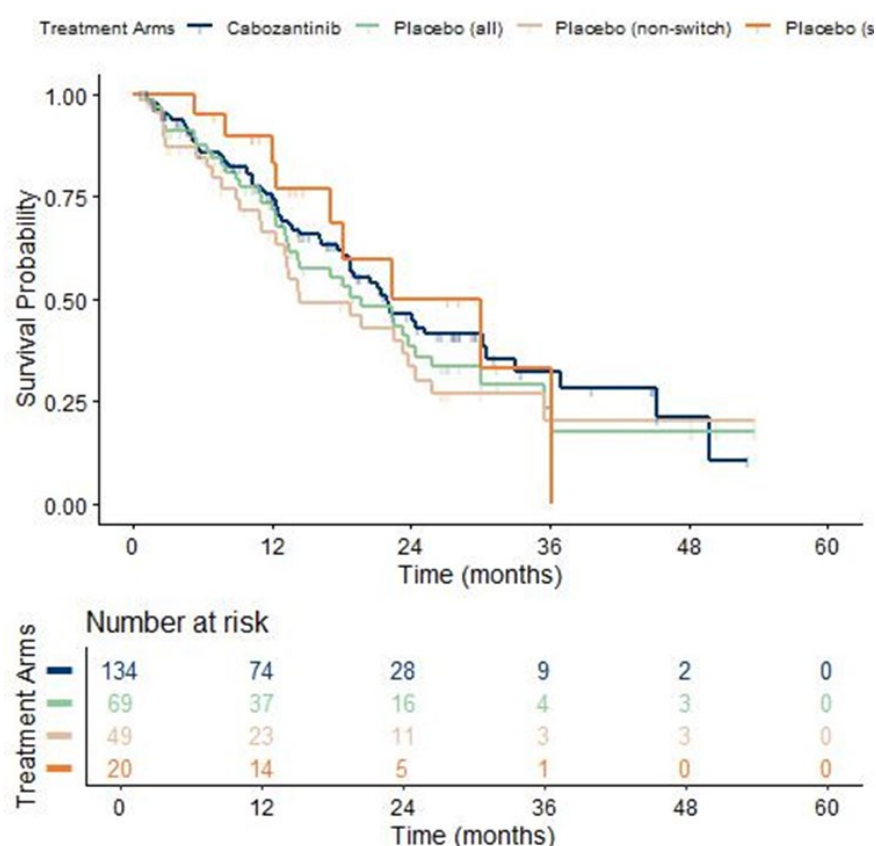
As noted in the response to B14a, TSD24 notes that the use of IPCW with stabilised weights (as per the analyses) requires that baseline prognostic factors used in the numerator model of the weight estimation are included as covariates in the weighted outcomes model.²⁶ It is therefore not appropriate to estimate a KM curve or extrapolation based on the IPCW re-weighted dataset without either adjusting for baseline prognostic factors or employing an adjusted KM estimator that would cancel out numerator probabilities.

B16. Please provide the OS KM data used to derive figure 32 and 33 from the appendix.

- a) Figure 32 appears to cut off early. Please explain why and provide a version of this which shows results up to 60 months

A revised figure has been presented below.

Figure 19. KM plot of OS by treatment arm and switching status: pNET cohort



Abbreviations: KM: Kaplan–Meier; OS: overall survival; pNET: pancreatic neuroendocrine tumour.

- b) Both of these figures appear to show OS survival for placebo (non-switch) patients significantly higher than that predicted in the model. In pNET the model predicts 33% OS at 50 months whereas its approximately 40-45% in the KM data. In epNET the model predicts approximately 9% OS at 50 months whereas its approximately 20-25% in the KM data. Please can the company explain the discrepancy?

Figures 32 and 33 presented in the appendix of the CS outline KM plots for the placebo arms, stratified by switchers and non-switchers. This is derived directly from the ITT data and so there is no expectation that the placebo (no switch) arm would match up with BSC modelled by an IPCW HR. IPCW incorporates data from both switchers and non-switchers to generate a probability of switching. This enables the crossover adjustment after censoring the placebo (switch).²⁵

Therefore, it is inappropriate to compare crossover adjusted BSC landmark survival with placebo (no switch) patients, as the latter artificially censors patients who switched which causes selection bias. In this case, where placebo patients switch to cabozantinib upon progression, it can be expected that this would bias results in favour of placebo. This is broadly in line with what the KM data shows.

Time to treatment discontinuation

B17. The assumption made in the BSC arm for TTD that discontinuation of SSAs occurs in line with discontinuation of placebo is not clinically justified. Please source an alternative value for discontinuation of SSAs.

Based on the findings of the clinical SLR, no alternative value for discontinuation of SSAs was identified. Therefore, sourcing another value by targeted searches is not likely and so TTD for placebo has been retained in the model. Scenarios exploring alternative TTD assumptions for concomitant SSAs have been presented in the response to question B28. Additionally, modelling discontinuation of SSAs in the BSC arm using PFS instead of TTD has minimal impact on the ICERs, reducing the ICERs to £24,235 and £12,049 for pNETs and epNETs, respectively.

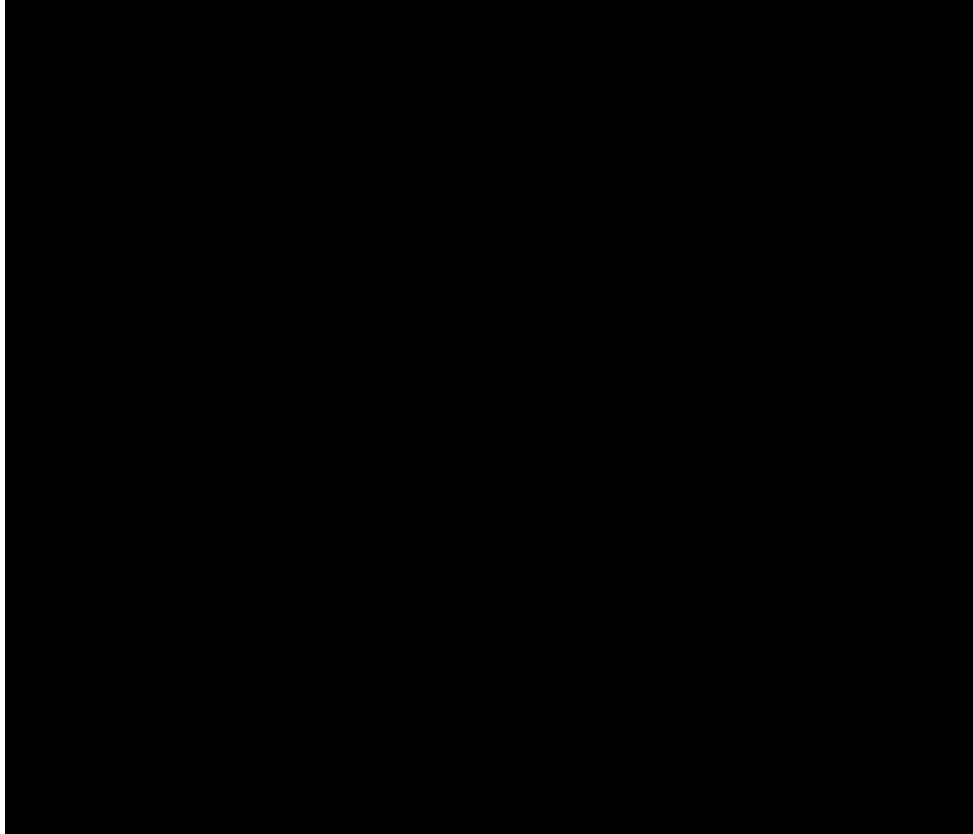
B18. In pNET and epNET cabozantinib shows increases in treatment discontinuation at 12 months. Is this an artefact of the clinical trial or would this take place in practice? Please provide a scenario that uses KM data to model TTD for cabozantinib.

The increased rate in treatment discontinuation at 12 months could reflect the fact that the patients included in the CABINET trial were heavily pre-treated and thus as result of treatment with cabozantinib and adverse events may have resulted in an increased discontinuation rate over time. Additionally, the assessment intervals in the CABINET trial (tumour response and progression assessed at 12-week intervals [± 1 week]) could contribute to a delay between treatment discontinuation and the recording of disease progression.

The model has been updated to include a scenario which models KM data for cabozantinib TTD,

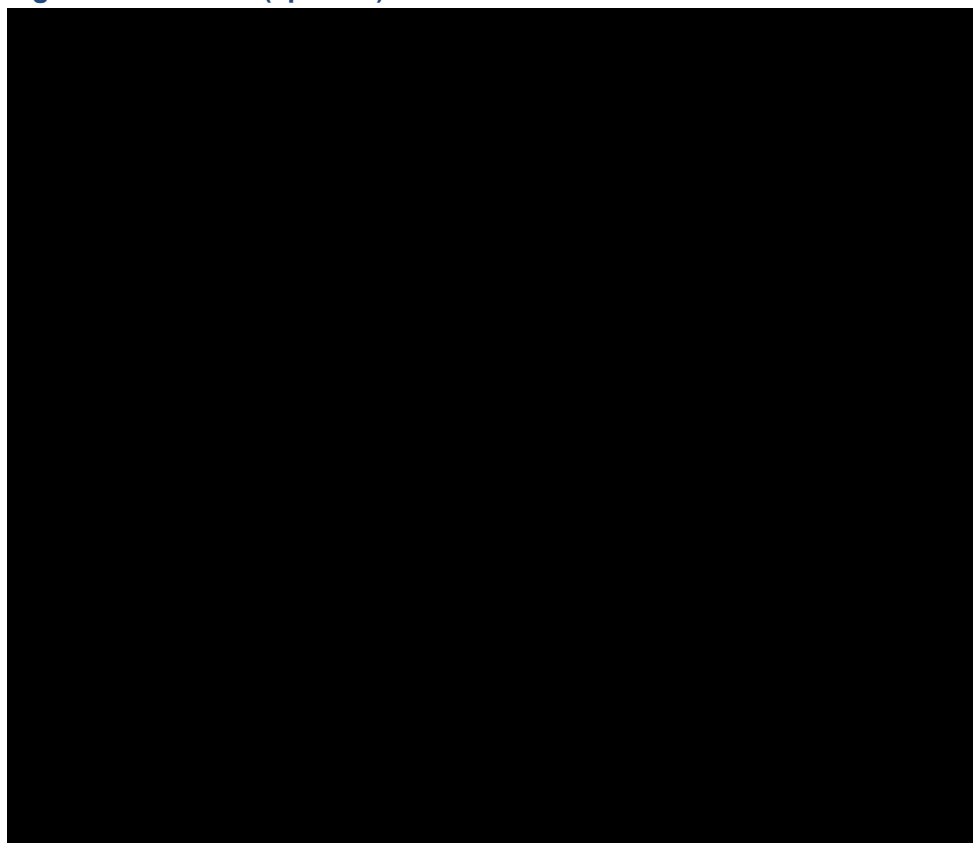
thereby assuming that once the TTD KM data ends, there is no further treatment discontinuation until progression, which is unlikely to be clinically plausible. The ICER is increased in the pNET population reflecting the longer treatment duration, and marginally change for the epNET population.

Figure 20: TTD KM (pNETs)



Abbreviations: KM: Kaplan-Meier; pNETs: pancreatic neuroendocrine tumours; TTD: time to treatment discontinuation

Figure 21: TTD KM (epNETs)



Abbreviations: epNETs: extra-pancreatic neuroendocrine tumours; KM: Kaplan-Meier; TTD: time to treatment discontinuation

Table 24: TTD Modelling Approach for Cabozantinib

Scenario	pNETs			epNETs		
	Inc costs	Inc QALYs	ICER	Inc costs	Inc QALYs	ICER
Base case: TTD base case extrapolations	██████	██	£24,815	██████	██	£12,849
Cabozantinib TTD KM	██████	██	£30,875	██████	██	£12,384

All epNET results qualify for a 1.2x severity modifier, which is applied here.

Abbreviations: epNETs: extra-pancreatic neuroendocrine tumours; ICER: incremental cost-effectiveness ratio; KM: Kaplan-Meier; QALY: quality-adjusted life year; pNETs: pancreatic neuroendocrine tumours; TTD: time to treatment discontinuation

Systematic literature reviews

B19. The EAG considers that the reporting of the results of the systematic review of published cost-effectiveness studies is unclear. Please clarify why the same studies appear multiple times in Table 21 of the CS.

Data in Table 21 of the company submission are grouped by NET type (pNETs Only; epNETs Only); similar to how the data are presented in Table 3. As such, studies that stratified data by NET type are presented twice. An updated table clearly stratifying by NET type is presented in

the Appendix to this response.

B20. The EAG notes that the systematic review of published cost-effectiveness studies included evaluations of patients with NETs published from 2014 onwards in 'priority markets' (Belgium, France, Italy, Spain, and the United Kingdom). Please clarify why these markets were selected.

Due to a lack of evidence identified by the initial searches, the eligibility criteria specified in the protocol were expanded. The UK was considered the highest priority market and data was supplemented by additional European data.

Population

B21. Please clarify how body surface area was calculated, and where the input data was sourced. Table 24 states that body surface area was calculated from Ipsen Data on File CABINET IPD but the EAG could not locate the data; please provide the relevant data.

Body surface area (BSA) was calculated for each participant in the CABINET trial using the Mosteller formula:

$$BSA = \sqrt{\frac{W \times H}{3600}},$$

where W is the weight in kg and H is the height in cm. As height was not collected during the CABINET trial, this was derived from the weight and BMI of each participant using the following formula:

$$H = \sqrt{\frac{W}{BMI}}$$

where H is the height in m, W is the weight in kg and BMI is recorded in kg/m². Once BSA had been calculated where possible for each participant, the mean and standard deviation were then summarised across participants. For input into the model, the standard error was then calculated from the standard deviation of BSA and the sample size for each of the cohorts with BSA data available.

Health-related quality of life

B22. Priority. The CS states that the utility value used for the progression-free health state in the base case was derived using a regression analysis adjusting for baseline utility and stratified by cohort, and that a secondary analysis investigated the impact of adjusting for relevant covariates. Please give details of both analyses; specifically, please include justification for the

selection of covariates, and relevant diagnostic plots for assessing goodness of fit.

Given that EuroQol-5 dimension (EQ-5D) was not collected in the CABINET trial, EORTC quality of life questionnaire-core 30 (QLQ-C30) data was mapped onto EQ-5D utility index scores to generate utility values for the economic model in line with the NICE manual for health economic evaluation.^{27, 28} The individual patient data (IPD) from EORTC QLQ-C30 data collected in CABINET were mapped to EQ-5D using the response mapping algorithm from Longworth *et al.* (2014) to estimate utility values for the PF and PD health states.²⁸

Primary analysis

The model formula for the primary analysis is shown below:

$$utility\ value \sim health\ state + baseline\ utility\ value + 1|patient\ ID.$$

This regression model derived the relationship between utility value and health state, whilst adjusting for baseline utility. Additionally, a random effect was included to account for the correlation in individual participant's repeated measurements. No random intercept for time was included due to convergence issues.

Secondary analysis

A further secondary analysis was conducted to investigate the impact of adjusting for prognostic factors, by including these as further covariates in the model as shown below:

$$utility\ value \sim health\ state + baseline\ utility\ value + prognostic\ factor\ 1 \\ + prognostic\ factor\ 2 + \dots + 1|patient\ ID$$

This only included a random intercept by individual as inclusion of both a random slope for time and a random intercept by individual caused convergence issues.

Relevant prognostic factors for consideration for inclusion in this model were identified through a brief review of relevant literature and Ipsen medical input. This is summarised in Table 25.

Table 25. Summary of potential prognostic factors

Characteristic	Advisor Perspective	Notes from Literature Searches ²⁹⁻³⁵ and CABINET Trial	Adjust for in Analysis	Data Format
Primary tumour site	Highlighted by clinicians as important (related to Ki-67 status, see below)	Potential prognostic factor	Yes in epNET No in pNETs	Categorised as: lung/thymus, GI tract (reference), unknown/other
Tumour grade	Highlighted by clinicians as important (related to Ki-67 status, see below)	Tumour grade was identified as one of the most important prognostic factors from a brief literature review	Yes	Categorised as: Grade 1 (reference), 2, 3 and unknown (if feasible)
Disease differentiation	Highlighted by clinicians, but patients should already be well differentiated. There are no poorly differentiated patients in CABINET	Potential prognostic factor	No, as few patients not well differentiated	-
Disease stage	Highlighted by clinicians as prognostic, but all epNET and most pNET (>94%) patients in CABINET had metastatic disease. Presence of specific metastasises is important, such as liver, peritoneal, bone and lung	Extent of disease is a potential prognostic factor. It was inconsistent as to whether this referred to simply presence, number or specific location	No, as very few patients locally advanced	-
Disease duration	Duration of metastatic disease was mentioned by clinicians as important, at least more so than duration since first therapy/diagnosis	Only information on duration since diagnosis in CABINET, not duration since onset of metastatic disease	No, as not defined from onset of metastatic disease	-
Absolute Ki-67 status	Highlighted as the most important factor by one of the clinicians as it incorporates other characteristics (e.g. tumour grade, tumour site)	No available data from CABINET on this characteristic	No, as not available in CABINET	-
Hormone syndrome/functional status	Highlighted by clinicians as important	Potential prognostic factor	Yes	Categorised as: Functional, non-functional (reference) and unknown (if feasible)

Prior therapy	Highlighted during the ad-board as important	Lack of prior surgical intervention was a potential further prognostic factor	Yes	Categorised as: Number of prior lines of therapy: 1 (reference), 2 or ≥ 3
ECOG Performance Status	Highlighted by clinicians as important	Potential prognostic factor	Yes	Categorised as: 0 (reference) and ≥ 1
Comorbidities	Of lower importance		No	-
Age	Highlighted during ad-board as potentially important, but not as relevant as other characteristics	Highlighted in the literature as prognostic	Yes	As a continuous variable
Sex	Of lower importance		No	-
Race	Of lower importance		No	-

Footnote: characteristics in **bold blue** are considered to be of primary importance.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; epNET, extra-pancreatic neuroendocrine tumours; pNET, pancreatic neuroendocrine tumours.

Model Fit Statistics

Based on initial data exploration of the distribution of EQ-5D-3L-based utility values, linear MMRMs were deemed appropriate for the analyses. Only models with random intercepts by individual converged; models with random intercepts and slopes for time, by individual, failed to converge.

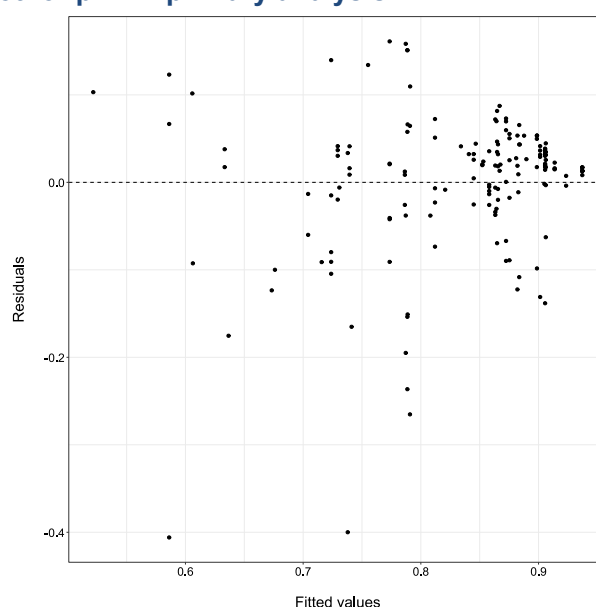
Although marginal R^2 demonstrated some improvement when adjusting for prognostic factors for the epNETs analysis, model fit was similar across primary and secondary analyses, with adjustment for treatment or prognostic factors not resulting in an improved model fit, as assessed by AIC, ME, MSE and RMSE, and the result from the primary analysis model were selected for inclusion in the economic model.

Table 26. Summary of model fit: pNET

Analysis		AIC	R^2		ME	MSE	RMSE
			Marginal	Conditional			
Primary		-255.047	0.256	0.51	<0.001	0.007	0.082
Secondary	Prognostic Factors	-199.307	0.284	0.551	<0.001	0.007	0.081

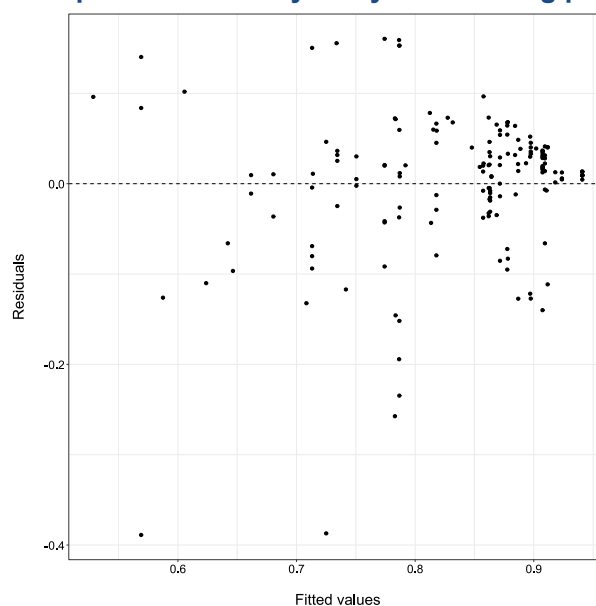
Abbreviations: AIC, Akaike Information Criterion; ME, mean error; MSE, mean squared error; pNET, pancreatic neuroendocrine tumours; PF, progression-free; RMSE, root mean squared error.

Figure 22. Residual plot for pNET: primary analysis



Abbreviations: pNET: pancreatic neuroendocrine tumours.

Figure 23. Residual plot for pNET: secondary analysis including prognostic factors



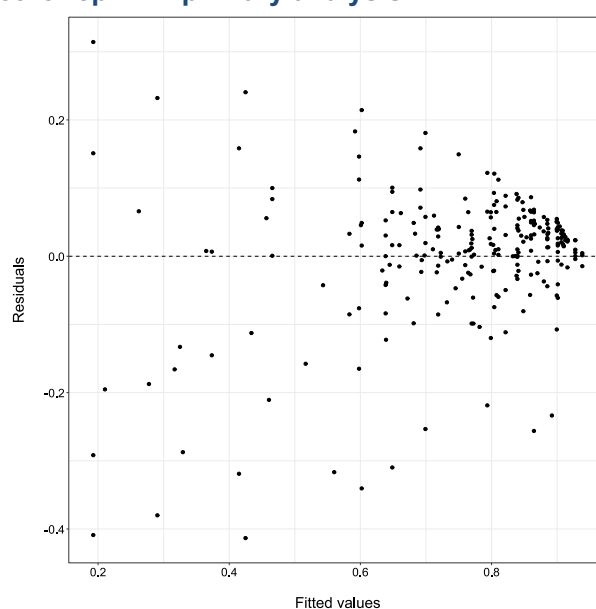
Abbreviations: pNET: pancreatic neuroendocrine tumour.

Table 27. Summary of model fit: epNET

Analysis		AIC	R^2		ME	MSE	RMSE
			Marginal	Conditional			
Primary		-171.646	0.282	0.716	<0.001	0.01	0.101
Secondary	Prognostic Factors	-120.92	0.377	0.726	<0.001	0.01	0.102

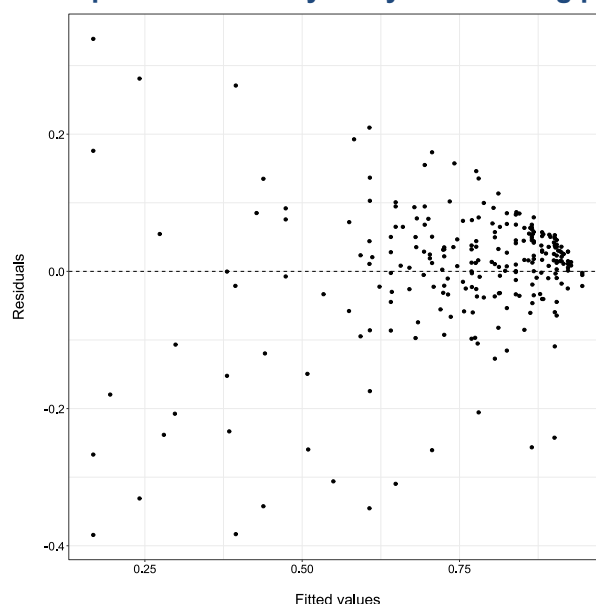
Abbreviations: AIC, Akaike Information Criterion; epNET, extra-pancreatic neuroendocrine tumours; ME, mean error; MSE, mean squared error; PF, progression-free; RMSE, root mean squared error.

Figure 24. Residual plot for epNET: primary analysis



Abbreviations: epNET: extra-pancreatic neuroendocrine tumour.

Figure 25. Residual plot for epNET: secondary analysis including prognostic factors



Abbreviations: epNET : extra-pancreatic neuroendocrine tumour.

B23. Please provide scenarios in which:

- a) The utility value for the progression-free (PF) health state for pNETs is taken from Swinburn *et al.* 2012,³⁶ and the progressed disease (PD) utility value is:
 - i) Obtained by applying the relative decrement sourced from Swinburn *et al.* 2012 to the PF utility value;³⁶
 - ii) Obtained by applying the relative decrement sourced from the ERASMUS trial to the PF utility value.³⁷
- b) The utility value for PF health state for epNETs is aligned with Mujica-Mota *et al.* 2018 (Table 22, both base case and alternative values),³⁸ and the progressed disease (PD) utility value is:
 - i) Obtained by applying the relative decrement sourced from Swinburn *et al.* 2012 to the PF utility value;³⁶
 - ii) Obtained by applying the relative decrement sourced from the ERASMUS trial to the PF utility value;³⁷
 - iii) Aligned with the absolute value from Swinburn *et al.* 2012;³⁶
 - iv) Aligned with the absolute value from the ERASMUS trial.³⁷

The proposed utilities (with the placebo PF value and pooled analysis for the alternative value from Mujica-Mota *et al.* (2018) have been included in the model as a scenario analysis.³⁸ The PF utility values from Swinburn *et al.* (2012) and Mujica-Mota *et al.*^{36, 38} (2018) were not included in the company submission as utility values were available directly from the CABINET trial for the

PF health state, best reflecting the population expected to be treated with cabozantinib, and which were validated at an advisory board and deemed appropriate by clinical experts. Use of utility values derived from the CABINET trial is in line with the NICE manual for health technology evaluation, which states that changes in HRQoL should be directly reported by patients.²⁷ Application of absolute values in the PD health state were explored as scenarios in the original company submission however the decrement method was chosen as the base case, based on clinical validation, as detailed in Section 3.4.3 of the company submission.

The requested utility scenarios for the pNETs population increase the ICER due to a lower PF utility value (0.771) from Swinburn *et al.* (2012) compared to CABINET (0.819).³⁶ The ICERs for epNETs decrease across all scenarios relative to the base case due to increased utility value in the PF state (0.807 for Mujica-Mota *et al.* (2018) base case and 0.779 alternative value, compared to in CABINET (0.731)).^{36, 38} As previously stated, the PF utilities derived directly from the CABINET trial best represent the patient population and are validated by clinical experts, making them the most appropriate for the base case. Similarly, using PD decrements applied to these robust baseline values ensures more accurate and reliable health utility estimates when direct data are inconsistent.

B24. The EAG considers that the following disutilities used for adverse events are inappropriate:

- a) Hypertension: this disutility was ultimately sourced from an analysis in TA428, in which all included adverse events were assigned the same disutility; therefore, this disutility is not specific to hypertension.

In the original company submission, a disutility of 0.085 is applied to patients who experience hypertension, as used in TA911.³⁹ An alternative disutility for hypertension was identified in Swinburn *et al.* (2010), a study which looked at health state utilities for patients receiving treatment for metastatic renal cell carcinoma in the UK, using time trade-off methodology.⁴⁰ A disutility of -0.153 (calculated by subtracting 0.642, representative of a 'stable with hypertension grade III' health state from 0.795, representative of a 'stable with no AE' health state) has been included as a scenario in the model for patients with experiencing hypertension. This disutility has been used in other NICE technology appraisals, such as TA917.⁴¹ Changing this disutility from 0.085 to 0.153 has a negligible impact on cost-effectiveness results.

- b) Small intestinal obstruction: this disutility was sourced from TA1011, and was ultimately derived from disutilities for urinary obstruction and incontinence; therefore, this disutility is not relevant to small intestinal obstruction.

At the time of the original company submission, extensive targeted searches were conducted to identify the most appropriate disutility for small intestinal obstruction. The most appropriate input that could be identified was the disutility of -0.255 assumed to be the same as other genitourinary complications. No alternative values were identified, however as noted in response to the previous part of this question, altering this input has a very limited impact on results.

- c) Embolism: this disutility was sourced from TA476, which in turn was sourced from the EAG report for rivoraxaban (2012). However, the value quoted does not match the original source given (Locadia et al. 2004).⁴²

The disutility for pulmonary embolism (-0.037) was aligned with the approach taken in TA287, which to our understanding was calculated from Locadia *et al.* (2004) as the difference between perfect health (assumed utility value of 1) and the health state utility value of a patient with pulmonary embolism (0.63).^{42, 43} A scenario has been included in the model which assumes the baseline health is 0.96 (akin to 'no VKA treatment' health state) rather than 1, generating a disutility of 0.330. Changing this disutility has a negligible impact on cost-effectiveness results.

Please update the model to include more appropriate disutility values for these adverse events.

B25. The EAG considers that insufficient justification has been given for the data used to inform the expected duration of adverse events.

- a) Please provide a justification for the sources used for duration of adverse events (in particular, justifying the use of an average of the duration of other adverse events for stomatitis, PPE syndrome and small intestinal obstruction).

Prior oncology appraisals reporting the duration of AEs were included in the model. Where a suitable value could not be identified, an average of all other AE durations was included which is a common approach used in prior appraisals. As outlined in B25b below, AE durations were varied in the deterministic sensitivity analysis (DSA) using a user-adjustable variation of 20%. These had a minimal impact on the ICER and so are not considered a key uncertainty in the model.

- b) Please provide a scenario in which the duration of adverse events is informed by data from the CABINET trial (for example, assuming the duration of adverse events aligns with the mean dose hold).

The AE disutilities are not highlighted as a key driver of the ICER in the DSA plot presented in the cost-effectiveness model (CEM). Therefore, the duration of adverse events is unlikely to be a source of great uncertainty, and a scenario has not been included.

Concomitant treatments

B26. Priority. In the results presented in the model and CS, SSAs in the progression-free health state are considered a concomitant treatment for the cabozantinib arm, but as part of the comparator treatment for the BSC arm.

The EAG considers this to be misleading. Please update the model so that SSAs are modelled as a concomitant treatment in both arms.

The results page of the model has been updated to present treatment acquisition and administration costs for BSC as £0 and the respective costs displayed as concomitant treatment.

B27. Priority. Costs for concomitant treatment with SSAs are applied in the model only up to the modelled time to treatment discontinuation of cabozantinib or placebo, as appropriate. However, the CS states that patients receiving concomitant SSAs would continue to receive treatment indefinitely.

- a) Please update the model to apply costs for concomitant SSA treatment up to disease progression in both treatment arms.**
- b) Please also provide a scenario in which patients receiving concomitant SSA treatment do so from baseline until death in both treatment arms, rather than modelling SSAs as a subsequent treatment.**

The company submission models concomitant therapy usage in the progression-free health state in line with the TTD of cabozantinib and BSC of the CABINET trial. As such, when a patient discontinues cabozantinib or BSC, they are also modelled to discontinue their concomitant SSA. As noted in the original company submission, clinician feedback indicated that concomitant SSAs would be continued (while a patient is on active treatment); that is to say, patients who were receiving concomitant SSAs when progression-free, would continue receiving SSAs when they progress alongside subsequent therapy. Therefore, in the original company submission, the same proportion of patients from the PF health state received concomitant therapy in the PD health state. Patients are not expected to receive concomitant therapy until death (implying no discontinuation of SSAs despite potential discontinuation due to lack of efficacy or AEs), as is evidenced from the CABINET trial where a lower proportion of patients had concomitant SSA usage after progression than when entering the trial (21–23% after progression, as provided in a scenario, versus 54–70% at baseline).

As requested, two scenarios have been included in the model to apply costs for concomitant SSA treatment until a) disease progression, and b) until death, in both arms. However, the latter scenario is not considered clinically plausible.

B28. Please confirm that Tables 14.3.1.2.1.a and 14.3.1.2.1.b in the CSR reflect the use of concomitant SSAs during the CABINET trial. In addition:

- a) Please explain why the proportion of patients using concomitant SSAs at baseline (Tables 14.1.4.1.a.1 and 14.1.4.1.b.1) were instead used to parametrise the model.**

Concomitant SSAs were permitted throughout the CABINET trial and values with UK clinicians validating that these would typically be administered indefinitely in the majority of patients whilst on systemic therapy. Therefore, the baseline values presented in Tables 14.1.4.1.a.1 and

14.1.4.1.b.1 were deemed to be reflective of UK clinical practice.⁸ The values presented in Tables 14.3.1.2.1.a and 14.3.1.2.1.b were investigated by the company and were found to represent subsequent treatment only.⁸

- b) Please also present a scenario in which the proportion of patients treated with concomitant SSAs aligns with Tables 14.3.1.2.1.a and 14.3.1.2.1.b.

As stated above, these tables are not appropriate to model concomitant therapies and have therefore not been added as a scenario to the model.

B29. Please clarify how the inputs for the proportion of patients treated with SSAs receiving lanreotide/octreotide, and the proportion receiving each dosage of these treatments, were derived. Please also provide scenarios exploring the impact of varying these inputs on overall results.

The proportion of patients receiving lanreotide and octreotide, and the proportion receiving each dosage, are based on internal estimates derived from UK sales data of lanreotide and octreotide and the proportions of each injection dosage that are sold. The model has been updated to vary the proportion of patients receiving lanreotide versus octreotide, and the market shares of each dose of a treatment within the DSA to identify the impact of varying these inputs on overall results. Given the similarity in cost, and overall low costs as a proportion of total costs in the CEM, none of these inputs appear in the top 10 drivers of the ICER tornado plot, presented in the CEM.

Subsequent treatments

B30. Priority. The EAG considers that the proportion of patients receiving subsequent treatment in the CABINET trial may not be reflective of the company's proposed positioning of cabozantinib as a second-line systemic treatment. Therefore, please provide a scenario in which the proportion of patients receiving each subsequent treatment is reflective of cabozantinib being given as a second-line systemic treatment.

The marketing authorisation for cabozantinib is for the treatment of [REDACTED]

[REDACTED]. This does not represent a second-line systemic treatment, but third-line or later use after an SSA and at least one prior systemic therapy such as everolimus, sunitinib or PRRT. Given the anticipated marketing authorisation has been informed by the CABINET trial, the subsequent treatment distribution in this heavily pre-treated population is appropriate for the anticipated population eligible for cabozantinib. Additionally, clinician feedback has suggested that subsequent treatments received in this population is highly variable and individualised, based on the prior therapies patients had received previously.¹

Therefore, including the above scenario would not be appropriate for the anticipated use of cabozantinib. Regardless, the distribution of subsequent treatments is varied in the DSA and are not a key driver of the ICER in the tornado plot presented in the CEM.

B31. Priority. Please clarify how the proportion of patients receiving each subsequent treatment was calculated in the economic model scenario using data from the CABINET trial (cells F92:P103 in the Subsequent Treatments sheet), as the values used do not align with the source given.

Relevant CABINET data (from CSR Tables 14.3.1.3.2.a.1 and 14.3.1.3.2.b.1) were used to populate inputs for cabozantinib and BSC for pNETs and epNETs, respectively.⁸ Subsequent treatments received by at least 5% of patients in the cabozantinib arm were included and were assumed to be relevant for BSC.

The distribution of subsequent treatments (except SSAs) was calculated as a proportion of all those who initiated any NPACT (N=25). The CSR instead presents these as a proportion of all those who discontinued blinded study treatment (N=49). For BSC, the distribution was adjusted to exclude cabozantinib received as a subsequent treatment.

As outlined in the company submission, clinician feedback suggested that SSAs would be continued indefinitely throughout the PF and PD health states. Therefore, the proportion of SSAs received concomitantly (derived from CSR Tables 14.1.4.1.a.1 and 14.1.4.1.b.1 for pNETs and epNETs, respectively) were included alongside the subsequent treatments.⁸ These were adjusted using Ipsen internal estimates of markets shares for lanreotide and octreotide.

B32. Priority. It is unclear how the base case distribution of subsequent treatments detailed in table 56 was derived from the clinical validation report. Please could the company clarify where these values originate from?

Clinician feedback regarding subsequent treatments in this population was very mixed with most highlighting that this is highly individualised and based on the prior treatments a patient has received. General consensus was that a more equal distribution of subsequent treatments would be more reflective of clinical practice than the distribution from the CABINET trial data. Multiple clinicians also noted that everolimus was less frequently used than in the CABINET trial (approximately 5 to 10% of patients). Therefore, everolimus was assumed to be received in 10% of patients with an equal distribution applied across the other subsequent treatments (except SSAs which are taken concomitantly as outlined in the company response to B31).

B33. Priority. In the model, the costs for subsequent treatments are applied for all patients upon leaving the progression-free health state. Therefore, subsequent treatment costs are applied to patients who die in the progression-free health state. Please update the model to ensure that subsequent treatment costs are applied only to patients entering the progressed disease health state.

The Company do not agree that subsequent treatment costs are applied for all patients upon leaving the progression-free health state. Rather, subsequent treatment costs are applied to the difference in patients in progressed disease state in each cycle, as it is understood is being requested. In pNETs this is applied to 43% and 72% of cabozantinib and BSC patients, respectively. In epNETs, this is applied to 38% and 57% of cabozantinib and BSC patients,

respectively. If this results in a negative number (i.e., more patients dying than entering the health state), this is capped at 0. It is acknowledged that this is a slight simplification, as the difference in patients in the PD health state each cycle is not solely due to progression but also patients dying (and effectively leaving this health state). This structural limitation is only an issue when the OS hazard exceeds the PFS hazard. and there are no cycles in the base case for pNETs and epNETs where OS hazard exceeds the PFS hazard.

B34. Please provide a scenario in which the proportions of patients receiving subsequent treatments directly reflect the CABINET trial, without adjusting so the proportions sum to 100% of patients receiving any subsequent treatment.

A scenario has been included in the model that pragmatically reflects the subsequent treatments received in the CABINET trial. To prevent unnecessarily complicating the model, those received in fewer than 5% of patients are omitted. If these proportions are not adjusted to sum to 100%, fewer patients will be modelled to receive subsequent treatments than seen in the trial. Furthermore, reweighting is necessary to adjust for the removal of the subsequent cabozantinib treatment that was received by some patients in the BSC arm (those who crossed-over after progression). Therefore, no additional scenarios have been provided in response to this request as the Company believe it is necessary to adjust the proportions to sum to 100%.

B35. The EAG was unable to validate the inputs used for subsequent treatment duration. Please provide clarification on the following points:

- a) The source given for the duration of treatment for sunitinib states that the medium duration of treatment was 7 months, but the model uses a duration of 10 months.

The duration of treatment value for sunitinib was informed by the PFS value of 10 months reported in the source. Feedback from a UK clinician at an advisory board suggested that sunitinib would typically be prescribed for between 9 and 12 months, which the PFS value from the source more closely aligns with.^{44, 45}

- b) The EAG could not identify the inputs for treatment with everolimus and SSAs in the stated source (Dasari et al. 2019).⁴⁶ Furthermore, please comment on the applicability of this source to the patient population of interest, given that the study was conducted in a population of patients with lung NETs only.

The per patient values for treatment duration in Figure 3 in Dasari *et al.* (2019) was used to derive a mean of the subsequent treatment durations for everolimus and SSAs.⁴⁶ This source provided treatment durations at later lines (2L+) which were deemed to be more appropriate than PFS values or treatment duration values from trial data given cabozantinib's later line positioning. Although conducted in a lung NET only population, the baseline characteristics were generally well aligned with those in the CABINET trial. Therefore, this source is applicable to the wider NET population in the absence of an alternative data source.

- c) No explanation is given for why the assumption was made that treatment with FOLFOX would have the same duration as treatment with CAPTEM.

The source used (Arrivi *et al.* 2022) provided a value for metronomic CAPTEM.⁴⁷ It was deemed reasonable due to a lack of alternative data, that the median duration presented for chemotherapy was also appropriate for FOLFOX.⁴⁷

- d) Please also provide a scenario in which treatment durations for sunitinib and PRRT are informed with modelled treatment durations in Mujica-Mota *et al.* 2018, and treatment duration for everolimus is aligned with the RADIANT-3 trial.⁴⁸

A scenario is presented to include the subsequent treatment duration for sunitinib of 7.51 months based on the mean treatment duration in the assessment group (AG) model reported in Mujica Mota *et al.*, 2018, and a duration for everolimus of 8.79 months reported in RADIANT-3. Both values are highly similar to the Company base case which equated to 10 and 9 months respectively. The duration for PRRT reported in Mujica-Mota *et al.*, 2018 was modelled over a fixed number of cycles of 4 administrations at intervals of 8 ± 1 week).³⁸ This is already aligned with the base case of the company submission model of 4 administrations every 8 weeks, resulting in a duration of 32 weeks (the fixed number of cycles as reported in the Lutathera SmPC). As displayed in Table 28, the EAG scenario are presented in Table 28 and these alternative treatment durations have a negligible impact on results.

Table 28: Everolimus and sunitinib subsequent treatment durations

Scenario	pNETs			epNETs		
	Inc costs	Inc QALYs	ICER	Inc costs	Inc QALYs	ICER
Base case subsequent treatment durations (everolimus, sunitinib)	████	██	£24,815	████	██	£12,849
EAG scenario (Mujica-Mota <i>et al.</i> , 2018, RADIANT-3) ⁴⁹	████	██	£24,818	████	██	£12,850

All epNET results qualify for a 1.2x severity modifier, which is applied here.

Abbreviations: ICER: incremental cost-effectiveness ratio; EAG: external assessment group; epNET: extra-pancreatic neuroendocrine tumour; inc: incremental; pNET: pancreatic neuroendocrine tumour; QALYs: quality-adjusted life years.

B36. The EAG notes that the company did not consider the impact of adverse events of subsequent treatments in the model. Please comment on the impact of this assumption on results.

As per the DSA results presented in Section 3.11.2 of the company submission, parameters associated with AEs were not among the top 10 most influential parameters. Given AE costs for subsequent treatments would be applied only to a proportion of patients who continue onto subsequent treatments, it is anticipated that the influence on cost-effectiveness would be further reduced. The omission of AEs for subsequent treatments is not considered a key uncertainty.

Costs

B37. Priority. The EAG considers that Casciano *et al.* 2013 is not appropriate for informing resource use estimates in the model, since this study collected data on the number of patients using resources, rather than the number of instances of resource use.⁵⁰ As a result, the estimates of resource use in the model are much lower than would be expected. Please update the model to use a more appropriate source for resource use frequencies (for example, Table 31 and Table 32 in Mujica-Mota *et al.* 2018).³⁸

The resource use categories and frequencies reported in Mujica-Mota *et al.* (2018) were validated in the global advisory board with clinical experts who agreed the source was not reflective of clinical practice and majority of categories not appropriate.^{38, 45} The base case resource use categories and frequencies, which were retrieved from Casciano *et al.* (2013), were further validated in the UK clinical validation exercise and were broadly aligned. A conservative scenario based on a combination of Casciano *et al.* (2013) and clinician feedback was explored which resulted in a small increase of the ICER to £27,677 and £15,431 in pNETs and epNETs, respectively.⁵⁰

B38. Priority. The model includes multiple costs sourced from the 2023 PSSRU report. Please update these costs to align with the 2024 report.

The model contains costs sourced from the 2023 PSSRU report, including the administrations costs for oral (one-off), oral (ongoing), subcutaneous (SC)/intramuscular (IM) injection for octreotide and deep SC injection for lanreotide, as well as terminal care costs. A scenario has been included to derive these costs from the latest 2024 PSSRU report.⁵¹

B39. The mean total dose hold lengths used in the formulae to calculate percentage dose hold (cells 39D:39E in the Direct Treatment Costs sheet) do not appear in the specified source; please clarify the source for these input values.

The mean total dose holds lengths used were derived using IPD from the CABINET trial for all patients who had a dose hold due to any reason.

B40. The approach for costing treatment administration for SSAs was aligned with Thorn *et al.* 2020.⁵²

a) Please explain why this approach was considered appropriate in this context.

The approach for costing treatment administration for SSAs was based on feedback from clinical experts at an advisory board who stated that 80–90% of patients with NETs receive SSAs through homecare administration.⁴⁵ A targeted literature review (TLR) was then conducted to identify costs for homecare administration. Thorn *et al.* (2020) was identified as an appropriate source for the cost of this homecare administration.⁵² The assumptions used in Thorn *et al.* (2020) were incorporated with updated reference costs added.⁵²

- b) Please provide a scenario in which the approach for costing administration of SSAs is aligned with the approach taken in Mujica-Mota et al. 2018 (see Table 29).³⁸

Mujica-Mota *et al.* (2018) assumed that SSAs would be delivered in a hospital setting, with different costs associated with treatment administration.³⁸ As outlined in the response above, feedback from clinical experts at an advisory board stated that the vast majority (80–90%) of patients with NETs would receive SSAs through homecare administration, and therefore, the Company do not agree that it is appropriate to align the administration cost approach with that taken in Mujica-Mota *et al.* (2018).^{38, 45}

For completeness, the inclusion of these costs have been explored in a scenario analysis, with results provided in Table 29. The administration cost for lanreotide was calculated using different costs for the first and subsequent visits in Mujica-Mota *et al.* (2018).³⁸ As a simplification, the subsequent visits cost from the NHS Schedule of Costs 2023/24 (£430.24, currency code SB15Z) has been applied in the current model. For octreotide, a 15-minute nurse time (band 5) at £88 per hour of patient contact was used, based on PSSRU 2015, to calculate administration costs.^{51, 53} Since this unit cost is not available in the latest 2024 PSSRU report, the nurse time cost has been inflated accordingly using the PSS pay & price index from the 2014/2015 cost year. This scenario has a minimal impact on the ICER, with the results presented in Table 29.

Table 29: SSA Treatment Administration Costs

Scenario	pNETs			epNETs		
	Inc costs	Inc QALYs	ICER (£/QALY)	Inc costs	Inc QALYs	ICER (£/QALY)
Base case: homecare SSA administration costs	■	■	£24,815	■	■	£12,849
Hospital SSA administration costs	■	■	£26,021	■	■	£13,417

All epNET results qualify for a 1.2x severity modifier, which is applied here.

Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years; SSA: somatostatin analogue.

B41. The unit cost used as an administration cost for PRRT includes the costs for directly accessed diagnostic services. Please update the model so only the cost for nuclear medicine is used.

The total healthcare resource group (HRG) cost, which contains both directly accessed diagnostic services and nuclear medicine costs, was used to derive the administration cost for PRRT which aligns with TA930 (lutetium-177 vipivotide tetraxetan for treating prostate-specific membrane antigen (PSMA)-positive hormone-relapsed metastatic prostate cancer). The administration cost for PRRT has been updated in the model to only account for nuclear medicine (£1,242.39). This change has a minor impact on the overall administration cost for PRRT, which previously also included the costs for directly accessed diagnostic services (£1,237.70). As such, this has an very minimal impact on the incremental costs, and therefore the ICER (~£1 for each).

B42. Please explain why the cost for administering chemotherapy was calculated by combining the unit costs for ‘Delivery of More Complex Parenteral Chemotherapy at First Attendance’ and ‘Non-Admitted Face-to-Face Attendance, Follow-up, Medical Oncology [Non-Consultant Led]’.

The costing approach for administering FOLFOX chemotherapy in the model aligns with TA948 (ivosidenib for treating advanced cholangiocarcinoma).⁵⁴ The cost of infusion was calculated by the delivery of complex parenteral chemotherapy at first attendance (£598.22, NHS Schedule of Costs, currency code SB14Z).⁵³ As fluorouracil is administered continuously over a 46-hour period, an additional cost (£157.13, NHS Schedule of Costs, currency code WF01A) per visit is required for patients returning to the hospital to have their peripherally inserted central catheter line removed by a nurse.

B43. The EAG notes that no costs for genetic testing were included in the model. Please comment on whether patients would be required to undergo genetic testing before receiving cabozantinib, and include any relevant costs of testing in the model.

The company can confirm that patients would not be required to undergo genetic testing ahead of receiving cabozantinib and as such, these costs have not been included within the model.

Results

B44. The company has only provided deterministic results for the scenario analyses (Section 3.11.3 of the CS) and clinical outcomes and disaggregated results (Appendix H of the CS). Please provide probabilistic results for these analyses.

Probabilistic results from the scenario analysis from the company submission are presented in Table 30 for pNETs and Table for epNETs.

Cabozantinib remained cost-effective across all scenarios explored for pNET and epNET populations. Overall, sensitivity analysis results demonstrate the base case results to be robust to uncertainties in inputs and assumptions.

Table 30: Probabilistic scenario analysis results for cabozantinib versus BSC, pNETs

Scenario		Cabozantinib versus BSC		
		Incr. costs, £	Incr. QALYs	ICER (£/QALY)
Base case				
	Cost-effectiveness analysis	██████	██	£23,534
Discounting				
1	Discount rate for costs and benefits: 6.0%	██████	██	£25,464
2	Discount rate for costs and benefits: 1.5%	██████	██	£21,942
Utilities				
3	CABINET trial (PF) and Swinburn Vignettes (PD)	██████	██	£23,411

4	CABINET trial (PF) and ERASMUS relative decrement (PD)	████	██	£23,911
5	CABINET trial (PF) and ERASMUS (PD)	████	██	£23,828
Disutilities				
6	AE disutilities: exclude	████	██	£23,456
Cabozantinib curve selection				
7	Alternative PFS/TTD curve selection for cabozantinib: PFS: Gompertz, TTD: Weibull	████	██	£24,807
8	Alternative OS curve selection for cabozantinib (based on clinical validation): loglogistic	████	██	£20,473
BSC survival method				
9	PFS/TTD: Direct extrapolation: PFS: Lognormal, TTD: Weibull	████	██	£23,426
10	Administration costs for orally administered drugs: £0	████	██	£23,318
11	Subsequent treatment distribution source: Ipsen Data on File, CABINET CSR	████	██	£19,884
12	CCT in PD distribution source: Ipsen Data on File, CABINET CSR (pooled SSA use alongside subsequent treatment)	████	██	£24,082
13	Resource use source: Casciano <i>et al.</i> (2013) (adjusted frequency)	████	██	£26,409

Abbreviations: AE: adverse event; BSC: best supportive care; CCT: concomitant therapy; CSR: clinical study report; ICER: incremental cost-effectiveness ratio; OS: overall survival; PD: progressed disease; PF: progression free; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumours; TTD: time to treatment discontinuation; QALY: quality-adjusted life year.

Table 31: Probabilistic scenario analysis results for cabozantinib versus BSC, epNETs (with 1.2 severity modifier applied)

Scenario		Cabozantinib versus BSC		
		Incremental costs, £	Incr. QALYs	ICER (£/QALY)
Base case				
	Cost-effectiveness analysis	████	██	£13,187
Discounting				
1	Discount rate for costs and benefits: 6.0%	████	██	£14,082
2	Discount rate for costs and benefits: 1.5%	████	██	£12,428
Utilities				
3	CABINET trial (PF) and Swinburn Vignettes (PD)	████	██	£12,902
4	CABINET trial (PF) and ERASMUS relative decrement (PD)	████	██	£12,371
5	CABINET trial (PF) and ERASMUS (PD)	████	██	£11,930
Disutilities				
6	AE disutilities: exclude	████	██	£13,178
Cabozantinib curve selection				
7	Conservative PFS/TTD curve selection cabozantinib: PFS: Weibull, TTD: Gompertz)	████	██	£14,184

8	Alternative curves aligned with clinical validation for cabozantinib: OS: Lognormal)	████	██	£13,144
BSC survival method				
9	PFS/TTD: Direct extrapolation, PFS: Lognormal, TTD: Loglogistic	████	██	£13,658
Costs				
10	Administration costs for orally administered drugs: £0	████	██	£13,045
11	Subsequent treatment distribution source: Ipsen Data on File, CABINET CSR	████	██	£10,855
12	CCT in PD distribution source: Ipsen Data on File, CABINET CSR (pooled SSA use alongside subsequent treatment)	████	██	£13,810
13	Resource use source: Casciano <i>et al.</i> (2013) (adjusted frequency)	████	██	£15,787

All epNET results qualify for a 1.2x severity modifier, which is applied here.

Abbreviations: AE: adverse event; BSC: best supportive care; CCT: concomitant therapy; CSR: clinical study report; epNET: extra-pancreatic neuroendocrine tumour; ICER: incremental cost-effectiveness ratio; OS: overall survival; PD: progressed disease; PF: progression free; PFS: progression-free survival; TTD: time to treatment discontinuation; QALY: quality-adjusted life year.

The probabilistic disaggregated costs for each of the health states from the cost-effectiveness model are presented in Table 32 below. The predicted disaggregated QALYs per health state from the cost-effectiveness model are presented in Table 33. A summary of the predicted disaggregated costs per cost category are present in Table 34.

Table 32: Summary of predicted costs per health state (probabilistic)

Health state	Progression-free	Progressed disease	Death
pNETs			
Cabozantinib	████	£11,105	£11,544
BSC	████	£12,697	£12,059
epNETs			
Cabozantinib	████	£9,034	£12,242
BSC	████	£12,072	£12,742

Abbreviations: BSC: best supportive care; epNET: extra-pancreatic neuroendocrine tumour; pNET: pancreatic neuroendocrine tumour.

Table 33: Summary of predicted QALYs per health state (probabilistic)

Health state	Progression-free	Progressed disease	Death
pNETs			
Cabozantinib	██	██	0.00
BSC	0.34	1.86	0.00
epNETs			
Cabozantinib	██	██	0.00
BSC	0.34	0.79	0.00

All epNET results qualify for a 1.2x severity modifier, which is applied here.

Abbreviations: BSC: best supportive care; epNET: extra-pancreatic neuroendocrine tumour; pNET: pancreatic neuroendocrine tumour; QALY: quality adjusted life year.

Table 34: Summary of predicted costs per category (probabilistic)

Item	Acquisition	Administration	Adverse event	Resource use	Concomitant therapy	Subsequent treatment	Terminal care
pNETs							
Cabozantinib	████	£196	£195	£6,788	£5,978	£6,260	£11,544
BSC	£0	£0	£53	£5,425	████	£7,780	£12,059
epNETs							
Cabozantinib	████	£134	£87	£4,162	£5,140	£6,058	£12,242
BSC	£0	£0	£17	£2,705	████	£9,879	£12,742

All epNET results qualify for a 1.2x severity modifier, which is applied here.

Abbreviations: BSC: best supportive care; epNET: extra-pancreatic neuroendocrine tumour; pNET: pancreatic neuroendocrine tumour.

Model issues

B45. Priority. Modelled PFS curves have been bounded above by the corresponding OS curve, and TTD curves have been bounded above by the corresponding PFS curves.

- a) Please update the implementation of bounding so that bounding is applied to the per-cycle hazard, analogously to the bounding of OS by general population mortality.**

While PFS should be bounded by OS to avoid logical inconsistencies (i.e., $PFS > OS$), it is clinically possible for the per-cycle hazard of death to be greater than the per-cycle hazard of progressing in a given cycle. For example, this may occur if the patients remaining in the PFS state are in a deeper state of response such that their probability of progression is low whilst there may be a higher number of progressed patients that have a high probability of death. Therefore, the company disagree that the implementation of bounding for PFS is OS is applied per-cycle, and therefore, the model has not been updated. Instead, the PFS curves are capped by the OS curve as a whole, rather than the probability of progression being capped by the probability of death.

- b) The OS, PFS and TTD plots in the CS and in the Efficacy sheet of the model do not incorporate the adjustment for bounding. Please provide the same plots with this adjustment included.**

The summary plots which show the selected extrapolation and the KM for each endpoint (OS, PFS and TTD) have been updated to incorporate the adjustment for bounding. Due to the way in which the bounding is applied in the model (once the extrapolation has been selected, applied on the respective treatments' Trace tab rather than applied to all extrapolations), it was not feasible within the time frame to amend the other plots to not include this adjustment for bounding.

However, the company would like to note that given the poor prognosis in this indication, the OS bounding by general population mortality (GPM) has a minimal impact on the survival extrapolations, as illustrated by the GPM curve that has been added to the OS extrapolation plots.

Similarly, the capping of TTD by PFS is rarely in place, aside from when outlier extrapolations for TTD are selected (e.g. loglogistic or lognormal in both populations). To facilitate the EAG's request, additional plots have been added which present the TTD and PFS extrapolations on the same plot, allowing a direct comparison and assessment of when this capping would and would not be relevant.

- c) Please add to the model a plot for each arm showing the estimated OS, PFS and TTD curves superimposed on a single set of axes, so the relationship between these curves can be assessed.**

Two plots have been included in the model on the Secondary Results tab, one for each treatment arm, showing the estimated bounded OS, PFS and on-treatment curves.

B46. Priority. The proportion of patients receiving each dosage of lanreotide and octreotide is currently hard-coded in the model (for example, in cells G81:G82 in the Subsequent Treatments sheet). Please update the model so these values are included as user-adjustable inputs which can be varied probabilistically.

The model has been updated to include user-adjustable inputs for the proportion of patients receiving each dosage of lanreotide and octreotide; these inputs can also be varied probabilistically.

B47. Priority. The EAG notes the following errors in the model, which should be corrected:

- a) The SE for BSA in the epNETs population is calculated assuming N=202, whereas the given source suggests N=203 (cell H28, Patient Characteristics sheet)**

As stated in question B21, BSA was calculated using the Mosteller formula, which requires data on weight and height. Since height information was unavailable, it was derived using weight and BMI data. The sample size (N) for weight is 203, while the sample size for BMI is 202, resulting in height and BSA calculations being performed for 202 participants instead of 203. Therefore, the Company believe this is not an error and no change has been made to the model.

- b) The incorrect curves are displayed in the 'summary' plots in the Efficacy sheet.**

The Company could not identify any incorrect curves displayed in the 'summary' plots in the Efficacy sheet of the model. However, some redundant VBA code was identified which held no functionality in the model and therefore was removed.

- c) The proportion of patients receiving subsequent treatments is incorrect for the scenario in which inputs for the CABINET trial are used, since the proportions are not adjusted to exclude external beam radiation therapy (cells D30:J35 in the Subsequent Treatments sheet).**

In the scenario in which inputs are derived based on the subsequent treatments received in the CABINET trial, external beam radiation therapy (EBRT) is an intended inclusion. As explained the Section 3.5.1 of the original company submission, subsequent treatments deemed relevant

for inclusion in the model for both cabozantinib and BSC were those received by at least 5% of patients. EBRT was received by three out of 25 patients (12%) in the cabozantinib arm for the pNET population, and is therefore a relevant treatment to include in this scenario. It was not received by more than 5% of patients in the BSC arm or the epNET population and is therefore not included.

Based on clinician feedback, EBRT is not expected to be a relevant subsequent treatment in the UK and therefore is not included in the company base case inputs which were adapted to reflect UK clinical practice.

- d) The probabilistic values for curve extrapolation parameters are not calculated correctly; the vector of sampled random values should be left-multiplied by the Cholesky decomposition matrix (cells R626:R770, Sensitivity Analysis Filter sheet).**

The model has been updated to correct the Cholesky decomposition matrices for the probabilistic variation of curve extrapolation parameters.

- e) Treatment costs should not be varied probabilistically (cells G96:G110, Sensitivity Analysis Filter sheet).**

The model has been updated to ensure treatment costs are not varied probabilistically.

B48. Please add the functionality for the user to specify a random seed for the probabilistic analyses, to facilitate reproducibility.

The company has incorporated a random seed for the probabilistic analyses in the model.

B49. Please update the model so the results of epNET and pNET are displayed side by side so the user does not have to manually switch between epNET and pNET.

The company has implemented a new tab in the model titled 'Base Case Results by Population' which includes macro functionality to generate both results for epNET and pNET simultaneously.

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Appendix A: A1A: ITC Feasibility Assessment

Identification of treatment effect modifying variables

In anchored ITCs, randomisation of included trials is preserved, ensuring prognostic variables are balanced across treatment arms. Therefore, the similarity of studies within such comparisons should be assessed for differences in TEMs specifically. If there is heterogeneity (between-study variation) in TEMs, relative differences in treatment effects may be due to differences in characteristics considered to be TEMs across studies, rather than due to treatments performing better or worse than each other. This would violate the assumption required for anchored ITCs of homogeneity in TEMs across studies and invalidate results. Therefore, it is crucial that TEMs are well-balanced across studies.

A review of the available literature revealed limited information on TEMs, specifically in NETs. Further information on TEMs was gathered by eliciting clinical opinion from a global advisory board, as well as reviewing subgroup results based on these characteristics from the CABINET trial.⁴⁵ Subgroup results from CABINET for PFS (by blinded independent review council [BIRC]) are presented in Section 2.8 of the company submission. Generally, subgroup results indicated consistency in relative effectiveness versus placebo, indicated by all confidence intervals overlapping for each subgroup. However, minor deviations of HR point estimates were observed across some subgroups. Although the subgroup results below are presented for PFS, the treatment modifying effect (if any) of characteristics on other outcomes such as OS and ORR was expected to be similar to PFS.

Primary tumour site (in epNETs only), tumour grade, hormone syndrome/functional status, prior therapy, age, sex and race were identified as potential TEMs for cabozantinib or other systemic treatments. Therefore, for the assessment of feasibility based on comparisons with pivotal trials, all patient baseline characteristics were assessed for heterogeneity, and specific attention was given to these characteristics considered to be potential TEMs.

Available evidence

As noted in the company submission, an SLR assessing the efficacy and safety of pharmacological treatments for epNETs and pNETs was performed. A total of 16 unique studies were prioritised for extraction, of which 13 (81%) were single-arm studies with relatively small sample sizes. Overall, there was a low volume of evidence, likely due to the rare nature of the disease combined with the poor reporting of prior treatment experience. Comparisons via a common comparator (e.g. anchored via the placebo arm of CABINET) were thus not feasible based on the 14 studies identified in the SLR. Additionally, as the key source to inform comparative effectiveness, it was deemed inappropriate to perform unanchored ITCs against single-arm studies and these were not explored further in the feasibility assessment.

Due to the lack of suitable evidence from the clinical SLR, relevant pivotal trials (A6181111, NETTER-1, NETTER-2, RADIANT-3 and RADIANT-4) for sunitinib, ¹⁷⁷Lu- dotatate and everolimus were inspected. Although these pivotal trials were excluded from the SLR, their trial design potentially allowed for anchoring via a common comparator with CABINET (i.e., placebo). Given that anchored ITCs are considerably more robust than unanchored comparisons (due to preservation of randomisation and using less strong assumptions), these pivotal trials were taken forward for an assessment of feasibility to inform the ITCs. The trials are summarised in Table 35.

Due to the lack of relevant data from the SLR to inform an anchored ITC, and since the pivotal trials contain key evidence on the effectiveness of other systemic therapies, the feasibility of comparisons of CABINET versus the pivotal trials was explored in depth.²⁻⁷ Despite initial differences between these studies and CABINET as evidenced by the reasons for exclusion of these studies from the SLR (Table 2), the feasibility assessment carefully assessed the similarity across these studies, particularly in terms of TEMs, to explore if analyses may be possible via population-adjustment methods, such as simulated treatment comparisons (STCs) or matching-adjusted indirect comparisons (MAICs), to account for any identified differences.

Table 35. Pivotal trials

Trial	Phase	N	Intervention	Comparator
A6181111 ^{55, 56}	Phase 3	171	Sunitinib + BSC	Placebo + BSC
NETTER-1 ^{4, 57}		229	¹⁷⁷ Lu-DOT PRRT + Oct 30 mg LAR	Oct 60 mg LAR
NETTER-2 ³		226	¹⁷⁷ Lu-DOT PRRT + Oct 30 mg LAR	Oct 60 mg LAR
RADIANT-3 ^{7, 48}		410	Everolimus + BSC	Placebo + BSC
RADIANT-4 ^{5, 58}		310	Everolimus + BSC	Placebo + BSC

Abbreviations: ¹⁷⁷Lu-DOT, Lutetium-177-DOTA0-Tyr3 octreotate; BSC, best supportive care; LAR, long-acting repeatable; N, number; Oct, octreotide; Ph, phase; PRRT, peptide receptor radionuclide therapy; SLR, systematic literature review; SSA, somatostatin analogues.

Heterogeneity in patient and study characteristics

Patient and study characteristics for relevant pivotal trials (A6181111, NETTER-1, NETTER-2, RADIANT-3 and RADIANT-4) for other systemic therapies (sunitinib, ¹⁷⁷Lu-dotatate and everolimus) were reviewed. Detailed comparisons of patient heterogeneity and study characteristics of the pivotal trials are presented in Table 36 for pNETs and Table 37 for epNETs.

Table 36: Study and patient characteristics for pNET cohorts

	CABINET (Ph 3)⁵⁹⁻⁶¹ Cabozantinib vs placebo (N=95)		A6181111 (Ph 3)^{55, 56} Sunitinib + BSC vs placebo + BSC (N=171)		RADIANT-3 (Ph 3)^{7, 48} Everolimus + BSC vs placebo + BSC (N=410)		NETTER-2 (Ph 3)³ ¹⁷⁷Lu-DOT PRRT + Oct 30 mg LAR vs Oct 60 mg LAR (N=226)	
Study start year	2018		2007		2007		2020	
Tumour cohort	Progressive pNET		Advanced pNET		Advanced pNET		Advanced SSTR+ GEP-NETs^{a,b}	
Arm (no. randomised)	Cabo (N=64)	Placebo (N=31)	Sun (N=86)	Placebo (N=85)	Eve + BSC (N=207)	Placebo + BSC (N=203)	¹⁷⁷Lu-DOT PRRT + Oct LAR (N=151)	Oct LAR (N=75)
Line of therapy	≥ 2L		≥ 1L		≥ 2L		1L	
Median prior therapies (range)	3 (1–8)	2 (1–7)	NR ^c	NR	NR	NR	NR	NR
Median age, years (range)	60 (29–79)	64 (39–79)	56 (25–84)	57 (26–78)	58 (23–87)	57 (20–82)	61 (IQR 51–72)	60 (IQR 51–69)
Female, n (%)	27 (42)	13 (42)	44 (51)	45 (53)	97 (47)	86 (42)	70 (46)	35 (47)
Race, n (%)								
White	54 (84)	25 (81)	48 (56)	53 (62)	NR	NR	115 (76)	50 (67)
Asian	4 (6)	0 (0)	13 (15)	10 (12)	NR	NR	23 (15)	11 (15)
Other	6 (9)	6 (19)	25 (29)	22 (26)	NR	NR	13 (9)	14 (19)
Disease stage, n (%)								
Early	0	0	0	0	NR	NR	NR	NR
Locally advanced	1 (2)	2 (6)	0	0	NR	NR	NR	NR
Advanced (unresectable or metastatic)	63 (98)	29 (94)	86 (100)	85 (100)	NR	NR	NR	NR

Differentiation, n (%)								
Well	59 (92)	30 (97)	86 (100)	85 (100)	170 (82)	171 (84)	151 (100)	75 (100)
Moderate	4 (6)	0	0	0	35 (17)	30 (15)	0	0
Unknown	1 (2)	1 (3)	0	0	2 (1)	2 (1)	0	0
Hormone syndrome present, n (%)	11 (17)	5 (16)	NR	NR	NR	NR	NR	NR
Tumour grade, n (%)	WHO classification		NR		NR		Grading system unspecified	
Grade 1	14 (22)	7 (23)	NR	NR	NR	NR	0	0
Grade 2	39 (61)	19 (61)	NR	NR	NR	NR	99 (66)	48 (64)
Grade 3	8 (13)	3 (10)	NR	NR	NR	NR	52 (34)	27 (36)
Unknown	3 (5)	2 (6)	NR	NR	NR	NR	0	0
Prior SSA, n (%)	63 (98)	30 (97)	30 (35)	32 (38)	NR	NR	24 (16)	18 (24)
Concurrent SSA use, %	55%	55%	27%	29%	40%	41%	100% ⁱ	100% ⁱ

^aSSTR+ (somatostatin receptor positive) tumours are defined by their expression of somatostatin receptors, making them suitable to specific therapeutic approaches, including SSAs. ^bThe data presented for NETTER-2 is for the full study population. ^cA sensitivity analysis was conducted for <2 vs >2 number of previous systemic therapies which suggests the number receiving ≥2L, which would be aligned with CABINET, may be substantial. ^dEligibility criteria included patients with advanced, progressive, low- or intermediate-grade pancreatic NET. ^eDisease stage data in NETTER-2 were provided only for the entire sample: two (1%) patients had locally advanced unresectable disease; the remaining 224 (99%) patients had distant metastatic disease.

Abbreviations: 1L, first-line; 2L, second-line; 177Lu-DOT, Lutetium-177-DOTA0-Tyr3 octreotate; BSC, best supportive care; Cabo, cabozantinib; Eve, everolimus; GEP, gastroenteropancreatic; IQR, interquartile range; LAR, long-acting repeatable; NET, neuroendocrine tumour; NR, not reported; Oct, octreotide; Ph, phase; pNET: pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue; SSTR, somatostatin receptor; SSTR+, somatostatin receptor positive; Sun, sunitinib; vs, versus.

Table 37: Study and patient characteristics for epNET cohorts

	CABINET (Ph 3) ⁵⁹⁻⁶¹ Cabozantinib vs placebo (N=203)	RADIANT-4 (Ph 3) ^{5, 58} Everolimus + BSC vs placebo + BSC (N=302)	NETTER-1 (Ph 3) ^{4, 57} ¹⁷⁷ Lu-DOT PRRT + Oct 30 mg LAR vs Oct 60 mg LAR (N=229)	NETTER-2 (Ph 3) ³ ¹⁷⁷ Lu-DOT PRRT + Oct 30 mg LAR vs Oct 60 mg LAR (N=226)
Study start year	2018	2012	2012	2020

Tumour cohort	Progressive epNET		Advanced GI or lung NET		SSTR+ GI NET ^a		Advanced SSTR+ GEP-NETs ^b	
Arm (no. randomised)	Cabo (N=134)	Placebo (N=69)	Eve + BSC (N=205)	Placebo + BSC (N=97)	¹⁷⁷ Lu-DOT PRRT + Oct LAR (N=116)	Oct LAR (N=113)	¹⁷⁷ Lu-DOT PRRT + Oct LAR (N=151)	Oct LAR (N=75)
Line of therapy	≥ 2L		≥ 1L ^c		≥ 2L ^d		1L	
Median prior therapies (range)	2 (1–5)	2 (1–6)	NR	NR	NR	NR	NR	NR
Median age, years (range)	66 (28–86)	66 (30–82)	65 (22–86)	60 (24–83)	63 (SD, 9)	64 (SD, 10)	61 (IQR 51–72)	60 (IQR 51–69)
Female, n (%)	74 (55)	31 (45)	116 (57)	44 (45)	53 (46)	60 (53)	70 (46)	35 (47)
Race, n (%)								
White	115 (86)	55 (80)	NR	NR	NR	NR	115 (76)	50 (67)
Asian	3 (2)	1 (1)	NR	NR	NR	NR	23 (15)	11 (15)
Other	16 (12)	13 (19)	NR	NR	NR	NR	13 (9)	14 (19)
Disease stage, n (%)							NR ^e	
Early	0	0	0	0	0	0	NR	NR
Locally advanced	0	0	0	0	0	0	NR	NR
Advanced (unresectable or metastatic)	134 (100)	69 (100)	205 (100)	97 (100)	116 (100)	113 (100)	NR	NR
Differentiation, n (%)								
Well	118 (88)	61 (88)	205 (100)	97 (100)	116 (100)	113 (100)	151 (100)	75 (100)
Moderate	6 (4)	5 (7)	0	0	0	0	0	0
Poor	0	0	0	0	0	0	0	0
Unknown	10 (7)	3 (4)	0	0	0	0	0	0

Hormone syndrome present, n (%)	41 (31)	25 (36)	NR	NR	NR	NR	NR	NR
Tumour grade, n (%)	WHO classification		WHO classification		By Ki67 index thresholds ^f		By Ki67 index thresholds ^g	
Grade 1	37 (28)	15 (22)	129 (63)	65 (67)	41 (35)	44 (39)	0	0
Grade 2	86 (64)	48 (70)	75 (37)	32 (33)	32 (28)	25 (22)	99 (66)	48 (64)
Grade 3	8 (6)	5 (7)	0	0	NR	NR	52 (34)	27 (36)
Unknown	3 (2)	1 (1)	1 (<1)	0	NR	NR	0	0
Primary site, n (%)								
GI tract	51 (38)	37 (54)	113 (55)	55 (67)	116 (100)	113 (100)	58 (38)	29 (39)
Pancreas	4 (3)	3 (4)	0	0	0	0	82 (54)	41 (55)
Lung	33 (25)	16 (23)	63 (31)	27 (28)	0	0	0	0
Unknown	22 (16)	2 (3)	23 (11)	13 (13)	0	0	0	0
Other	24 (18)	11 (16)	6 (3)	2 (2)	0	0	11 (7)	5 (7)
Prior SSA, n (%)	124 (93)	64 (93)	109 (53)	54 (56)	NR ^h	NR ^h	24 (16)	18 (24)
Concurrent SSA use, %	69% ⁱ	70% ⁱ	2%	1%	100% ^j	100% ^j	100% ^j	100% ^j

^aSSTR+ (somatostatin receptor positive) tumors are defined by their expression of somatostatin receptors, making them suitable to specific therapeutic approaches including SSAs. ^bThe data presented for NETTER-2 is for the full study population. ^cRADIANT-4 included patients previously treated with SSA, interferon, one prior line of chemotherapy; peptide receptor radionuclide therapies (PRRT) were allowed if disease progression was documented during or after last treatment. RADIANT-4 excluded patients who received more than one line of chemotherapy; prior therapy with mTOR inhibitors (sirolimus, temsirolimus, or everolimus); hepatic intra-arterial embolization within 6 months, or cryoablation or radiofrequency ablation of hepatic metastases within 2 months of randomisation; or chronic treatment with corticosteroids or other immunosuppressive agents.

^dIn NETTER-1, approximately 80% of the patients had undergone previous surgical resection (78% in the 177Lu-dotatate group and 82% in the control group), and nearly half the patients had undergone a previous form of systemic therapy other than somatostatin analogue therapy (41% of patients in the 177Lu-dotatate group and 45% in the control group). ^eDisease stage data in NETTER-2 were provided only for the entire sample: two (1%) patients had locally advanced unresectable disease; the remaining 224 (99%) patients had distant metastatic disease. ^fGrades were defined as Ki67 ≤2% (Grade 2) and Ki67 3–20% (Grade 3). ^gGrades were defined as newly diagnosed higher grade 2 (Ki67 ≥10% and ≤20%) and grade 3 (Ki67 >20% and ≤55%). ^hAlthough not directly reported, the paper refers to patients with advanced midgut NETs who have had disease progression during first-line somatostatin analogue therapy. This suggests ~100% of the patients included in this study had prior SSA use. ⁱConcurrent SSA use provided per OPEN registration system. ^jDuring the study, all patients received octreotide LAR, an SSA.

Abbreviations: 1L, first-line; 2L, second-line; 177Lu-DOT, Lutetium-177-DOTA0-Tyr3 octreotate; BSC, best supportive care; Cabo, cabozantinib; Eve, everolimus; ep, extra-pancreatic; GI, gastrointestinal; GEP, gastroenteropancreatic; IQR, interquartile range; LAR, long-acting repeatable; NET, neuroendocrine tumour; NR, not reported; Oct, octreotide; Ph, phase; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue; SSTR+, somatostatin receptor positive; vs, versus.

Reported Outcomes

The availability of reported outcomes for the pivotal trials, including OS, PFS and TTD, varied across the trials, and it was found that median OS was not reached for RADIANT-4 and NETTER-2 (epNETs), or A6181111 and NETTER-2 (pNETs), which would restrict comparisons between CABINET and these trials.^{2, 3, 5, 6} Comparative analyses of TTD versus CABINET would not be feasible due to lack of reporting of TTD for the other studies.

epNET cohort

Specifically for the epNETs cohort, RADIANT-4, NETTER-1, and NETTER-2 were not considered suitable for comparison with CABINET, as indicated by the summary in Table 38.

Comparisons with RADIANT-4 were not considered suitable due to uncertainties in the number of prior lines of therapy (if any) received by patients in RADIANT-4 and the inability to adjust for median prior number of therapies. Despite the fact that all patients were in advanced stage of the disease, differences were also observed in tumour grade and sex (which could be adjusted for in an analysis), and concurrent SSA usage (which would likely be challenging to adjust for, given the large discrepancy across trials). Since NETTER-1 only included patients with GI tract as the primary site, only a comparison versus a GI subgroup of CABINET could be conducted, which would break randomisation. However, this is also complicated by a lack of reporting of key baseline characteristics in NETTER-1; sex could be adjusted for in the analysis, while potential differences in prior lines of therapy would remain unadjusted for. Comparisons versus NETTER-2 could be adjusted for sex but would be severely constrained by the known difference in line of therapy (1L treatment in NETTER-2 and $\geq$ 2L treatment in CABINET).

Table 38. Suitability of epNET cohorts for comparison with CABINET

Trial	Key discrepancies with CABINET
RADIANT-4	• Included patients receiving $\geq$ 1L therapy; CABINET included patients receiving $\geq$ 2L therapy • Tumour grade data were available to adjust for in analyses, and an imbalance was identified: the majority of patients in RADIANT-4 had a Grade 1 tumour (>63%), whereas in CABINET, the majority of patients had a Grade 2 tumour (>64%) • 1–2% of patients in RADIANT-4 used concurrent SSAs, compared to ~70% in CABINET; it would be challenging to adjust for this difference, as it would require weighting or restricting to ~30% of the CABINET epNETs population • Data were not reported for median number of prior therapies or hormone syndrome/functional status, therefore, adjusting for these variables would not be possible in an ITC • TTD not reported
NETTER-1	• All patients in NETTER-1 had GI tract as the primary site; CABINET included patients with GI, pancreas, lung, unknown and other primary sites; it would be challenging to attempt to adjust for this difference in analyses, and likely require analyses including only the GI subgroup from CABINET • Tumour grade data were available to adjust for in analyses, and an imbalance was identified: CABINET included more than 64% of patients with a grade 2 tumour compared to less than 30% in NETTER-1 • Data were not reported for median number of prior therapies, hormone syndrome/functional status, and race, therefore, adjusting for these variables would not be possible in an ITC

	• TTD not reported
NETTER-2	• Included patients with advanced SSTR+ GEP-NETs; CABINET included patients with progressive pNETs • NETTER-2 included patients receiving 1L therapy; CABINET included patients receiving $\geq$ 2L therapy • Tumour grade data were available to adjust for in analyses, and an imbalance was identified: CABINET included 28% of patients with a Grade 1 tumour in the cabozantinib arm while NETTER-2 included no patients with a Grade 1 tumour. CABINET included 6% of patients with a Grade 3 tumour compared to $>34\%$ with a Grade 3 tumour in NETTER-2 • Data were not available for hormone syndrome/functional status, concurrent SSA use and median number of prior therapies, therefore, adjusting for these variables would not be possible in an ITC • TTD not reported and OS data are immature

Abbreviations: 1L, first-line; 2L, second-line; epNET, extra-pancreatic neuroendocrine tumour; GI, gastrointestinal; ITC, indirect treatment comparison; SSA, somatostatin analogues.

pNET cohort

For the pNETs cohorts, A6181111, RADIANT-3, and NETTER-2 were not considered suitable for robust comparisons with CABINET, as indicated by the summary in Table 39.

Specifically, comparisons versus A6181111 would not be suitable due to limited overlap in prior line of therapy, and the inability to adjust for median prior number of therapies, and missing data on tumour grade. While subgroup analyses for PFS were presented for A6181111 in TA449 as HRs for subgroups defined by number of previous systemic regimens (0 or 1 [n=121], ≥ 2 [n=50]), aggregate baseline data for the ≥ 2 subgroup are not available for the 50 patients that would permit matching the CABINET population to this subgroup in a population-adjusted ITC.¹¹

Comparisons with RADIANT-3 would not be suitable, as although eligibility criteria for prior therapy aligned with CABINET, key characteristics, most notably tumour grade, were missing and therefore could not be adjusted for. Similar considerations as for the epNET cohort applied for NETTER-2 in particular, that comparisons would be caveated by the known difference in line of therapy.

Table 39. Suitability of pNET cohorts for comparison with cabinet

Trial	Key discrepancies with CABINET
A6181111	• Included patients receiving $\geq$ 1L therapy; CABINET included patients receiving $\geq$ 2L therapy • SSA data were available to adjust for in analyses, and an imbalance was identified: 28% of patients in A6181111 used concurrent SSAs, compared to 55% in CABINET • Data were not reported for tumour grade, hormone syndrome/functional status and median number of prior therapies, therefore, adjusting for these variables would not be possible in an ITC • TTD not reported
RADIANT-3	• Data were not reported for tumour grade, hormone syndrome/functional status and median number of prior therapies, therefore, adjusting for these variables would not be possible in an ITC • TTD not reported
NETTER-2	• Included patients with advanced SSTR+ GEP-NETs; CABINET included patients with progressive pNETs • NETTER-2 included patients receiving 1L therapy; CABINET included

	patients receiving $\geq$ 2L therapy • Tumour grade data were available to adjust for in analyses, and an imbalance was identified: CABINET included 22% of patients with a grade 1 tumour in the cabozantinib arm while NETTER-2 included no patients with a grade 1 tumour. CABINET included >10% of patients with a Grade 3 tumour while NETTER-2 included >34% with a Grade 3 tumour • Data were not reported for hormone syndrome/functional status, concurrent SSA use and median number of prior therapies, therefore, adjusting for these variables would not be possible in an ITC • TTD and a HR for OS are not reported

Abbreviations: 1L, first-line; 2L, second-line; GEP-NET, gastroenteropancreatic neuroendocrine tumour; ITC, indirect treatment comparison; pNET, pancreatic neuroendocrine tumour; SSA, somatostatin analogues; SSTR+, somatostatin receptor positive; TTD, time to treatment discontinuation.

Appendix B: B19: Published cost-effectiveness studies

Table 40: Summary list of published cost-effectiveness studies

Study characteristics			Economic outcomes			Model features		
pNETs only (N=5)								
Study name	Disease characteristics (functional status; grade [net type]) ^a	Intervention and comparator	Total costs (£)	Total benefits	ICER (costs [£] per QALY gained)	Cost year; discount	Model structure	Health states
Glover 2021 ⁶²	NR; NR	¹⁷⁷ Lu-dotatate ^b	113,103	QALYs: 5.11	21,827	2017/2018; 3.5% for costs and benefits	Model: partitioned survival TH: 20 years CL: NR Perspective: NHS/PSS	PFS; PPS; death
		Everolimus	72,497	QALYs: 3.25	NA			
		¹⁷⁷ Lu-dotatate ^b	117,915	QALYs: 5.87	15,768			
		Sunitinib	81,350	QALYs: 3.55	NA			
		¹⁷⁷ Lu-dotatate ^b	111,289	QALYs: 4.49	28,038			
		SoC 1 (high dose octreotide LAR) ^b	60,326	QALYs: 3.12	NA			
		¹⁷⁷ Lu-dotatate ^b	118,525	QALYs: 5.64	22,146			
		SoC 2 (high dose octreotide LAR) ^c	53,033	QALYs: 2.96	NA			
Mujica-Mota 2018 ⁴⁹	NR; low or intermediate grade	Everolimus (analysed as an intervention and comparator)	Pre-progression: 27,559 Post-progression: 15,087 Total: 42,646	LYs: Pre-progression: 1.28 Post-progression: 3.41 Total: 4.69	Total (vs BSC): 45,493	2016; 3.5% for costs and benefits (no PAS discount)	Model: semi-Markov partitioned survival TH: 40 years CL: 28 days	Pre-progression; post-progression; death

	Mixed; NR	Sunitinib	Pre-progression: 24,566 Post-progression: 18,627 Total: 43,192	LYs: Pre-progression: 1.60 Post-progression: 4.79 Total: 6.39	Total (vs everolimus): 745 Total (vs BSC): 20,717		Perspective: NHS/PSS		
	NR; NR	BSC (intervention not specified)	Pre-progression: 2,712 Post-progression: 13,049 Total: 15,761	LYs: Pre-progression: 0.57 Post-progression: 2.89 Total: 3.46	NA				
	NR; NR	Everolimus	36,933	QALYs: 2.73 LYs: 4.18	NR	2015; 3.5% for costs (no PAS discount)	Model: semi-Markov partitioned survival TH: 20 years CL: 1 month Perspective: NHS/PSS	SD; PD; death	
		Sunitinib	38,569	QALYs: 2.71 LYs: 4.18	NA	2015; 3.5% for costs (PAS discount; first cycle of sunitinib free)			
		Sunitinib	36,247		NR				
		177Lu-dotatate	NR	NR	NA	NR; 3.5% for costs and benefits		PFS; PPS; death	
		Everolimus			9,847				
		Sunitinib			-68,916f				
	SMC 2018 ⁶³	NR; NR	¹⁷⁷ Lu-dotatate	NR	NR	NA	NR; NR	Model: partitioned survival TH: 20 years CL: NR	PFS; PPS; death
			Everolimus			26,103			
Sunitinib			17,487						
BSC 1 (octreotide LAR) ^e			25,068						

		BSC 2 (octreotide LAR) ^e			26,964		Perspective: NHS Scotland	
SMC 2023 ⁶⁴	NR; NR	Belzutifan	NR	NR	68,375	NR; simple discount (not elaborated)	Model: Markov TH: Lifetime (59 years based on assumed starting age of 41) CL: NR Perspective: NHS Scotland	Pre-surgery; surgery; event-free after surgery; metastatic disease; death
		SoC (immediate surgery or active surveillance)	NR	NR	NA			
Smith-Palmer 2021 ⁶⁵	NR; NR	¹⁷⁷ Lu-dotatate	117,922 ^d	QALYs: 4.78 ^d	25,068	NR; 3.5% for costs	Model: partitioned survival TH: 20 years CL: 4 weeks Perspective: NHS Scotland	PFS; PPS; death
		BSC (60 mg octreotide LAR)	52,470	QALYs: 2.16	NA			
		¹⁷⁷ Lu-dotatate	113,423 ^d	QALYs: 4.88 ^d	16,390			
		Sunitinib	81,303	QALYs: 2.92	NA			
		¹⁷⁷ Lu-dotatate	108,445 ^d	QALYs: 4.12 ^d	26,103			
		Everolimus	70,974	QALYs: 2.69	NA			
epNETs only (N=5)								
Glover 2021 ⁶²	NR; NR (GI NETs)	¹⁷⁷ Lu-dotatate	100,584	QALYs: 4.17	24,145	2017/2018; 3.5% for costs and benefits	Model: partitioned survival TH: 20 years CL: NR Perspective: NHS/PSS	PFS; PPS; death
		Everolimus	74,687	QALYs: 3.10	NA			
		¹⁷⁷ Lu-dotatate	100,073	QALYs: 4.17	26,528			
		SoC (high dose octreotide LAR)	67,454	QALYs: 2.94	NA			
Mujica-Mota 2018 ⁴⁹	Non-functioning; NR (GI midgut and lung NETs)	Everolimus	Pre-progression: 30,513	QALYs: Pre-progression: 1.04	44,557	2016; 3.5% for costs and benefits	Model: semi-Markov	Pre-progression; post-

			Post-progression: 16,882 Total: 47,334	Post-progression: 2.70 Total: 3.74 LYs: Pre-progression: 1.42 Post-progression: 4.79 Total: 6.21		partitioned survival TH: 40 years CL: 28 days Perspective: NHS/PSS	progression; death
		BSC (intervention not specified)	Pre-progression: 2,450 Post-progression: 14,076 Total: 16,526	QALYs: Pre-progression: 0.65 Post-progression: 2.39 Total: 3.05 LYs: Pre-progression: 0.83 Post-progression: 3.99 Total: 4.82	NA		
	Non-functioning; NR (GI midgut NETs)	Everolimus	Pre-progression: 38,215 Post-progression: 17,627 Total: 55,842	QALYs: Pre-progression: 1.49 Post-progression: 2.88 Total: 4.37 LYs: Pre-progression: 2.08 Post-progression: 5.42 Total: 7.5	199,233		

		BSC (intervention not specified)	Pre-progression: 4,194 Post- progression: 16,925 Total: 21,119	QALYs: Pre-progression: 1.10 Post-progression: 3.09 Total: 4.19 LYs: Pre-progression: 1.44 Post-progression: 5.62 Total: 7.05	NA			
	NR; NR (lung NETs)	Everolimus	49,168	QALYs: 3.18 LYs: 5.12	31,016	NR; 3.5% for costs	Model: semi- Markov partitioned survival TH: 40 years CL: 4 weeks Perspective: NHS/PSS	NR
		BSC (intervention not specified)	12,249	QALYs: 1.99 LYs: 2.96	NA			
	NR; NR (GI midgut NETs)	Everolimus	52,018	QALYs: 3.57 LYs: 5.75	78,330			
		BSC (intervention not specified)	16,628	QALYs: 3.11 LYs: 4.9	NA			
		177Lu- dotatate	83,667	QALYs: 4.19 LYs: 6.66	NA			
		Everolimus	52,018	QALYs: 3.57 LYs: 5.75	50,499			
		BSC (intervention not specified)	16,628	QALYs: 3.11 LYs: 4.9	62,158			

	Non-functioning; NR (GI midgut and lung NETs)	Everolimus	59,720	QALYs: 4.29 LYs: 5.79	43,642	2015; 3.5% for costs	Model: semi- Markov partitioned survival TH: 30 years CL: 1 month Perspective: NHS/PSS	SD; PD; death
		BSC (intervention not specified)	25,817	QALYs: 3.51 LYs: 4.78	NA			
	NR; NR (GI midgut NETs)	¹⁷⁷ Lu-dotatate	NR	NR	19,816	NR; 3.5% for costs and benefits	Model: semi- Markov partitioned survival TH: 20 years CL: 1 month Perspective: NHS/PSS	PFS; PPS; death
		Everolimus (intervention not specified)			NA			
SMC 2017 ⁶⁶	Non-functioning; Grade 1/2 (GI and lung NETs)	Everolimus	NR	NR	26,241	NR; simple discount (not elaborated)	Model: Markov TH: 30 years CL: 1 month Perspective: NHS Scotland	SD; PD; death
		BSC (mixed ⁹)			NA			
SMC 2018 ⁶³	NR; NR (GI NETs)	¹⁷⁷ Lu-dotatate	NR	NR	26,830	NR; NR	Model: partitioned survival TH: 20 years CL: NR Perspective: NHS Scotland	PFS; PPS; death
		BSC (LAR octreotide LAR)			NA			
Smith- Palmer 2021 ⁶⁵	NR; NR (GI NETs)	¹⁷⁷ Lu-dotatate + 30 mg octreotide	84,990	QALYs: 3.25	26,830	NR; 3.5% for costs	Model: partitioned survival TH: 20 years CL: 4 weeks Perspective: NHS Scotland	PFS; PPS; death
		BSC (60 mg octreotide LAR)	49,289	QALYs: 1.92	NA			

N represented the number of studies that reported economic outcomes. Cost and cost-effectiveness data has been rounded to integers; benefits have been presented to two decimal places. ^a Functional status, grade and Ki-67 index were prespecified at the start of extraction as disease characteristics of interest. Notably, none of the included studies reported Ki-67 index. As such, this has not been presented in the table. For epNET data, specific NET types have been specified, where reported. ^b ¹⁷⁷Lu-dotatate data were based on a MAIC between the Dutch cohort of ERASMUS and RADIANT-3 (for comparison with everolimus and SOC 1) or NCT00428597 (for comparison with sunitinib and SOC 2). ^c SoC 1 and SoC 2 data were derived from RADIANT-4 and NCT00428597 respectively. ^d ¹⁷⁷Lu-dotatate data were based on a MAIC between the Dutch cohort of ERASMUS and A6181111 (assuming equivalence between octreotide and BSC; for comparison with BSC), A6181111 (for comparison with sunitinib) or RADIANT-3 (for comparison with everolimus). ^e BSC data were based on a MAIC between the Dutch cohort of ERASMUS and a sunitinib study (not elaborated) for BSC 1 or an everolimus study (not elaborated) for BSC 2. ^f ¹⁷⁷Lu-dotatate was less expensive and more effective than the comparator (sunitinib), saving costs while improving outcomes, as such the ICER is negative. ^g BSC was comprised of several treatments including analgesics, other pain medication, somatostatin analogues and external beam radiation therapy.

Abbreviations: BSC: best supportive care; CL: cycle length; epNET: extra-pancreatic neuroendocrine tumour; GI: gastrointestinal; HR: hazard ratio; HRQoL: health-related quality-of-life; LAR: long-acting release; LYs: life-years; NA: not applicable; NETs: neuroendocrine tumours; NHS/PSS: National Health Service/Personal Social Services; NR: not reported; OS: overall survival; PAS: patient access scheme; PD: progressed disease; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour; PPS: post-progression survival; QALYs: quality-adjusted life years; SD: stable disease; SoC: standard of care; TH: time horizon.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

Addendum to Clarification Question Response

June 2025

File name	Version	Contains confidential information	Date
ID6474 Cabozantinib in NETs_Addendum to Clarification Question Responses_19June25_CON	1.0	Yes	19 th June 2025

The EAG believe that the committee will need to see analyses using the more mature OS data in order to make a decision, so are suggesting an extension to the deadline to allow you to update the analyses.

- 1. Use the latest data cut OS data to generate independent extrapolations for cabozantinib and BSC, using ITT, and crossover-adjusted OS curves (including both RPSFTM and IPCW). KM curves should be provided for all of these, as well as extrapolations**

Limitations of the OS data from the updated DCO (4th September 2024)

The model has now been updated to include the additional descriptive OS analysis (updated DCO: 4th September 2024), providing an additional 12 months of survival follow-up compared to the primary DCO. The updated OS data were presented in the company response to external assessment group (EAG) clarification question (CQ) A11. It should be noted that these data were derived from an unplanned OS sweep requested during marketing authorisation assessment, not from a pre-specified analysis.

Findings from this descriptive analysis should be interpreted with caution as there are three major limitations.

There are observed imbalances in prognostic factors across treatment arms within the largest stratum for the pNETs cohort, and the impact of these imbalances is more pronounced in the updated DCO

First, while there was already a degree of variation between stratified and unstratified HRs in the pNET cohort at the original, pre-specified analysis, with stratified HRs estimating a smaller relative treatment effect for cabozantinib compared with unstratified HRs, these differences have become more pronounced in the unplanned OS sweep. In fact, for the largest stratum (patients with concomitant SSA use and without prior sunitinib use), patients receiving cabozantinib were observed to have substantially shorter OS compared with patients receiving placebo, which is the opposite trend of what was observed for the three remaining strata. This is also contrary to the findings for PFS where cabozantinib arms had consistently longer survival than placebo arms in all strata, implying that post-progression events might have impacted the reversed trend in OS observed for the largest stratum. Median PFS and OS for cabozantinib and BSC by strata for the primary and updated DCOs are presented in full in Appendix 1. Since there is no clinical reason why the treatment effect should be reversed in this stratum, an investigation of baseline prognostic factors within the strata was conducted.

This investigation corroborated the hypothesis that the prognosis at baseline might have been unfavourable for patients receiving cabozantinib in this stratum, with regard to baseline characteristics that were not stratification factors at randomisation for pNETs. Baseline characteristics for cabozantinib and BSC by strata are presented in full in Appendix 1. In particular, in this stratum, comparing patients receiving cabozantinib vs patients receiving placebo, more cabozantinib patients had prior treatments at baseline (■% of cabozantinib patients vs ■% of placebo patients with three or more prior treatments), Grade 3 tumours (■% vs ■%), and an ECOG status greater than 0 (■% vs ■%). While stratified HRs are typically more robust than unstratified HRs as they are based on a model allowing for separate baseline

hazards in each stratum, it is not expected that treatment effects would differ between strata to the degree observed in the unplanned OS sweep, and this may be an artefact of the trial data. It is important to note that this imbalance is isolated to this largest stratum for pNETs, and the balance of prognostic factors is not of concern in the overall pNETs and epNETs cohorts. As such, the stratified HR for the pNET cohort might give undue weight to a single stratum with an implausible treatment effect that may be influenced by imbalances in prognostic factors within the stratum.

There is a high proportion of censoring in the updated DCO, with the tails of the OS curves informed by very few patients at risk; given the data sweep was not pre-specified, there is a particular risk of non-random or informative censoring

Second, while the unplanned OS sweep is based on a longer follow-up period, there is still a high proportion of patients censored for OS, mostly patients known to be alive at the data cut-off. In the epNET cohort, █ (█%) cabozantinib and █ (█%) placebo patients were censored alive after a median (IQR) follow-up of █ (█) months and █ (█) months, respectively. In the pNET cohort, █ (█%) cabozantinib and █ (█%) placebo patients were censored alive after a median (IQR) follow-up of █ (█) months and █ (█) months, respectively. In the unplanned OS sweep, the tails of the overall survival curves are informed by very few patients at risk, and suggest a smaller proportion of patients alive for cabozantinib compared with placebo in both cohorts. It is expected that additional data informing the tails at a later data cut-off could lead to very different results, especially regarding long-term survival and the HR between both treatments. Of note, compared to the primary DCO, a high number of patients in both cohorts are censored in relatively close proximity prior to the intersection of cabozantinib and placebo curves at later timepoints. Combined with the small number of patients at risk for later timepoints, there is high uncertainty arising from fewer events being observed as time progresses, which diminishes the precision and reliability of survival estimates at later timepoints. This means that the tails and estimated HRs should be interpreted with caution. Given the data sweep was not pre-specified, there is a particular risk of non-random or informative censoring, which could bias survival estimates further due to censored individuals differing systematically from those remaining. The expected impact of this could not be sufficiently addressed within the scope and timelines of the responses to clarification questions.

A higher proportion of patients had received subsequent treatment at the updated DCO, which may impact the performance of crossover-adjustment methods

Third, results are influenced by a higher proportion of patients receiving subsequent treatment compared with the primary DCO (pNET cohort: █ in the cabozantinib and █ in the placebo arm; epNET cohort: █ in the cabozantinib and █ in the placebo arm), including the proportion of placebo patients crossing over to cabozantinib (pNET: █; epNET: █). As discussed in the company submission, ITT analyses provide a biased estimate for the true relative treatment effect for cabozantinib versus placebo since patients initially receiving placebo will likely benefit more from subsequent treatment (including subsequent cabozantinib) compared with patients randomised to cabozantinib who had longer progression-free survival and stayed on their randomised treatment for longer. While crossover-adjusted analyses using inverse probability of censoring weights (IPCW) and rank-preserving structural failure time models (RPSFTM) were conducted, these methods were unable to fully account for the impact of crossover and subsequent treatment, especially given the high degree of censoring at the data cut-off (see above).

In summary, the results from the unplanned OS sweep are associated with a number of

limitations. As such, it is more appropriate to use data from the pre-specified data cut-off rather than from this ad-hoc OS data sweep to inform decision-making. Therefore, the company maintain that the model base case remains unchanged and with OS efficacy informed by data from the primary DCO.

Proportional hazards testing

As outlined in NICE TSD 14, the PH assumption was investigated through inspection of Schoenfeld residuals, log cumulative and smoothed hazard plots for the ITT data derived from the updated DCO (presented in Appendix 1 for cabozantinib and BSC). Schoenfeld residual plots were also produced for the IPCW weighted outcomes model based on the updated DCO. These showed there was no compelling evidence of PH violation for the pNET and epNET cohorts. Therefore, the PH assumption between cabozantinib and BSC for OS was considered appropriate and OS for BSC was derived by applying IPCW-adjusted HRs from the CABINET trial to the cabozantinib OS curve.

As stated in Section 3.3.4 of the company submission and reiterated in the response to the EAG CQ B12, due to unblinding and crossover which was permitted in CABINET after confirmation of progressed disease, ITT results overestimate OS for patients receiving placebo and thereby underestimate the relative benefits in OS for patients receiving cabozantinib. Further, as presented in Appendix L of the company submission, the KM of OS by treatment arm and switching status shows that patient populations who did not switch treatment had poorer OS than patients who switched to cabozantinib. Thus, crossover-adjusted analyses to account for the impact of patients switching from placebo to cabozantinib after disease progression on OS are essential and results based on the ITT OS that do not adjust for crossover are not appropriate for decision making. However, to address the EAG's request, OS extrapolations were also fitted separately for the cabozantinib and placebo arms to explore the impact of independent modelling in a scenario.

Overall pNET and epNET cohorts

Cabozantinib

The selection of the most appropriate extrapolation for the updated DCO cabozantinib OS was informed by the recommendations of NICE DSU TSD 14.¹ Specifically, goodness-of-fit statistics were calculated and assessed to understand which parametric form had the best statistical fit to the KM data. Assessment of visual fit was also conducted.

The model fit statistics (AIC and BIC) for the parametric survival functions explored for the cabozantinib PFS data are presented in Table 1 and Table 2 for pNETs and epNETs, respectively. Visual assessment of the parametric survival functions to the KM data for cabozantinib was performed using the extrapolations presented in Figure 1 and Figure 2.

Table 1: Model fit statistics for OS parametric survival functions for cabozantinib (pNETs)

	OS			
	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	312.70	3	314.86	1
Weibull	312.39	2	316.71	3
Lognormal	315.09	6	319.40	5
Loglogistic	313.75	4	318.07	4
Gompertz	312.23	1	316.55	2

Generalised gamma	313.82	5	320.30	6

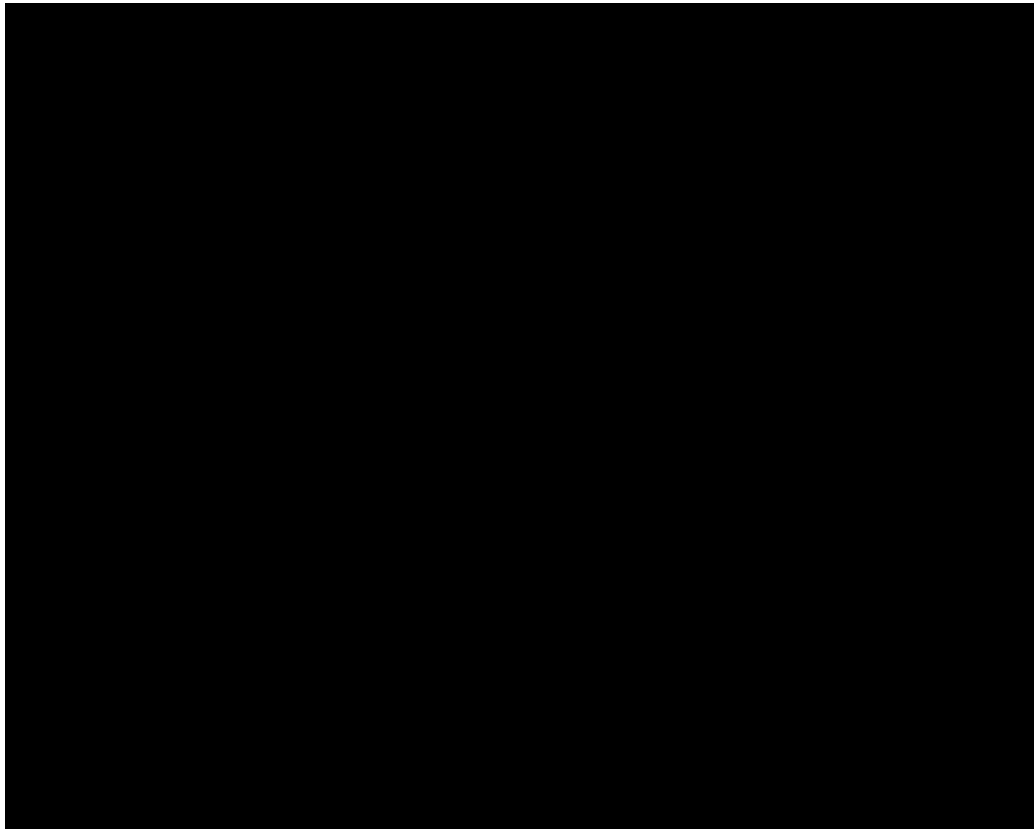
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; pNET: pancreatic neuroendocrine tumour; ITT: intent-to-treat; OS: overall survival.

Table 2: Model fit statistics for OS parametric survival functions for cabozantinib (epNETs)

Function	OS			
	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	753.66	6	756.56	2
Weibull	751.13	3	756.92	4
Lognormal	750.51	1	756.31	1
Loglogistic	750.98	2	756.77	3
Gompertz	753.57	5	759.37	5
Generalised gamma	751.35	4	760.05	6

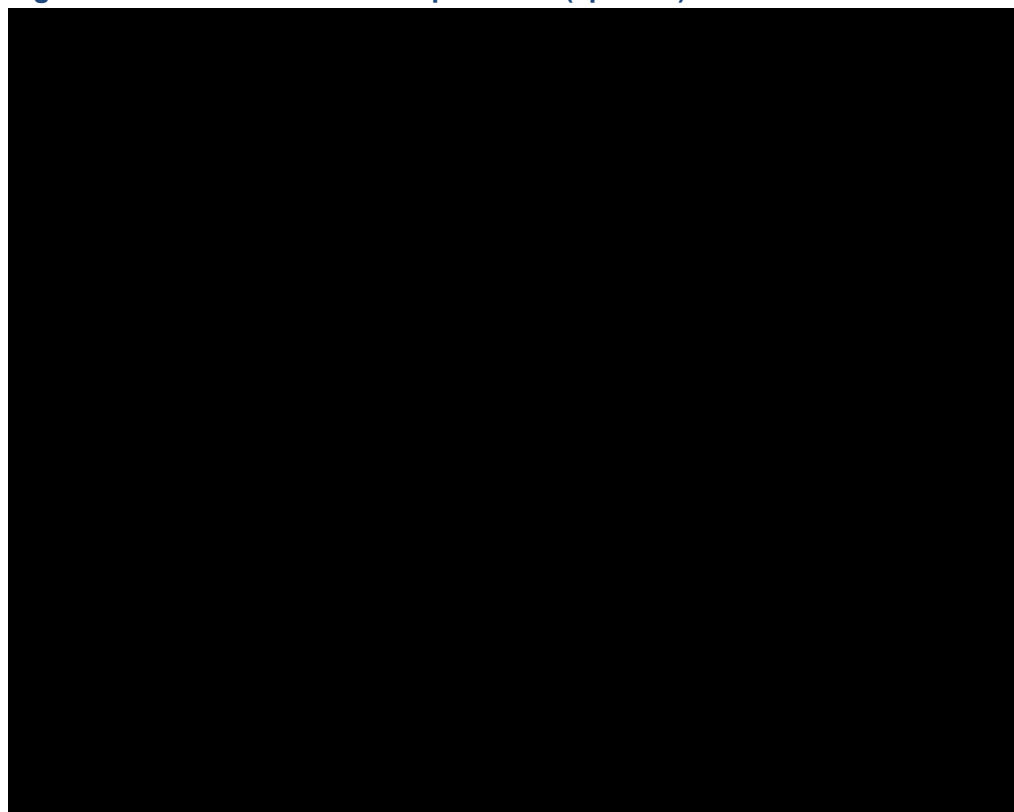
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; epNET: extra-pancreatic neuroendocrine tumour; ITT: intent-to-treat; OS: overall survival.

Figure 1. Cabozantinib OS extrapolations (pNETs)



Abbreviations: KM: Kaplan-Meier; OS: overall survival; pNET: pancreatic neuroendocrine tumour.

Figure 2. Cabozantinib OS extrapolations (epNETs)



Abbreviations: epNET: extra pancreatic neuroendocrine tumour; KM: Kaplan-Meier, OS: overall survival.

There were no substantial differences between the AIC and BIC values for the fitted OS curves, with the majority of extrapolations showing a difference of <5 points, suggesting a similar goodness of fit to the KM data. Additionally, all extrapolations appeared to provide a similar fit to the observed KM data in the assessment of visual fit, falling well within the 95% confidence intervals. The selection of the base case curves was informed by clinical expert opinion; given OS for BSC was derived by applying the IPCW-adjusted HRs from the CABINET trial to the cabozantinib OS curve, base case curve selection for cabozantinib was informed by clinical plausibility across cabozantinib and BSC, simultaneously, as discussed below.

BSC: crossover-adjusted HRs

As with the primary DCO, unblinding and crossover from placebo to cabozantinib were permitted after confirmation of progressed disease by central radiology review. As such, ITT analysis overestimate the OS of placebo patients and underestimate the relative benefits in OS for patients receiving cabozantinib. A crossover-adjusted HR was therefore applied to the cabozantinib curve in the base case analysis rather than using direct extrapolations or applying the ITT HR.

In line with the approach explored for the primary DCO, and as per NICE DSU TSD 16 and 24, the rank-preserving structural failure time model (RPSFTM) and IPCW were explored to adjust for crossover.^{2, 3} The OS HRs for the updated DCO are presented in Table 3, alongside the results from the corresponding analyses for the primary DCO. It should be noted that the point estimates of the HRs derived for the pNETs subgroup are all above 1, implying a numerical benefit for placebo over cabozantinib in terms of OS. Based on clinical expectations of long term survival (as shown in Table 8 below), the statistically significant and clinically meaningful improvement in PFS in the pNET cohort (HR: 0.23; 95% CI: 0.12, 0.42; stratified 2-sided

p<0.0001), which represents an validated surrogate endpoint for OS patients with metastatic NETs,⁴ and the observed limitations of the OS data derived from the updated DCO, modelling a numerical benefit for OS for BSC versus cabozantinib was not considered clinically plausible. As such, scenarios were also explored applying a hazard ratio of 1 (i.e., no OS benefit for cabozantinib versus BSC); scenarios have been explored directly using the IPCW-adjusted HRs for pNETs derived from the updated DCO for completeness but are not suitable for decision-making.

Table 3. OS hazard ratios (cabozantinib vs BSC)

Population	Measure	ITT Analysis (95% CI)	IPCW (95% CI)	RPSFTM ^a (95% CI)
Primary DCO				
pNET	Stratified HR ^b	0.95 (0.45, 2.00)	0.74 (0.36, 1.52)	██████████
epNET	Stratified HR ^b	0.86 (0.56, 1.31)	0.65 (0.39, 1.07)	██████████
Updated DCO				
pNET	Stratified HR ^b	██████████	██████████	██████████
epNET	Stratified HR ^b	██████████	██████████	██████████

^a 95% CI for RPSFTM are based on adjusted standard errors obtained by dividing the point estimate by the square root of the Chi-square statistic of the ITT analysis, this was done in order to reflect the uncertainty associated with estimating the RPSFTM counterfactual dataset; ^b Stratified HRs were based on the relevant stratification factors for each population (pNET: concomitant SSA use and prior sunitinib use; epNET: concomitant SSA use and primary site [midgut/unknown vs non-midgut GI/lung/other]).

Abbreviations: BSC: best supportive care; epNET: extra pancreatic neuroendocrine tumour; GI: gastrointestinal; HR: hazard ratio; IPCW: inverse probability coefficient weighting; ITT: intention-to-treat; NET: neuroendocrine tumour; OS: overall survival; pNET: pancreatic neuroendocrine tumour; RPSFTM: rank-preserving structural failure time model; SSA: somatostatin analogue.

BSC: Independent extrapolation

Parametric survival models were also fitted directly to BSC OS data to inform the scenario exploring independent extrapolation of cabozantinib and BSC OS data. The model fit statistics (AIC and BIC) for the parametric survival functions explored for the cabozantinib PFS data are presented in Table 4 and Table 5 for pNETs and epNETs, respectively. The BSC OS KM curves with the associated extrapolations for pNETs and epNETs are presented in Figure 3 and Figure 4.

Table 4: Model fit statistics for OS parametric survival functions for BSC (pNETs)

	OS			
	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	152.0547	1	153.4887	1
Weibull	154.0193	5	156.8873	5
Loglogistic	153.2007	2	156.0687	2
Lognormal	153.2375	3	156.1055	3
Generalised gamma	155.2257	6	159.5276	6
Gompertz	153.845	4	156.713	4

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; pNET: pancreatic neuroendocrine tumour; ITT: intent-to-treat; OS: overall survival.

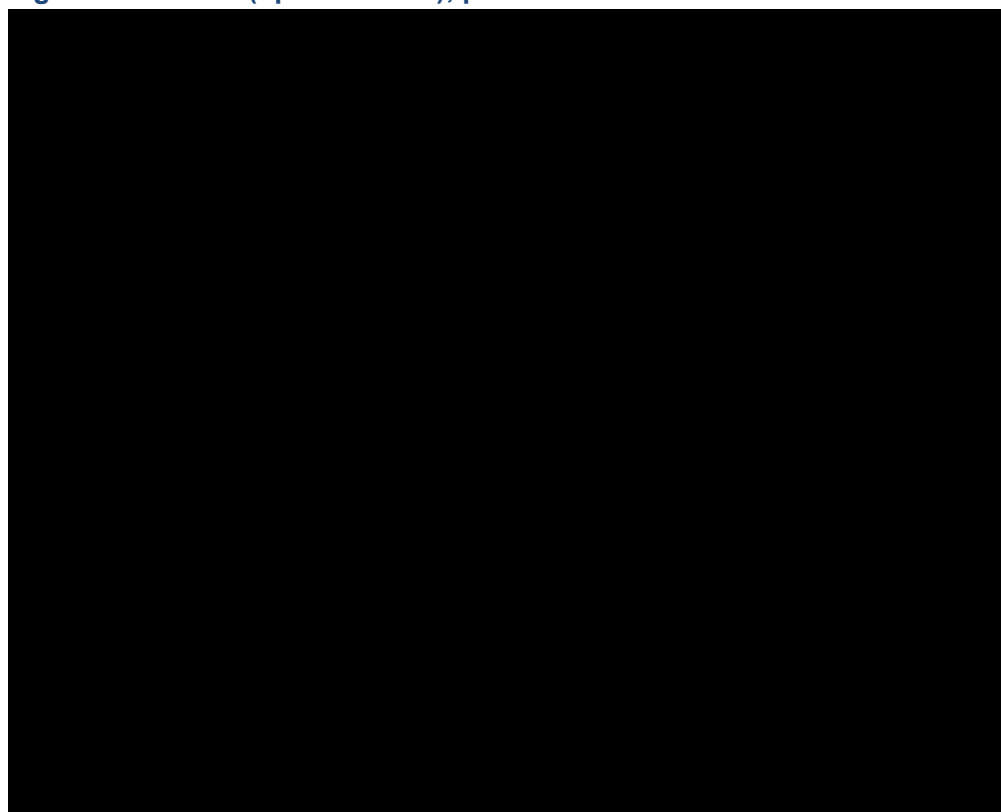
Table 5: Model fit statistics for OS parametric survival functions for BSC (epNETs)

Function	OS

	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	379.6123	3	381.8464	1
Weibull	380.6407	4	385.109	4
Loglogistic	378.9954	2	383.4636	3
Lognormal	378.8867	1	383.3549	2
Generalised gamma	380.7171	5	387.4194	6
Gompertz	381.5835	6	386.0517	5

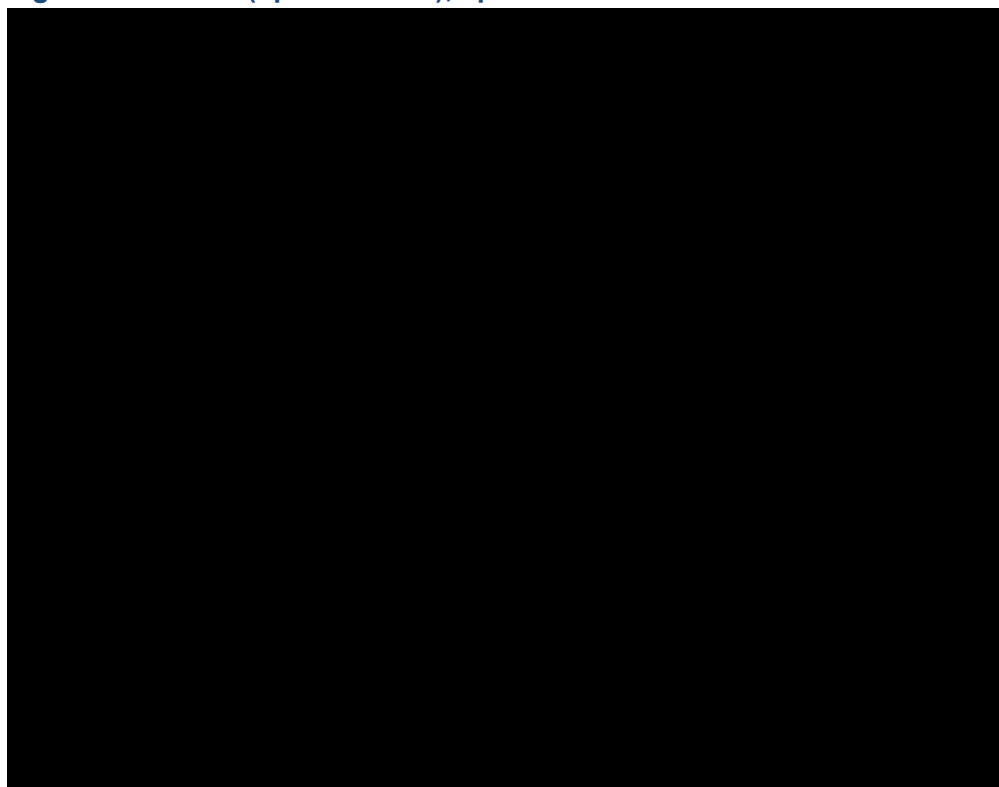
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; epNET: extra-pancreatic neuroendocrine tumour; ITT: intent-to-treat; OS: overall survival.

Figure 3. BSC OS (updated DCO); pNETs



Abbreviations: DCO: data cut-off; KM: Kaplan-Meier; OS: overall survival; pNET: pancreatic neuroendocrine tumour.

Figure 4. BSC OS (updated DCO); epNETs



Abbreviations: DCO: data cut-off; epNET: extra pancreatic neuroendocrine tumour; KM: Kaplan-Meier, OS: overall survival.

There were no substantial differences between the AIC and BIC values for the fitted OS BSC curves, with the majority of extrapolations showing a difference of <5 points, suggesting a similar goodness of fit to the KM data for all curves. Additionally, most extrapolations appeared to provide a similar fit to the observed KM data in the assessment of visual fit, falling within the 95% confidence intervals. The selection of the curves for the scenario investigating independent extrapolation of BSC OS was informed by clinical expert opinion.

Curve selection for OS: Cabozantinib and BSC

The IPCW approach was considered the most appropriate approach to adjust for crossover, given Latimer *et al.* (2024) suggested that RPSFTM may perform relatively poorly compared with other crossover adjustment methods when ITT analyses provided HRs close to 1,⁵ which is the case for the epNET and pNET cohorts in CABINET; IPCW does not suffer from the same limitation.

However, results from the updated DCO were derived from an unplanned OS sweep and should be interpreted with caution for the following reasons (further detailed at the start of this response):

- There are differences in patient prognostic factors in the largest stratum where a reversed treatment effect was observed, these differences suggest that the prognosis at baseline might have been unfavourable for patients receiving cabozantinib, and the impact of the imbalances is more pronounced at the updated DCO.
- There is a continued high proportion of patient censoring resulting in tails of KM curves based on very few patients and potential for informative censoring. Additionally, given

the data sweep was not pre-specified, there is a particular risk of non-random or informative censoring.

- There was higher proportion of patients receiving subsequent treatment and crossover cabozantinib in the updated DCO which may lead to poorer performance of crossover adjustment methods.

Therefore, whilst based on less mature OS data, IPCW-adjusted HRs based on the primary DCO (as shown in Table 3) may provide more robust estimates of the true treatment effect between cabozantinib and BSC, and produce survival predictions that are more closely aligned with clinical expert estimates. A number of different approaches were explored to understand the range of possible estimates for the treatment effect on OS, as described in Table 6, as well as the source of OS data for the cabozantinib arm of the model.

As described in the company submission, five independent clinician interviews were conducted to help inform the most appropriate curve selections. Within these interviews, clinicians were asked to estimate predictions of survival through providing a most plausible estimate, as well as upper and lower limits, of overall survival (life expectancy) for cabozantinib and BSC at 5-, 10- and 15-years post treatment initiation. The predicted survival associated with each parametric extrapolation and the various approaches to model the treatment effect on OS was compared against the average clinician estimates, as shown in Table 7 to Table below.

Table 6: Exploratory scenarios varying the treatment effect for OS for cabozantinib versus BSC

	DCO informing cabozantinib OS curve	BSC extrapolation method	DCO informing HR between cabozantinib and BSC	Crossover adjustment method
Base case: Cabozantinib OS curve (primary DCO) + IPCW HR (primary DCO)	<i>Primary DCO</i>	<i>Crossover-adjusted HRs applied to cabozantinib curve</i>	<i>Primary DCO</i>	<i>IPCW</i>
Scenario 1: Cabozantinib OS curve (updated DCO) + IPCW HRs (primary DCO)	Updated DCO	Crossover-adjusted HRs applied to cabozantinib curve	Primary DCO	IPCW
Scenario 2: Cabozantinib OS curve (updated DCO) + IPCW HRs (updated DCO)	Updated DCO	Crossover-adjusted HRs applied to cabozantinib curve	Updated DCO	IPCW
Scenario 3: Cabozantinib OS curve (updated DCO) + RPSFTM HRs (updated DCO)	Updated DCO	Crossover-adjusted HRs applied to cabozantinib curve	Updated DCO	RPSFTM
Scenario 4 (pNETs only): Cabozantinib OS curve (updated DCO) + HR=1	Updated DCO	HRs applied to cabozantinib curve	Assumption that HR=1	NA
Scenario 5: Independent extrapolations (updated DCO)	Updated DCO	Independent extrapolation	NA	NA

The primary DCO corresponds to a pre-specified cut-off date of 24th August 2023. The updated DCO corresponds to an unplanned OS sweep conducted for a cut-off data of 4th September 2024. Results based on HRs that exceed 1 (implying a survival benefit for BSC over cabozantinib) are presented for completeness but are not considered clinically plausible and thus are greyed out.

Abbreviations: BSC: best supportive care; DCO: data cut-off; HR: hazard ratio; IPCW: inverse probability of censoring weights; OS: overall survival; RPSFTM: rank preserving structural failure time model.

Curve selection of OS: Cabozantinib

The appropriate curve for the cabozantinib extrapolation was selected based on alignment with the clinician estimates, as shown in Table 7 for pNETs and epNETs. For pNETs, the loglogistic curve was selected as the most appropriate model for cabozantinib, producing predicted survival in line with the clinician estimates at all timepoints, and associated with a reasonable statistical fit (ranked fourth for AIC and BIC) and acceptable visual fit to the KM curve. For epNETs, the loglogistic curve was also selected as the most appropriate model for cabozantinib, producing predicted survival in line with the clinician estimates at all timepoints, and associated with a good statistical fit (ranked second and third for AIC and BIC, respectively) and acceptable visual fit to the KM curve.

The plausibility of the respective extrapolation for the BSC curve (across all scenarios explored) was also considered, with loglogistic predicting survival that was most closely aligned with clinician estimates for Scenario 1 and 2 (for epNETs only). As noted below, for Scenario 2 (for pNETs only), 3 and 4, no models produce survival predictions compatible with clinical expert predictions for cabozantinib and BSC simultaneously, given a lack of overlap in the clinician's estimates for cabozantinib and BSC at later timepoints.

Table 7: Clinician and parametric survival landmark estimates for OS for cabozantinib (pNETs and epNETs)

Category		Curve	OS %		
			5	10	15
pNETs					
Average clinician estimates	Lower plausible limit	24.1%	13.4%	6.8%	
	Most likely	36.0%	19.2%	10.8%	
	Upper plausible limit	44.0%	23.6%	15.0%	
Extrapolations	Exponential				
	Weibull				
	Log-logistic				
	Lognormal				
	Generalised gamma				
	Gompertz				
epNETs					
Average clinician estimates	Lower plausible limit	12.3%	6.0%	1.0%	
	Most likely	21.1%	10.5%	3.5%	
	Upper plausible limit	24.0%	13.8%	4.7%	
Extrapolations	Exponential				
	Weibull				
	Loglogistic				
	Lognormal				
	Generalised gamma				
	Gompertz				

Light red shading indicates that the predicted survival of the selected curve falls below the lower plausible limit of the clinician's estimate of overall survival. Light blue shading indicates that the curves predict survival that exceeds the clinician's upper estimate of overall survival.

Abbreviations: BSC: best supportive care; epNET: extra pancreatic neuroendocrine tumour; HR: hazard ratio; NET: neuroendocrine tumour; OS: overall survival; pNET: pancreatic neuroendocrine tumour.

Scenarios varying treatment effect and impact on BSC OS

The curve selection for cabozantinib (loglogistic across all scenarios for both pNET and epNET cohorts) and the approach informing BSC OS resulted in a large variation in long-term survival predictions for BSC. The clinical plausibility of predictions across scenarios was considered through comparisons to clinician estimates of long-term survival for BSC.

- **Scenario 1: BSC OS derived by applying IPCW-adjusted HRs (primary DCO) to the cabozantinib curve (updated DCO)** For pNETs, when applying the IPCW-adjusted HR from the primary DCO (HR: 0.74) the loglogistic curve predicted survival for BSC in line with all except at the 15-year timepoint, where predicted survival was above the clinicians' highest plausible estimate, thereby representing a conservative selection. For epNETs, when applying the IPCW-adjusted HR from the primary DCO (HR: 0.65), the loglogistic curve also predicted survival for BSC most closely aligned with clinician estimates, falling within clinician's higher and lower plausible estimates at all except the 10-year timepoint. Whilst the updated DCO was associated with limitations in terms of generating a robust relative treatment effect between cabozantinib and BSC (particularly in the pNETs subgroup), it is acknowledged that this DCO provides a considerable increase in maturity in OS data. This scenario was considered the most robust approach to incorporate the data from the updated DCO, utilising the more mature data to inform the extrapolation of cabozantinib, but generating BSC OS based on the more robust relative treatment effect derived from the IPCW analysis of the primary DCO.
- **Scenario 2: BSC OS derived by applying IPCW-adjusted HRs (updated DCO) to the cabozantinib curve (updated DCO)** For epNETs, when applying the IPCW-adjusted HR from the updated DCO (HR: ■■■), the loglogistic curve predicted survival for BSC most closely aligned with clinician estimates, falling within clinician's higher and lower plausible estimates at all timepoints. For pNETs, the IPCW-adjusted HR from the updated DCO (HR: ■■■) suggests a numerical benefit in OS for BSC over cabozantinib and was not considered clinically plausible. Accordingly, no models produce survival predictions compatible with clinical expert predictions for cabozantinib and BSC simultaneously, given a lack of overlap in the clinician's estimates for cabozantinib and BSC at later timepoints. An analysis has been explored for completeness but is not considered suitable for decision-making.
- **Scenario 3 (pNETs only): BSC OS derived by applying a HR of 1 to the cabozantinib curve (updated DCO)** For pNETs, a scenario was explored where a HR of 1 was applied to the OS curve for cabozantinib, assuming no OS benefit for cabozantinib over BSC. Given the statistically significant and clinically meaningful improvement in PFS observed in the pNET cohort (HR: 0.23; 95% CI: 0.12, 0.42; stratified 2-sided $p < 0.0001$), which represents a validated surrogate endpoint for OS patients with metastatic NETs,⁴ and the observed limitations of the OS data derived from the updated DCO, an assumption of no OS benefit is considered overly pessimistic. Accordingly, no models produce survival predictions compatible with clinical expert predictions for cabozantinib and BSC simultaneously, given a lack of overlap in the clinician's estimates for cabozantinib and BSC at later timepoints.
- **Scenario 4: BSC OS derived by applying RPSFTM-adjusted HRs (updated DCO) to the cabozantinib curve (updated DCO):** It should be acknowledged that RPSFTM may perform relatively poorly compared with other crossover adjustment methods when ITT analyses provide HRs close to 1. For pNETs and epNETs, the RPSFTM-adjusted HRs from the updated DCO (HR: ■■■ and ■■■, respectively) suggest a numerical benefit in OS for BSC over cabozantinib and are not considered clinically plausible. Accordingly, no models produce survival predictions compatible with clinical expert predictions for cabozantinib and

BSC simultaneously, given a lack of overlap in the clinician's estimates for cabozantinib and BSC at later timepoints. An analysis has been explored for completeness but is not considered suitable for decision-making.

- Approach 5: Independent extrapolations (updated DCO):** When using direct extrapolations for BSC, an exponential distribution was selected for both pNETs and epNETs. The exponential model was associated with good statistical fit in both cohorts (ranked first in terms of AIC and BIC for pNETs and first in terms of BIC for epNETs). For epNETs, the exponential curve overestimates survival at 5 years relative to clinician's average estimates, but may underestimate survival at later timepoints; it was selected on the basis of producing estimates that fall in the middle of the range of models explored, and given the best statistical fit for BIC. However, none of the generated extrapolations for pNETs provided plausible long term OS rates, with consistent overestimation compared to clinical estimates, exceeding the upper plausible value provided by clinicians at all timepoints. Given the lack of clinical plausibility of the BSC OS extrapolations, it is advised that these results are interpreted with caution and not relied upon for decision-making.

Table 8: Clinician and parametric survival landmark estimates for OS for BSC (pNETs)

Category	Curve	OS %		
		5	10	15
Average clinician estimates	Lower plausible limit	11.0%	2.8%	0.5%
	Most likely	20.0%	6.0%	2.0%
	Upper plausible limit	27.8%	9.8%	2.8%
Scenario 1: Cabozantinib curve (updated DCO) + IPCW HRs (primary DCO)	Exponential	■	■	■
	Weibull	■	■	■
	Log-logistic	■	■	■
	Lognormal	■	■	■
	Generalised gamma	■	■	■
	Gompertz	■	■	■
Scenario 2: Cabozantinib curve (updated DCO) + IPCW HRs (updated DCO)	Exponential	■	■	■
	Weibull	■	■	■
	Log-logistic	■	■	■
	Lognormal	■	■	■
	Generalised gamma	■	■	■
	Gompertz	■	■	■
Scenario 3: Cabozantinib curve (updated DCO) + RPSFTM HRs (updated DCO)	Exponential	■	■	■
	Weibull	■	■	■
	Log-logistic	■	■	■
	Lognormal	■	■	■
	Generalised gamma	■	■	■
	Gompertz	■	■	■
Scenario 4: Cabozantinib curve (updated DCO) + HR=1	Exponential	■	■	■
	Weibull	■	■	■
	Log-logistic	■	■	■
	Lognormal	■	■	■
	Generalised gamma	■	■	■

	Gompertz	■	■	■
Scenario 5: Independent extrapolation	Exponential	■	■	■
	Weibull	■	■	■
	Log-logistic	■	■	■
	Lognormal	■	■	■
	Generalised gamma	■	■	■
	Gompertz	■	■	■

Light red shading indicates that the predicted survival of the selected curve falls below the lower plausible limit of the clinician's estimate of overall survival. Light blue shading indicates that the curves predict survival that exceeds the clinician's upper estimate of overall survival.

Abbreviations: BSC: best supportive care; HR: hazard ratio; NET: neuroendocrine tumour; OS: overall survival; pNET: pancreatic neuroendocrine tumour.

Table 9: Clinician and parametric survival landmark estimates for OS for BSC (epNETs)

Category	Curve	OS %		
		5	10	15
Average clinician estimates	Lower plausible limit	5.8%	2.0%	0.5%
	Most likely	10.8%	3.8%	1.5%
	Upper plausible limit	15.5%	6.8%	2.3%
Scenario 1: Cabozantinib curve (updated DCO) + IPCW HRs (primary DCO)	Exponential	■	■	■
	Weibull	■	■	■
	Loglogistic	■	■	■
	Lognormal	■	■	■
	Generalised gamma	■	■	■
	Gompertz	■	■	■
Scenario 2: Cabozantinib curve (updated DCO) + IPCW HRs (updated DCO)	Exponential	■	■	■
	Weibull	■	■	■
	Loglogistic	■	■	■
	Lognormal	■	■	■
	Generalised gamma	■	■	■
	Gompertz	■	■	■
Scenario 3: Cabozantinib curve (updated DCO) + RPSTFM HRs (updated DCO)	Exponential	■	■	■
	Weibull	■	■	■
	Loglogistic	■	■	■
	Lognormal	■	■	■
	Generalised gamma	■	■	■
	Gompertz	■	■	■
Scenario 4: Independent extrapolation	Exponential	■	■	■
	Weibull	■	■	■
	Loglogistic	■	■	■
	Lognormal	■	■	■
	Generalised gamma	■	■	■
	Gompertz	■	■	■

Light red shading indicates that the predicted survival of the selected curve falls below the lower plausible limit of the clinician's estimate of overall survival. Light blue shading indicates that the curves predict survival that exceeds the clinician's upper estimate of overall survival.

Abbreviations: BSC: best supportive care; epNET: extra pancreatic neuroendocrine tumour; HR: hazard ratio; NET: neuroendocrine tumour; OS: overall survival.

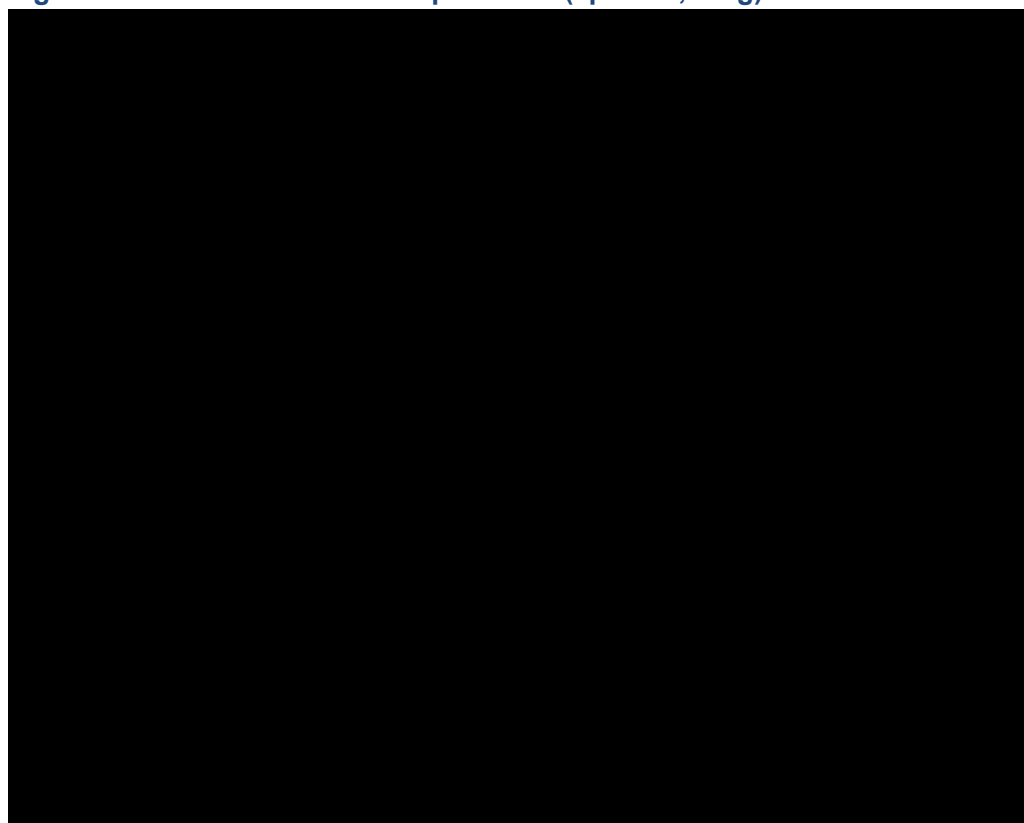
Subgroup analyses for epNET lung and epNET without lung

Subgroup analyses for epNET lung and epNET without lung using data from the updated DCO have been provided below. However, as noted in the response to the EAG clarification question A6, given the limitations of the post-hoc subgroup analyses such as lack of stratified randomisation and small sample sizes, the full epNETs cohort provides the most robust data to inform the comparative efficacy of cabozantinib versus BSC in all epNETs patients.

Cabozantinib

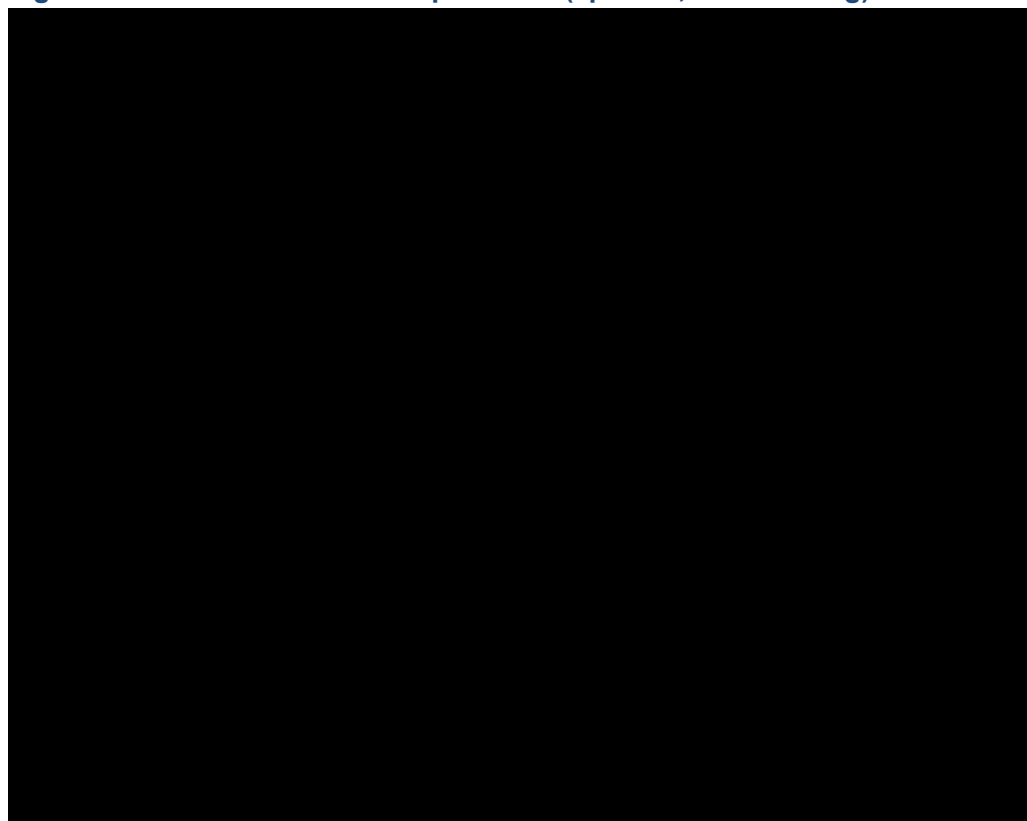
Visual assessment of the parametric survival functions to the KM data for cabozantinib was performed using the extrapolations presented in Figure 5 and Figure 6 for the epNETs lung and without lung subgroups respectively. The model fit statistics (AIC and BIC) are also presented in the associated figures.

Figure 5. Cabozantinib OS extrapolations (epNETs; lung)



Abbreviations: KM: Kaplan-Meier; OS: overall survival; epNET: extra-pancreatic neuroendocrine tumour.

Figure 6. Cabozantinib OS extrapolations (epNETs; without lung)



Abbreviations: KM: Kaplan-Meier; OS: overall survival; epNET: extra-pancreatic neuroendocrine tumour.

There were no substantial differences between the AIC and BIC values for the fitted OS curves, with the majority of extrapolations showing a difference of <5 points, suggesting a similar goodness of fit to the KM data for all curves. Additionally, all extrapolations appeared to provide a similar fit to the observed KM data in the assessment of visual fit.

The Gompertz model was selected as the OS extrapolation in the epNET lung subgroup as this had the best statistical fit for both AIC and BIC (see Figure 5), a good visual fit with the KM data, and a plausible long-term survival estimate of <5% survival after 5 years. In a large-scale observational study of retrospective data on 14,834 patients with NETs and NECs, collected by the NCRAS in England between 2012 and 2018, five-year survival for patients with Stage IV NETs originating in the lung was 12%; prognosis is expected to be even poorer in those patients who have progressed on prior systemic treatments.⁶

The loglogistic model was selected as the OS extrapolation in the epNET without lung subgroup as this was associated with good statistical fit (ranked second and third for AIC and BIC, respectively) and estimated similar long-term survival at 5, 10 and 15 years to that predicted by clinicians for overall epNETs as described in Table 9.

BSC

In line with the base case approach, a HR was applied to the cabozantinib extrapolation to derive BSC efficacy in epNET lung and epNETs without lung subgroups. As outlined in the response to question 2 below, the full epNETs cohort provides the most robust data to inform the comparative efficacy of cabozantinib versus BSC in all epNETs patients, and thus the HRs derived from the overall epNETs cohort from the updated DCO (as shown in Table 3) were applied to the cabozantinib extrapolation for the epNET lung and epNETs without lung subgroups to estimate

BSC efficacy. This approach allows for differences in prognosis to be reflected in the model (as per the feedback from the EAG's clinical experts), whilst ensuring the modelled treatment effect is robust. This also represents a conservative approach for lung NETs, given the HRs from the lung epNETs subgroup are more favourable than the HRs derived from the overall epNETs cohort. Nevertheless, the results of this analysis should be interpreted with caution, given the extrapolated data for cabozantinib in the lung subgroup are based on small patient numbers. All other model inputs were assumed to align to the overall epNET data. PRRT was not modelled as a subsequent treatment in lung NETs as it is not reimbursed in the UK for this population, and subsequent treatments were reweighted accordingly.

Cost-effectiveness results

Deterministic scenario analysis results for pNETs, epNETs, epNETs (lung) and epNETs (without lung) are presented in Table 10.

When incorporating the updated OS data (scenario 1), cabozantinib was found to be cost-effective compared to BSC in both pNETs and epNETs at a willingness to pay (WTP) threshold of £30,000 per QALY and produced an ICER well below the threshold of £20,000 in the epNET cohort. For pNETs, the ICER improved when the more mature OS data were used to inform the extrapolation for cabozantinib. Scenarios 2 and 3 demonstrate increased ICERs compared to those seen when using the primary DCO OS data; however, as described in detail above, these results are not clinically plausible given they are based on HRs reflecting a OS benefit for BSC over cabozantinib, and as such, are not appropriate to inform decision making. The assumption in Scenario 4 that cabozantinib OS is equal to that of BSC (HR=1) is considered overly pessimistic, given the statistically significant and clinically meaningful improvement in PFS observed in the pNET cohort, which represents a validated surrogate endpoint for OS patients with metastatic NETs.⁴ The corresponding ICER should therefore be interpreted with caution. Scenario 5, in which independent extrapolations are considered for both cabozantinib and BSC, produces similar ICERs to the base case. However, as independent extrapolation does not adjust for the impact of crossover to cabozantinib, these results are likely biased in favour of BSC.

Table 10: Updated DCO cost-effectiveness results

Scenario		pNETs			epNETs			Lung NETs			epNETs (without lung NETs)		
		Inc costs	Inc QALYs	ICER	Inc costs	Inc QALYs	ICER	Inc costs	Inc QALYs	ICER	Inc costs	Inc QALYs	ICER
Base case: Cabozantinib curve (primary DCO) + IPCW HR (primary DCO)		████	██	£24,815	████	██	£12,849	NA	NA	NA	NA	NA	NA
Subgroups: Cabozantinib curve (primary DCO) + IPCW HR (primary DCO, full epNETs cohort)		NA	NA	NA	NA	NA	NA	████	██	£20,904	████	██	£13,718
1	Cabozantinib curve (updated DCO) + IPCW HRs (primary DCO)	████	██	£21,716	████	██	£12,856	████	██	£24,957	████	██	£13,765
2	Cabozantinib curve (updated DCO) + IPCW HRs (updated DCO)	████	██	Cabozantinib dominated	████	██	£15,716	████	██	£32,317	████	██	£16,951
3	Cabozantinib curve (updated DCO) + RPSFTM HRs (updated DCO)	████	██	Cabozantinib dominated	████	██	Cabozantinib dominated	████	██	£235,466	████	██	Cabozantinib dominated
4	Cabozantinib curve (updated DCO) + HR=1	████	██	£97,337	NA	NA	NA	NA	NA	NA	NA	NA	NA
5	Updated DCO independent extrapolations	████	██	£27,545	████	██	£15,807	NA	NA	NA	NA	NA	NA

All epNET results (including lung NETs and epNETs [without lung NETs]) qualify for a 1.2x severity modifier, which is applied here. Results based on HRs that exceed 1 (implying a survival benefit for BSC over cabozantinib) are presented for completeness but are not considered clinically plausible and thus are greyed out.

Abbreviations: epNETs: extra-pancreatic neuroendocrine tumours; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; IPCW: inverse probability of censoring weights; OS: overall survival; pNETs: pancreatic neuroendocrine tumours; QALY: quality-adjusted life year; RPSFTM: rank preserving structural failure time model.

2. Provide us with the HRs for OS (non-adjusted for crossover) and PFS HR for the epNETs without lung subgroup analysis. Provide us with the OS HRs for lung and non-lung epNET patients using the RPSFTM and IPCW adjustment as requested in B13b.

It is important to note that randomisation was not stratified according to classification of subgroups by primary tumour type (instead, randomisation was stratified by midgut GI/unknown versus non-midgut GI/lung/other); results of subgroup analyses for epNET (lung) and epNET (without lung) are likely to be subject to bias due to imbalances in patient characteristics across treatment arms and associated confounding. The post-hoc subgroups also have very small sample sizes and should therefore be interpreted with considerable caution. Furthermore, whilst remaining limited by small sample sizes, pre-specified subgroup analysis by primary tumour location in the stratified subgroups (where randomisation is maintained) of midgut GI/unknown versus non-midgut GI/lung/other demonstrated a broadly consistent PFS benefit, with HRs of 0.33 (95% CIs: 0.19, 0.57) and 0.57 (95% CIs: 0.24, 1.29), respectively, as shown in Section 2.8 of the company submission. Given the limitations of the post-hoc subgroup analyses, the full epNETs cohort provides the most robust data to inform the comparative efficacy of cabozantinib versus BSC in all epNETs patients.

However, to address the EAG's request, subgroup analysis results for PFS and OS results for the epNET (without lung) subgroup are presented in full below. Stratified randomisation was done at the cohort level for pNETs and epNETs, where stratified hazard ratios were a pre-specific outcome measure. However, for these post-hoc analyses where randomisation is not maintained, unstratified hazard ratios have been reported.

epNET (without lung) subgroup

Baseline characteristics

The subgroups were based on very small sample sizes, with differences in baseline characteristics observed across treatment arms, as outlined in Table 11. A greater proportion of patients in the cabozantinib arm had an ECOG status of 1 or 2 in comparison to the placebo arm. Additionally, patients in the cabozantinib arm had a shorter mean disease duration from diagnosis prior to randomisation and generally had more prior therapies.

Table 11: Patient disease and treatment characteristics by treatment arm in epNET (without lung) subgroup

Patient characteristic		Treatment arm	
		Cabozantinib	Placebo
Sample Size		■	■
Age (in years)		■	■
Sex	Female	■	■
	Male	■	■
Race	White	■	■
	Asian	■	■
	Black or African American	■	■
	Not reported	■	■

	Unknown		
Ethnicity	Hispanic/ Latino		
	Not Hispanic/ Latino		
	Not Reported		
	Unknown		
ECOG status	0		
	1		
	2		
Weight (kg)			
BMI (kg/m ²)			
Number of prior therapies	1		
	2		
	≥3		
Con. SSA use	Yes		
	No		
Disease duration to randomisation (mean, months)			
Tumour grade	Grade 1		
	Grade 2		
	Grade 3		
	Unknown		
Histological differentiation	Well differentiated		
	Moderately differentiated		
	Not specified		
Carcinoid tumour histological type	Missing		
	Carcinoid tumour		
	Atypical carcinoid tumour		
	Not specified		
Functional status	Functional		
	Non-functional		
	Unknown		

Abbreviations: BMI: body mass index; Con.: concurrent; ECOG: Eastern Co-operative Oncology Group; epNET: extra-pancreatic neuroendocrine tumours; GI: gastrointestinal; pNET: pancreatic neuroendocrine tumours; SSA: somatostatin analogue.

Progression-free survival

The post-hoc PFS HR and median PFS for cabozantinib versus placebo for the epNET (without lung) subgroup are presented in Table 12. The KM plot by treatment arm is provided in Figure 7. Given stratified randomisation was conducted at the cohort level and not with subgroups by primary tumour subtype, unstratified HRs have been presented for all outcomes.

Table 12: PFS in the epNET (without lung) subgroup: ITT population

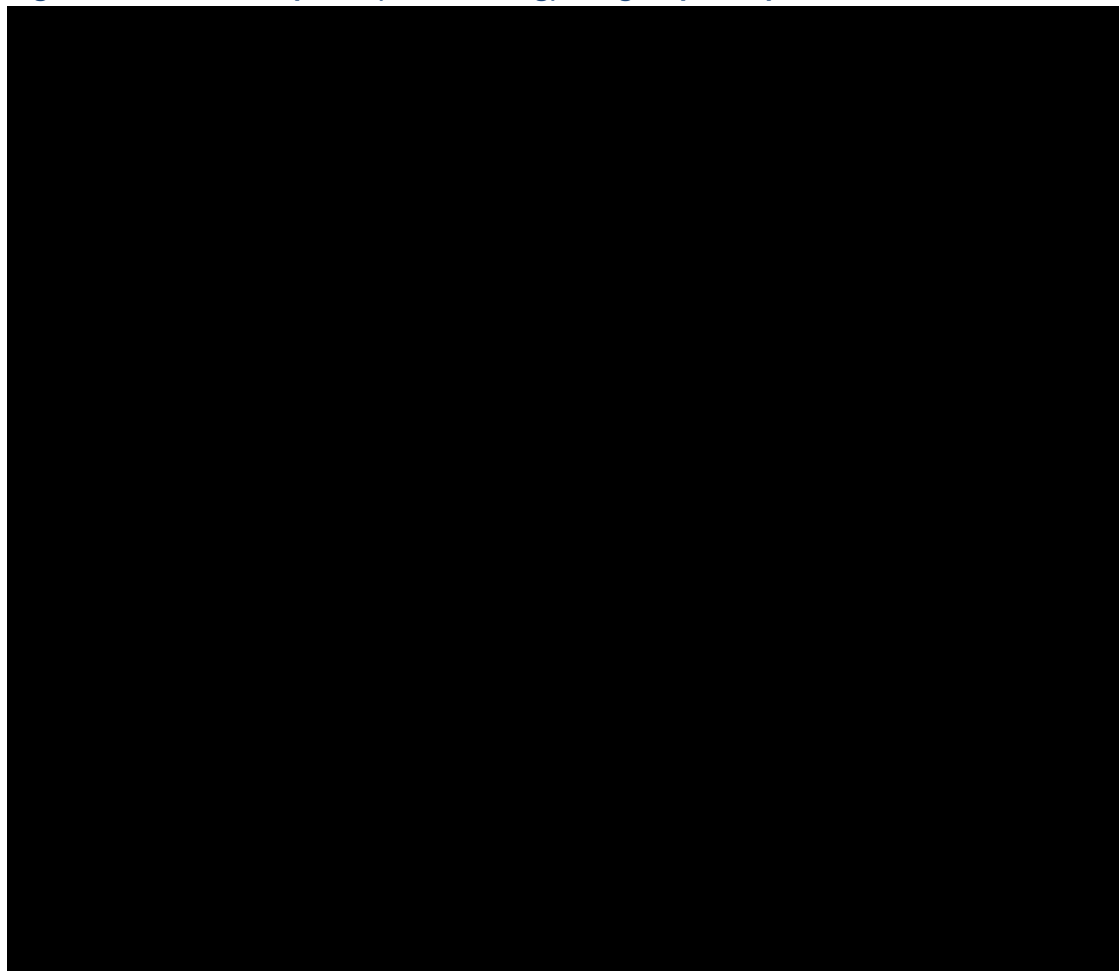
Analysis	Cabozantinib N/Evt/Med	Placebo N/Evt/Med	Unstratified HR (95% CI) Cabozantinib vs Placebo

ITT			

DCO: 4th September 2024.

Abbreviations: CI: confidence interval; epNET: extra-pancreatic neuroendocrine tumour; Evt: number of patients with events; HR: hazard ratio; ITT: intent-to-treat; Med: median; N: number of patients; PFS: progression-free survival.

Figure 7: PFS in the epNET (without lung) subgroup: KM plot



Abbreviations: epNET, extra-pancreatic neuroendocrine tumour; KM, Kaplan-Meier; PFS: progression-free survival.

Overall survival

The IPCW-adjusted HRs of OS and median OS for cabozantinib versus placebo are presented in Table 13 and Table 14, respectively. An IPCW-adjusted KM plot of OS by treatment arm only (i.e., not accounting for baseline covariates) is provided in Figure 8 (primary DCO) and Figure 9 (updated DCO).

Table 13: IPCW-adjusted OS in the epNET (without lung) subgroup: unstratified HRs

Analysis	Unstratified HR (95% CI) Cabozantinib vs Placebo	
	Primary DCO	Updated DCO
ITT		
IPCW (untruncated weights)		
IPCW (truncated weights)		

IPCW HRs are adjusted HRs from a Cox model which includes all baseline prognostic factors used as part of the weight estimation procedure as covariates. Cut-off for weight truncation was the most extreme percentile of observations ($p<0.01$).

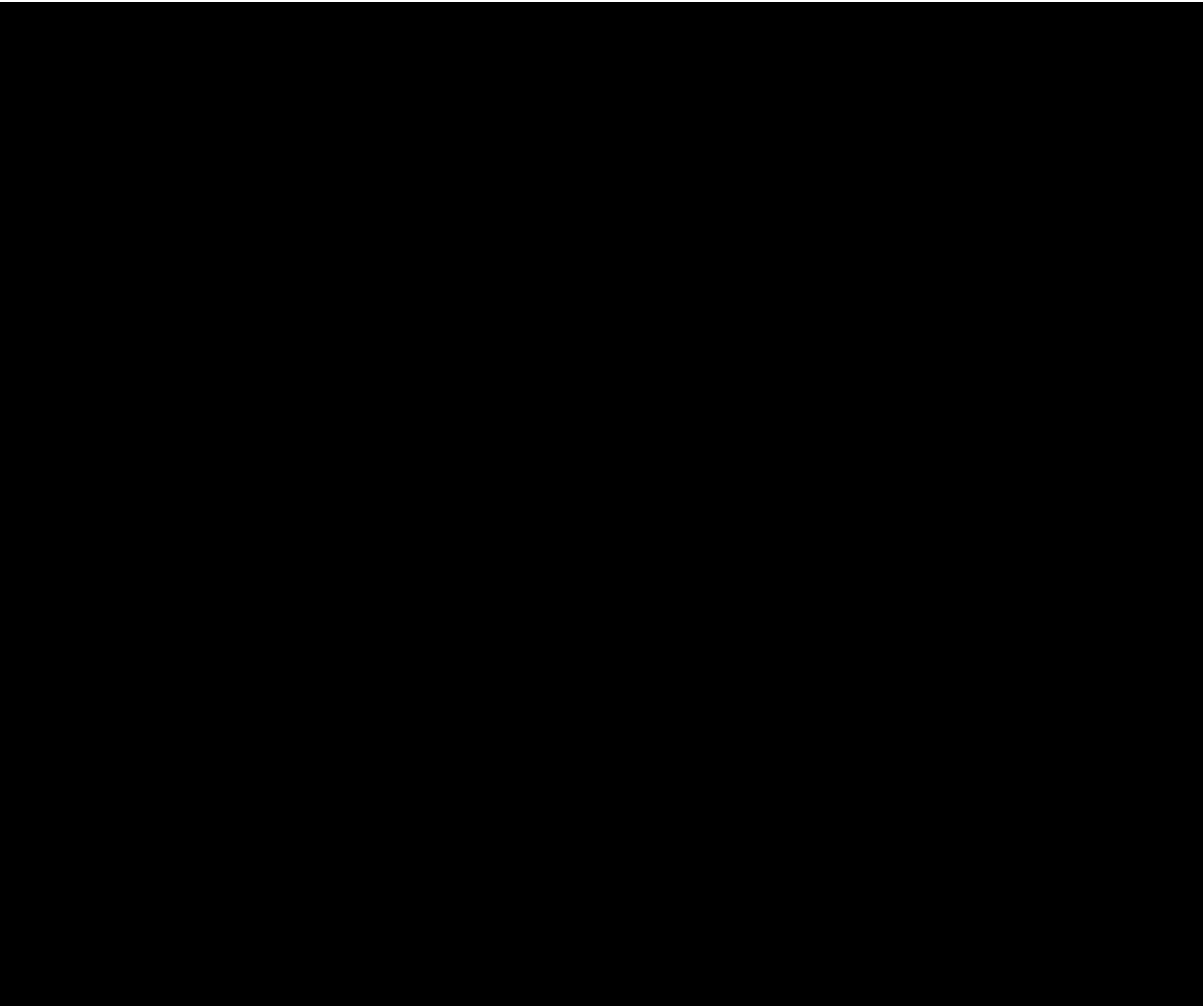
Abbreviations: CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; IPCW, inverse probability of censoring weights; ITT, intention to treat.

Table 14: Median OS in the epNET (without lung) subgroup: ITT population

	Primary DCO		Updated DCO	
Analysis	Cabozantinib	Placebo	Cabozantinib	Placebo
Median survival (months)	■	■	■	■

Abbreviations: epNET: extra-pancreatic neuroendocrine tumour; ITT: intent-to-treat; OS: overall survival.

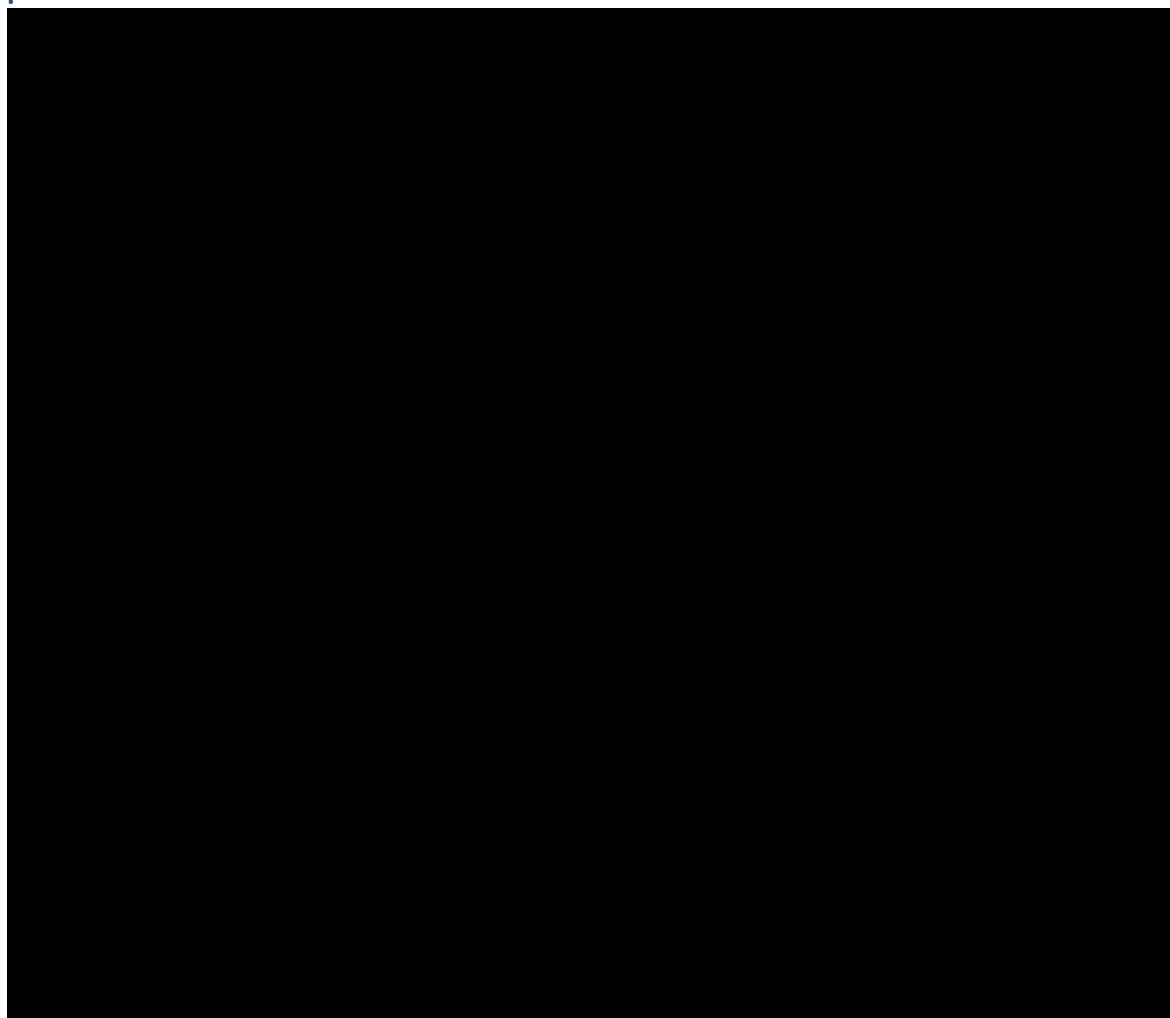
Figure 8. IPCW-adjusted OS in the epNET (without lung) subgroup (primary DCO): KM plot



Patients have been censored upon switching from placebo to cabozantinib, and placebo patients who have not switched are re-weighted based on stabilised IPCW weights. Note that the IPCW-adjusted KM curves, unlike the adjusted HRs obtained from the weighted outcomes models, do not account for variation in baseline covariates. Thus, they do not align with the adjusted HRs and should not be interpreted in conjunction with them. Rather, these plots should be inspected in conjunction with the ITT KM curves to illustrate the impact of artificial censoring and re-weighting without adjusting for baseline covariates in the estimation of treatment differences.

Abbreviations: epNET, extra-pancreatic neuroendocrine tumour; IPCW, inverse probability of censoring weights; KM, Kaplan-Meier; OS: overall survival.

Figure 9. IPCW-adjusted OS in the epNET (without lung) subgroup (updated DCO): KM plot



Patients have been censored upon switching from placebo to cabozantinib, and placebo patients who have not switched are re-weighted based on stabilised IPCW weights. Note that the IPCW-adjusted KM curves, unlike the adjusted HRs obtained from the weighted outcomes models, do not account for variation in baseline covariates. Thus, they do not align with the adjusted HRs and should not be interpreted in conjunction with them. Rather, these plots should be inspected in conjunction with the ITT KM curves to illustrate the impact of artificial censoring and re-weighting without adjusting for baseline covariates in the estimation of treatment differences.

Abbreviations: epNET, extra-pancreatic neuroendocrine tumour; IPCW, inverse probability of censoring weights; KM, Kaplan-Meier; OS: overall survival.

The RPSFTM-adjusted HRs of OS and median OS for cabozantinib versus placebo are presented in Table 15 and Table 14, respectively. An RPSFTM-adjusted KM plot of OS by treatment arm only (i.e., not accounting for baseline covariates) is provided in in Figure 10 (primary DCO) and Figure 11 (updated DCO).

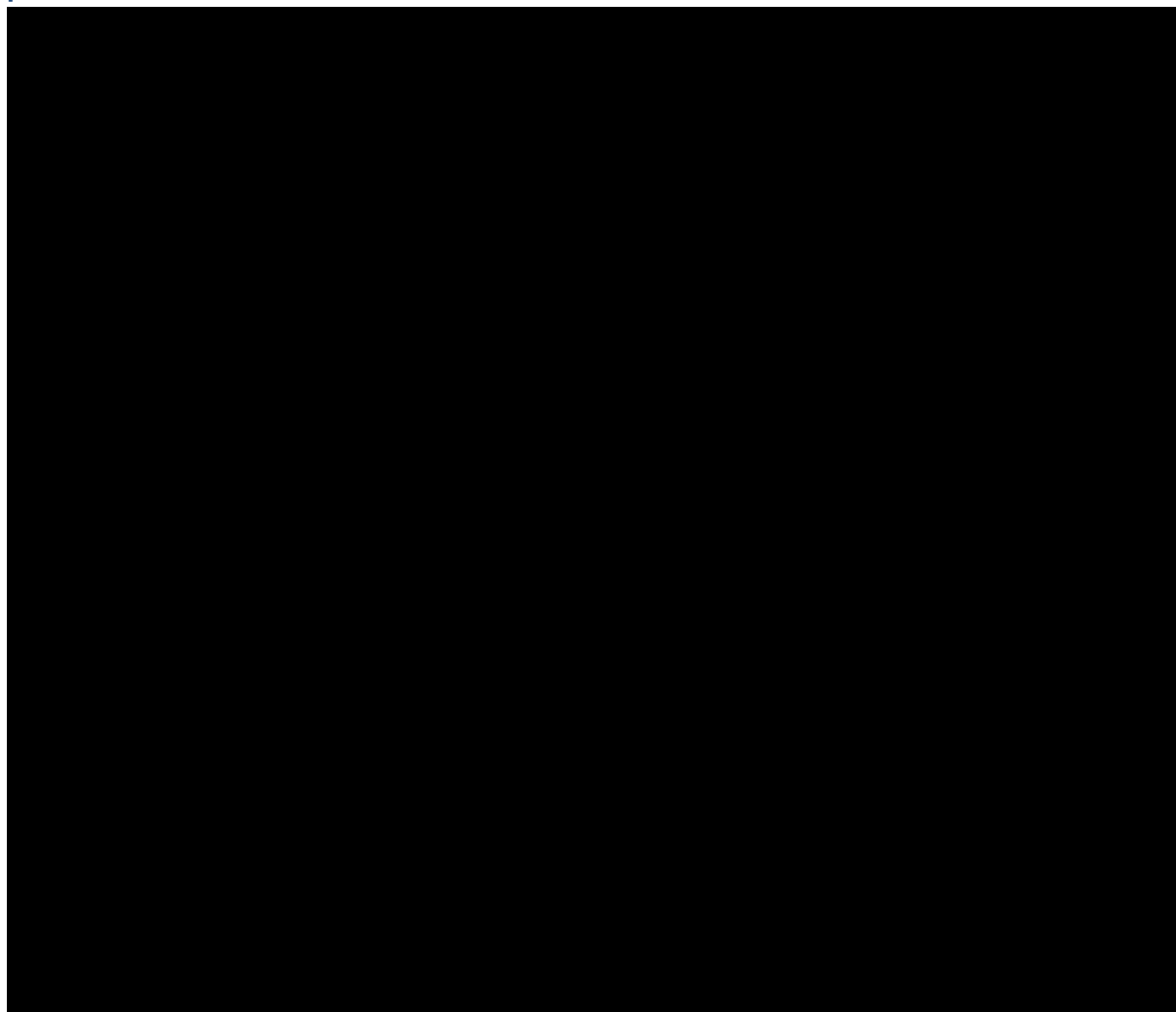
Table 15: RPSFTM-adjusted OS in the epNET (without lung) subgroup: unstratified HRs

Analysis	Unstratified HR (95% CI) Cabozantinib vs Placebo	
	Primary DCO	Updated DCO
ITT		
RPSFTM ^a		

^a 95% CI for RPSFTM are based on adjusted standard errors obtained by dividing the point estimate by the square root of the Chi-square statistic of the ITT analysis, this was done in order to reflect the uncertainty associated with estimating the RPSFTM counterfactual dataset

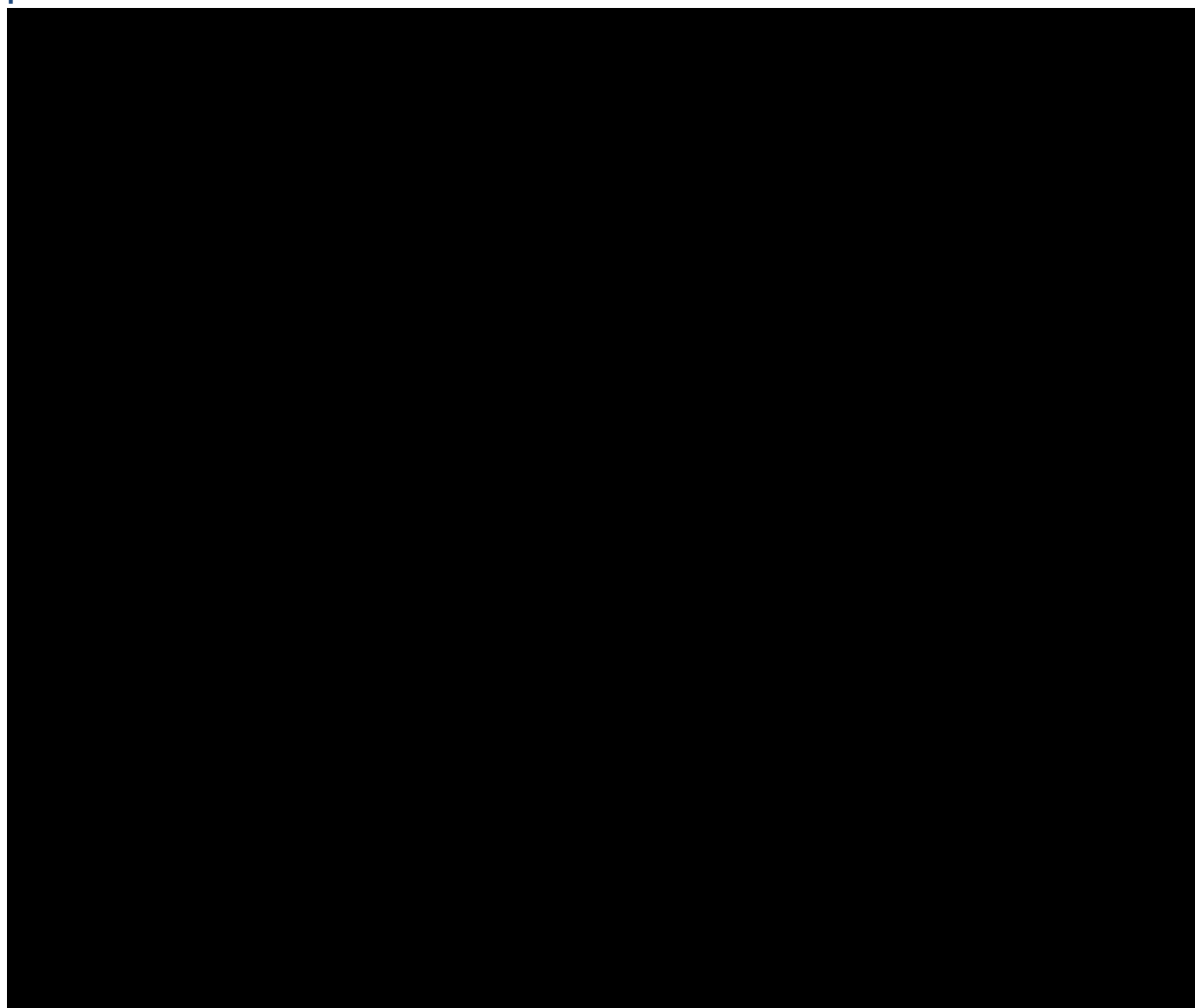
Abbreviations: CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; ITT, intention to treat; RPSFTM, rank preserving structural failure time model.

Figure 10. RPSFTM-adjusted OS in the epNET (without lung) subgroup (primary DCO): KM plot



Abbreviations: epNET, extra-pancreatic neuroendocrine tumour; KM, Kaplan-Meier; OS: overall survival; RPSFTM, rank preserving structural failure time model.

Figure 11. RPSFTM-adjusted OS in the epNET (without lung) subgroup (updated DCO): KM plot



Abbreviations: epNET, extra-pancreatic neuroendocrine tumour; KM, Kaplan-Meier; OS: overall survival; RPSFTM, rank preserving structural failure time model.

epNET (lung) subgroup

Overall survival

The primary DCO results for the epNET (lung) subgroup are presented in the company response to EAG CQ A5. The subgroup results for the updated DCO data are presented below.

The IPCW-adjusted HRs of OS and median OS for cabozantinib versus placebo (updated DCO) are presented in Table 16 and Table 17, respectively. An IPCW-adjusted KM plot of OS by treatment arm only (i.e., not accounting for baseline covariates) is provided in Figure 12.

Table 16: IPCW-adjusted OS in the epNET lung subgroup (updated DCO): unstratified HRs

Analysis	Unstratified HR (95% CI) Cabozantinib vs Placebo
ITT	
IPCW (untruncated weights)	
IPCW (truncated weights)	

IPCW HRs are adjusted HRs from a Cox model which includes all baseline prognostic factors used as part of the weight estimation procedure as covariates. Cut-off for weight truncation was the most extreme percentile of observations ($p < 0.01$).

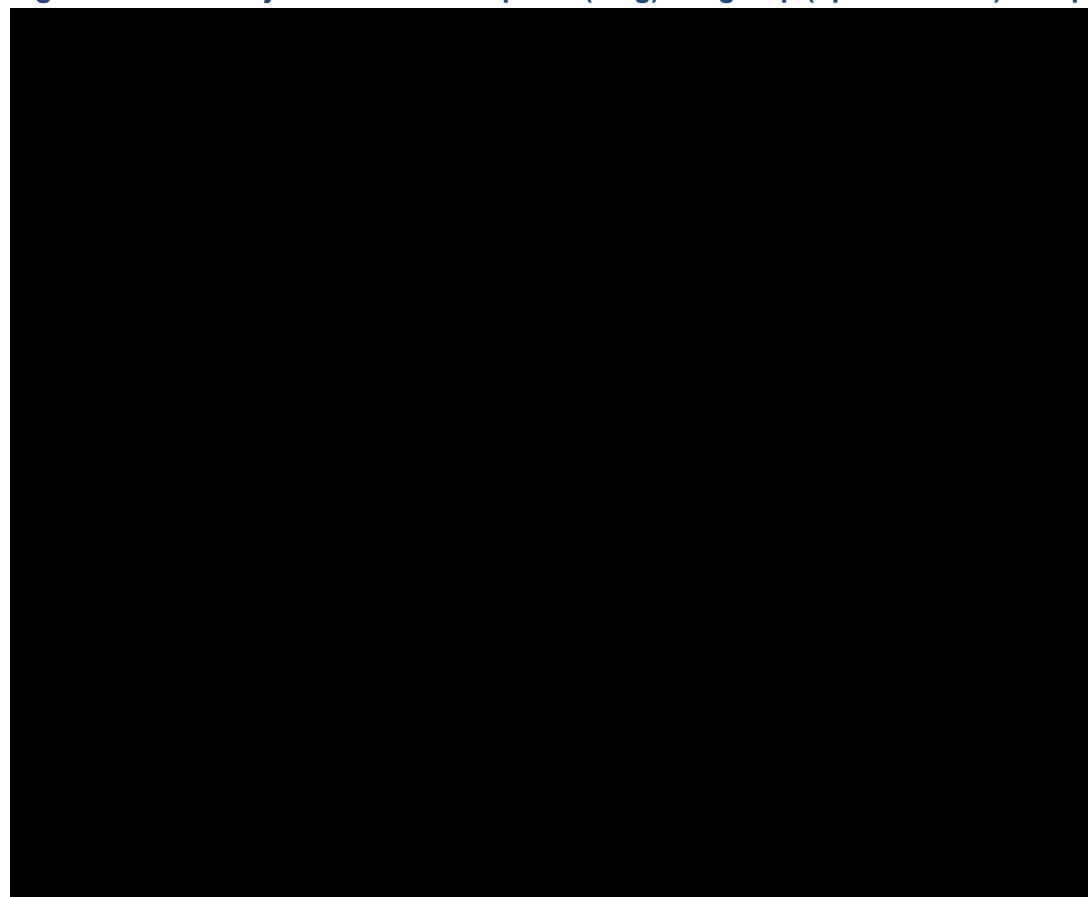
Abbreviations: CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; IPCW, inverse probability of censoring weights; ITT, intention to treat.

Table 17: Median OS in the epNET (lung) subgroup (updated DCO): ITT population

Analysis	Cabozantinib	Placebo
Median survival (months)	■	■

Abbreviations: epNET: extra-pancreatic neuroendocrine tumour; ITT: intent-to-treat; OS: overall survival.

Figure 12. IPCW-adjusted OS in the epNET (lung) subgroup (updated DCO): KM plot



Patients have been censored upon switching from placebo to cabozantinib, and placebo patients who have not switched are re-weighted based on stabilised IPCW weights. Note that the IPCW-adjusted KM curves, unlike the adjusted HRs obtained from the weighted outcomes models, do not account for variation in baseline covariates. Thus, they do not align with the adjusted HRs and should not be interpreted in conjunction with them. Rather, these plots should be inspected in conjunction with the ITT KM curves to illustrate the impact of artificial censoring and re-weighting without adjusting for baseline covariates in the estimation of treatment differences.

Abbreviations: epNET, extra-pancreatic neuroendocrine tumour; IPCW, inverse probability of censoring weights; KM, Kaplan-Meier; OS: overall survival.

The RPSFTM-adjusted HRs of OS and median OS for cabozantinib versus placebo are presented in Table 18 and Table 17, respectively. An RPSFTM-adjusted KM plot of OS by treatment arm only (i.e. not accounting for baseline covariates) is provided in Figure 13.

Table 18: RPSFTM-adjusted OS in the epNET lung subgroup (updated DCO): unstratified HRs

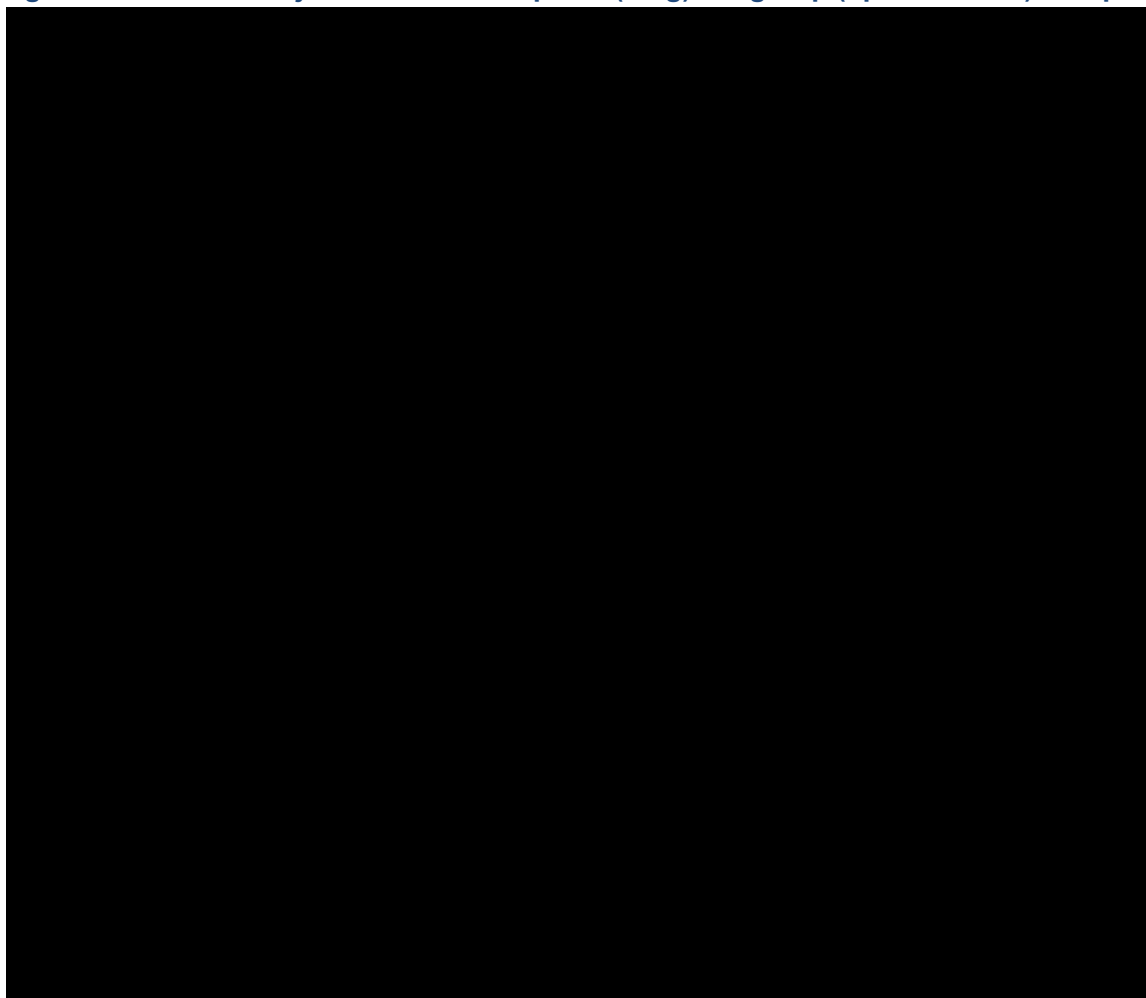
Analysis	Unstratified HR (95% CI) Cabozantinib vs Placebo

ITT	
RPSFTM ^a	

^a 95% CI for RPSFTM are based on adjusted standard errors obtained by dividing the point estimate by the square root of the Chi-square statistic of the ITT analysis, this was done in order to reflect the uncertainty associated with estimating the RPSFTM counterfactual dataset.

Abbreviations: CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; ITT, intention to treat; RPSFTM, rank preserving structural failure time model.

Figure 13. RPSFTM-adjusted OS in the epNET (lung) subgroup (updated DCO): KM plot



Abbreviations: epNET, extra-pancreatic neuroendocrine tumour; KM, Kaplan-Meier; OS: overall survival; RPSFTM, rank preserving structural failure time model.

3. Provide the option to independently fit curves for OS and PFS in the lung NET and epNET without lung populations (as per CQ B5b and B11)

As discussed in the response to clarification question A6, randomisation was not stratified according to this classification of subgroups by primary tumour type; results of subgroup analyses for epNET (without lung) and epNET (lung) patients are subject to bias due to imbalances in patient characteristics across treatment arms and associated confounding, and limited by small patient numbers. Additionally, as noted in the response to clarification question B11, the company investigated the feasibility of conducting independent extrapolation for these subgroups but concluded that the application of the adjusted HR obtained using IPCW with stabilised weights represents the most accurate estimate of comparative efficacy of cabozantinib and BSC with crossover adjustment. Analyses based on independent extrapolation of

cabozantinib and BSC curves within these subgroups are not appropriate.

4. Provide us with the splines derived in response to B6 as an alternative option (via means of a drop down menu) in the model to generate survival curves and estimate effectiveness in the model

Given the uncertainty of long-term extrapolations in oncology, the fit of the tail ends of the standard parametric extrapolations to the KM curves should not be overinterpreted. These can often be biased due to low numbers at risk for later timepoints, particularly for extrapolations already based on small patient numbers.

The standard extrapolations for offer good visual fit the KM curves, sitting well within the 95% CIs of the KM curves at all later timepoints. There are very few patients at risk at the tail end of the curves respectively, and thus the tail of the KM curve should not be overinterpreted. The use of flexible spline models is not justified and would likely result in overfitting of the data; more parsimonious models are preferred. Nevertheless, to address the EAG's request, flexible spline models have been generated and parameters provided in the reference pack.

5. Clarify if the baseline characteristics provided in Table 12 of the clarification responses are the characteristics of all participants at baseline, or if they are characteristics of participants at any point during the trial (response to CQ A10b).

The company can confirm that the baseline characteristics provided in Table 12 are the characteristics of all participants at baseline (i.e., all participants that opted into the study).

References

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6. White BE, Rous B, Chandrakumaran K, et al. Incidence and survival of neuroendocrine neoplasia in England 1995-2018: A retrospective, population-based study. *Lancet Reg Health Eur* 2022;23:100510.

Appendix 1 Comparison of Strata (pNET Cohort)

Table 19. Baseline characteristics by treatment arm and stratum (pNET cohort)

Characteristic	Stratum							
	Concurrent SSA Use: N				Concurrent SSA Use: Y			
	Prior Sunitinib Use: N		Prior Sunitinib Use: Y		Prior Sunitinib Use: N		Prior Sunitinib Use: Y	
	Cabozantinib (N=19) ^a	Placebo (N=8) ^a	Cabozantinib (N=10) ^a	Placebo (N=6) ^a	Cabozantinib (N=28) ^a	Placebo (N=14) ^a	Cabozantinib (N=7) ^a	Placebo (N=3) ^a
Age								
Sex								
Female								
Male								
Race								
American Indian or Alaska native								
Asian								
Black or African American								
Multiple								
Native Hawaiian or other pacific islander								
Not reported								
Unknown								
White								
Ethnicity								
Hispanic or Latino								
Not Hispanic or Latino								
Not reported								
Unknown								
ECOG status								
0								
1								
2								
Weight (kg)								
BMI (kg/m2)								

Number of prior treatments								
1	████	████	████	████	████	████	████	████
2	████	████	████	████	████	████	████	████
≥3	████	████	████	████	████	████	████	████
Duration of disease to randomisation	██████	██████	██████	██████	██████	██████	██████	██████
Tumour grade								
Grade 1	████	████	████	████	████	████	████	████
Grade 2	████	████	████	████	████	████	████	████
Grade 3	████	████	████	████	████	████	████	████
Unknown	████	████	████	████	████	████	████	████
Histological differentiation								
Moderately differentiated	████	████	████	████	████	████	████	████
Well differentiated	██████	██████	██████	██████	██████	██████	██████	██████
Not specified	████	████	████	████	████	████	████	████
Carcinoid tumour histological type								
NR	██████	██████	██████	██████	██████	██████	██████	██████
Atypical carcinoid tumour	████	████	████	████	████	████	████	████
Carcinoid tumour	████	████	████	████	████	████	████	████
Not specified	██████	████	████	████	████	████	████	████
Functional status								
Functional tumour	████	████	████	████	████	████	████	████
Non-functional tumour	██████	██████	██████	██████	██████	██████	██████	██████
Unknown	████	████	████	████	████	████	████	████

^aMean (SD); n (%)

Abbreviations: BMI: body mass index; N: no; NR: not reported; pNET: pancreatic neuroendocrine tumour; SSA: Somatostatin analogue; Y: yes.

Table 20. Median PFS and OS by stratum (pNET cohort)

Characteristic	Stratum							
	Concurrent SSA Use: N				Concurrent SSA Use: Y			
	Prior Sunitinib Use: N		Prior Sunitinib Use: Y		Prior Sunitinib Use: N		Prior Sunitinib Use: Y	
	Cabozantinib (N=19)	Placebo (N=8)	Cabozantinib (N=10)	Placebo (N=6)	Cabozantinib (N=28)	Placebo (N=14)	Cabozantinib (N=7)	Placebo (N=3)
Primary DCO								
Progression-free survival								
Events	████	████	████	████	████	████	████	████
Censored	████	████	████	██	████	████	████	████
Median (95% CI)	████████	████████	████████	████████	████████	████████	████████	████████
Overall survival								
Events	████	████	████	████	████	████	████	████
Censored	████	████	████	████	████	████	████	██
Median (95% CI)	████████	████████	████████	████████	████████	████████	████████	████████
Updated DCO (unplanned OS sweep)								
Overall survival								
Events	████	████	████	████	████	████	████	████
Censored	████	████	████	████	████	████	████	██
Median (95% CI)	████████	████████	████████	████████	████████	████████	████████	████████

Abbreviations: DCO: data cutoff; OS: overall survival; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumours; SSA: somatostatin analogue.

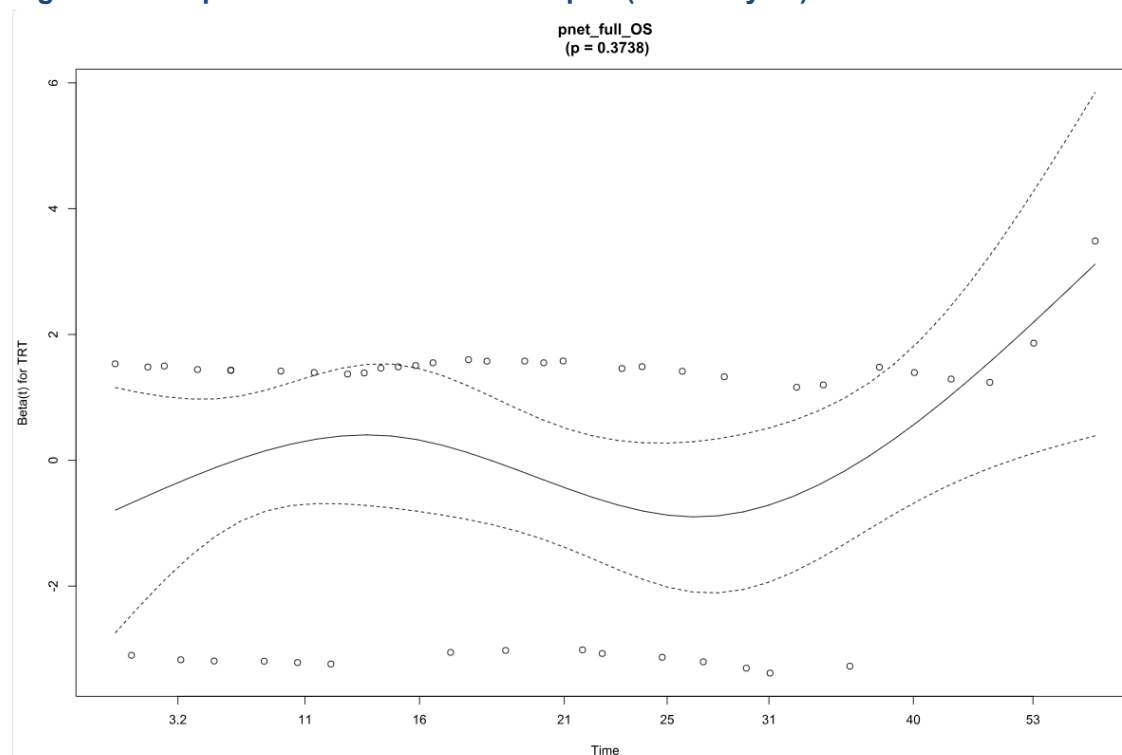
Appendix 2 *Assessment of proportional hazards*

ITT analysis

In line with NICE TSD 14, the PH assumption was assessed for OS derived from the updated DCO (4th September 2024).¹

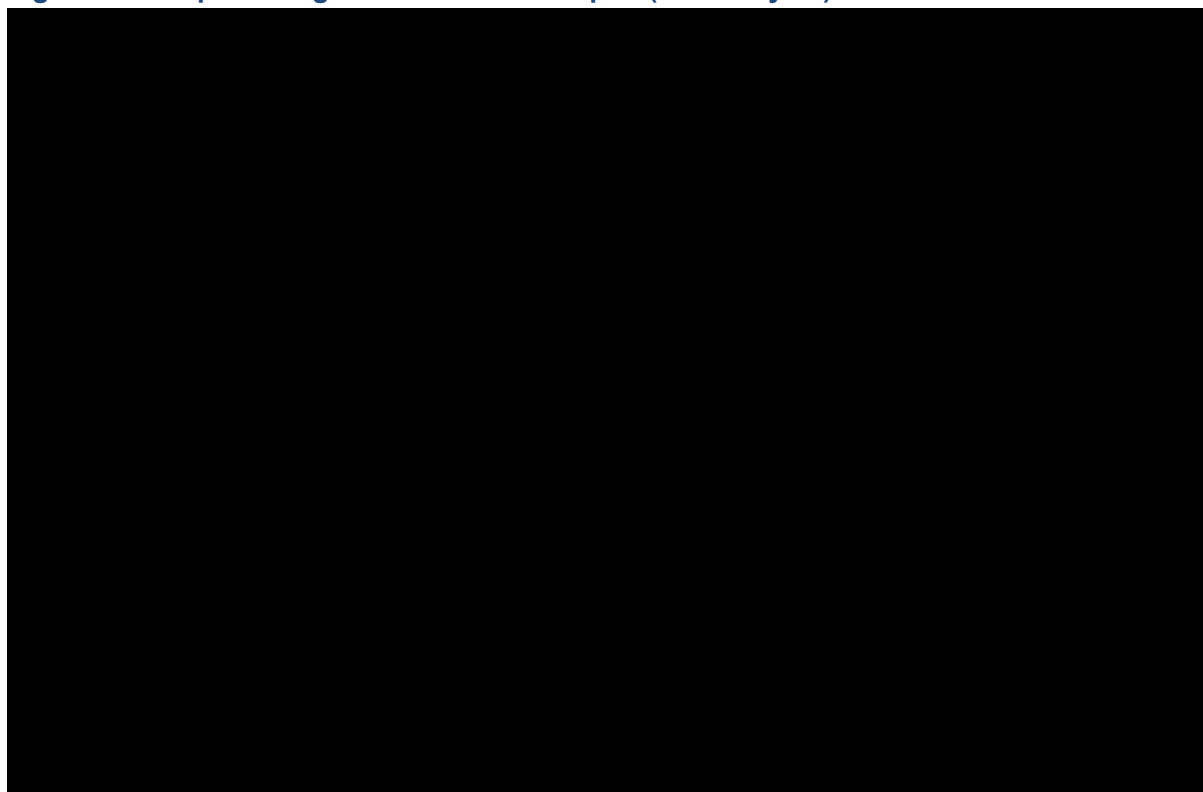
Schoenfeld residual, log cumulative and smoothed hazard plots for OS from the ITT analysis are presented in Figure 14, Figure 15 and Figure 16 for pNETs and Figure 17, Figure 18 and Figure 19 for epNETs, respectively. These show no compelling evidence of PH violation for the pNET and epNET cohorts. All Schoenfeld tests had p-values higher than 0.1, suggesting that there was not sufficient evidence to reject the null hypothesis of proportional hazards in pNET or epNET cohorts. Thus, the PH assumption between cabozantinib and BSC for OS was therefore considered appropriate.

Figure 14: OS pNET: Schoenfeld residual plot (ITT Analysis)



Abbreviations: ITT: intention-to-treat; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour.

Figure 15: OS pNET: log cumulative hazard plot (ITT Analysis)

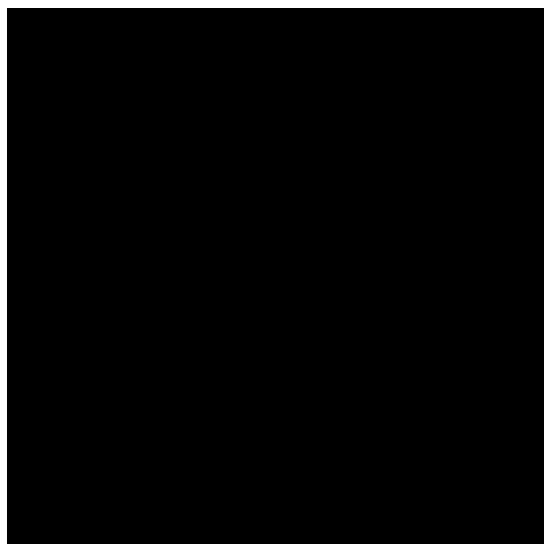


Abbreviations: ITT: intention-to-treat; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour.

Figure 16: OS pNET: Smoothed hazard plots (ITT Analysis)

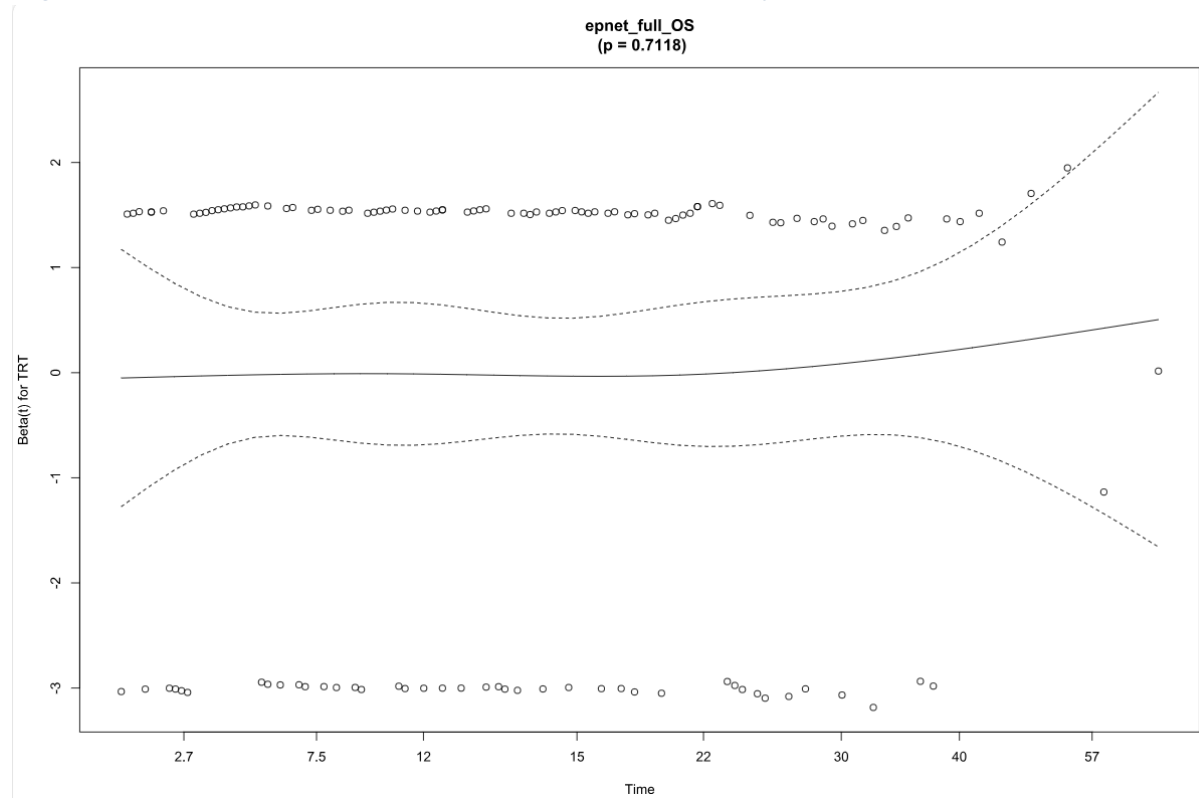
Cabozantinib

Placebo



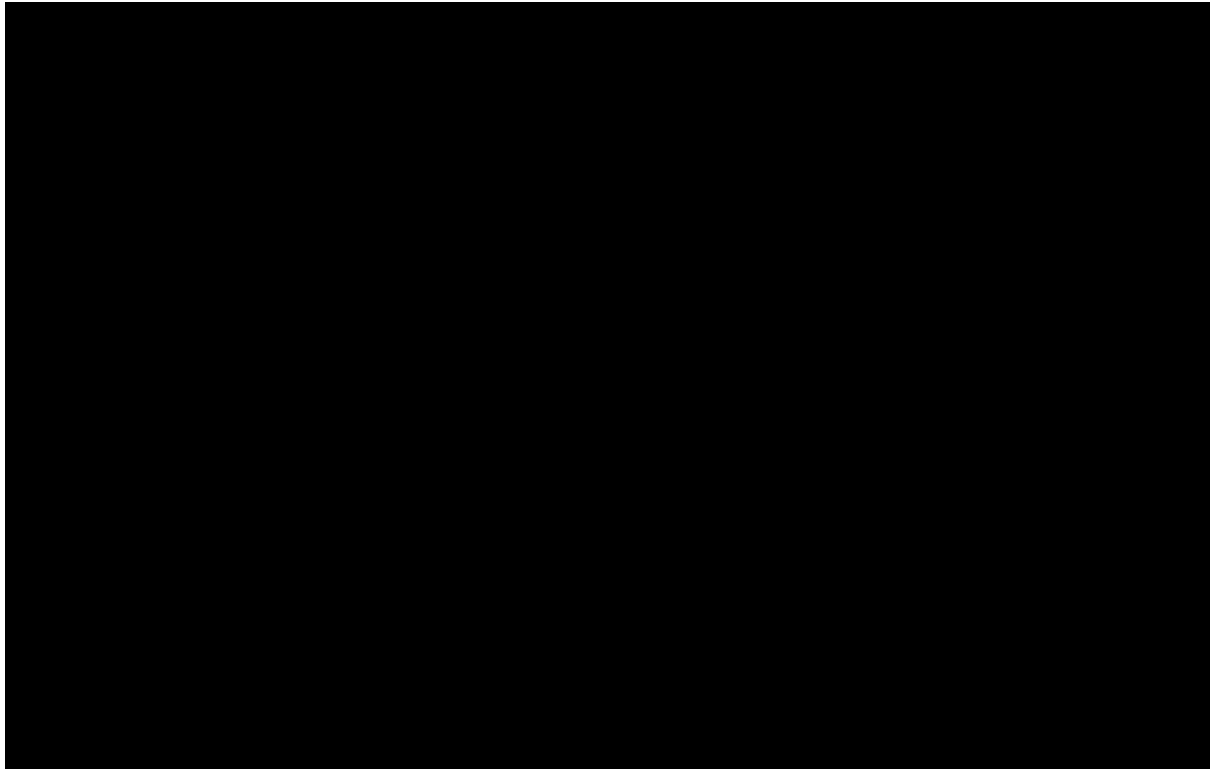
Abbreviations: ITT: intention-to-treat; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour.

Figure 17: OS epNET: Schoenfeld residual plot (ITT Analysis)



Abbreviations: ITT: intention-to-treat; epNET; extra-pancreatic neuroendocrine tumour; PFS: progression-free survival.

Figure 18: OS epNET: log cumulative hazard plot (ITT Analysis)



Abbreviations: ITT: intention-to-treat; epNET; extra-pancreatic neuroendocrine tumour; PFS: progression-free survival.

Figure 19: OS epNET: Smoothed hazard plots (ITT Analysis)

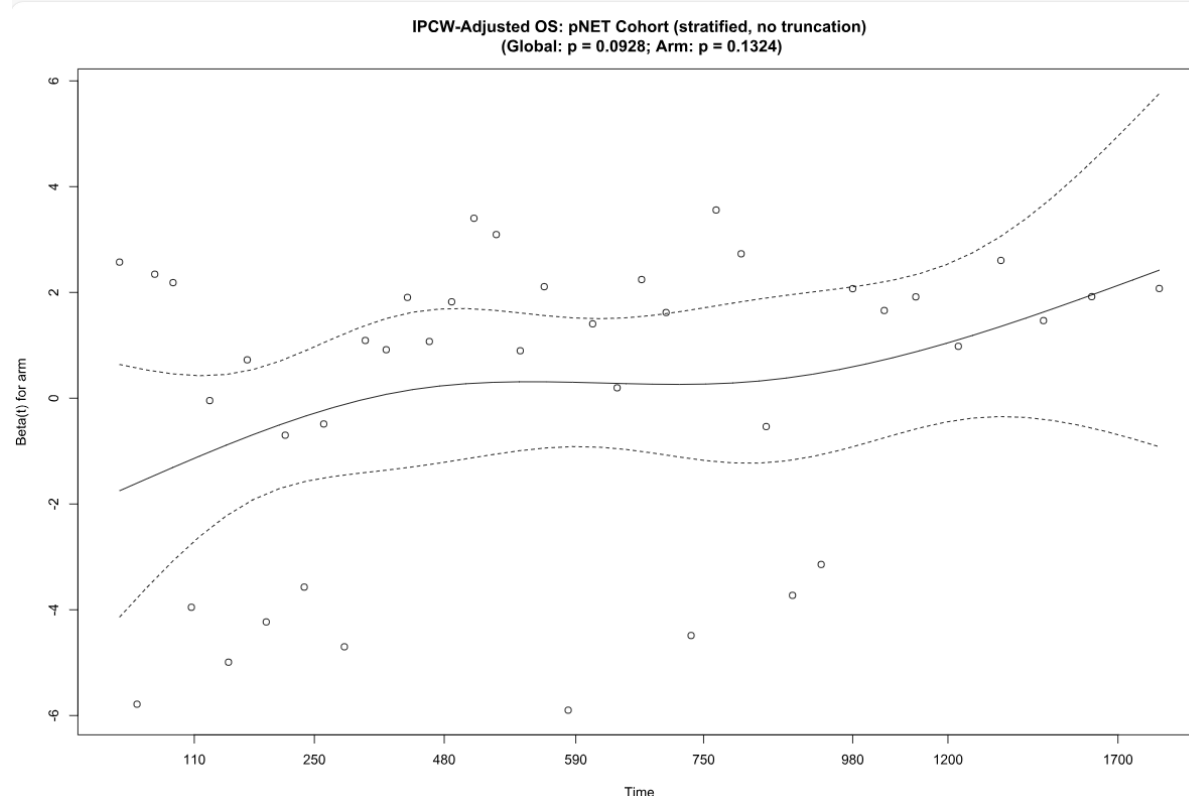


Abbreviations: ITT: intention-to-treat; epNET; extra-pancreatic neuroendocrine tumour; PFS: progression-free survival.

IPCW-adjusted analysis

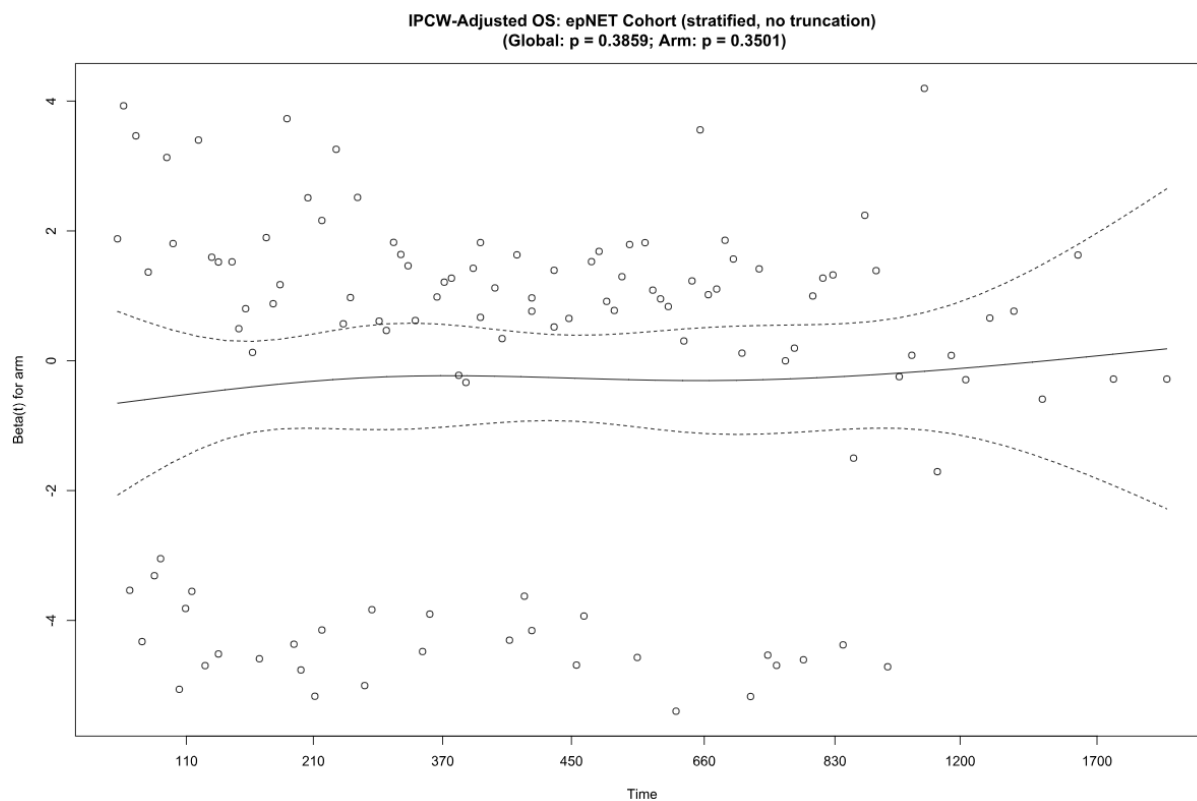
Schoenfeld residuals of the IPCW weighted outcomes model explored for OS from the updated DCO, which included baseline prognostic factors as covariates, were inspected, and are presented in Figure 20 for pNETs and Figure 21 for epNETs, respectively. Log cumulative and smoothed hazard plots were not produced because they do not account for the effect of other covariates and are thus less reliable for assessing the proportional hazards assumption for a Cox model with multiple covariates. As for OS from the ITT analysis, all Schoenfeld tests had p-values higher than 0.1, suggesting that there was not sufficient evidence to reject the null hypothesis of proportional hazards in pNET or epNET cohorts.

Figure 20: OS pNET: Schoenfeld residual plot (crossover-adjusted analysis)



Abbreviations: IPCW: inverse probability of censoring weights; OS: overall survival; pNET: pancreatic neuroendocrine tumour.

Figure 21: OS epNET: Schoenfeld residual plot (crossover-adjusted analysis)



Abbreviations: epNET; extra-pancreatic neuroendocrine tumour; IPCW: inverse probability of censoring weights; OS: overall survival.

Single Technology Appraisal

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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- Your response should not be longer than 10 pages.

About you

1. Your name	
2. Name of organisation	Insulinoma Support Network – Insulinoma Charity UK
3. Job title or position	Insulinoma Support Network and Insulinoma Charity UK
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Insulinoma Support Network and Insulinoma Charity UK is dedicated to supporting, educating, and advocating for individuals affected by insulinomas. Established 18 years ago, we are the first and only UK charity focused exclusively on insulinomas, providing medically verified information, personalised support, and access to the latest advancements in treatment and research. We operate on a fully voluntary basis, with every penny raised going directly towards research, awareness, and patient support. We have no salaries and no overhead costs—just a genuine commitment to helping those affected by insulinomas. All resources we provide are current, accurate, and reviewed by medical professionals, ensuring that patients and families have access to trusted, high-quality information tailored specifically to insulinomas. Our support groups are the largest peer networks for insulinoma patients worldwide, offering safe spaces to share experiences, knowledge, and support. Membership includes: 1,500 members in the Suspected Insulinoma Group - Over 1,000 members in the Biochemically Diagnosed Insulinoma Group 98 members in the Metastatic Insulinoma Group 37 members in the Non-Insulinoma Pancreatic Hypoglycaemia Syndrome (NIPS) Group These groups are also open to caregivers, family, and friends who wish to better understand insulinomas and support their loved ones. Collaboration and Research We collaborate with The Children's Hyperinsulinism Charity to address overlapping challenges and increase

Patient organisation submission

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

2 of

	awareness across age groups. In addition, we are funding critical research to better understand the lived experience of being diagnosed with an insulinoma, ensuring that patient voices inform future care and treatment.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	None
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information in my submission is based on my own lived experience of being diagnosed with a malignant insulinoma in 2007 and managing the condition through surgery, medical therapies, and long-term care. This has given me first-hand understanding of the physical, emotional, and social challenges patients face, including the constant fear of recurrence and the difficulty of accessing suitable treatments. In addition, through my role as Founder of The Insulinoma Support Network and Insulinoma Charity UK, I have gained unique insights into the wider patient and carer community, highlighting consistent unmet needs in treatment, care, and long-term support.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with an insulinoma is unpredictable and exhausting. Persistent hypoglycaemia can cause sudden episodes of confusion, dizziness, weakness, and loss of consciousness, making everyday life uncertain and sometimes unsafe. Treatments such as surgery or medication may bring stability, but they rarely remove the constant fear of recurrence in the case of a malignant diagnosis. The condition affects diet, social life, employment, and independence, leaving patients anxious about being alone or away from immediate support. Many feel isolated due to the rarity of the tumour and the lack of general awareness among healthcare professionals and the wider public. Carers often live with the anxiety of monitoring for hypoglycaemic episodes and needing to act quickly when they occur. This responsibility can be overwhelming and tiring, particularly at night when sleep is disrupted by the need to check glucose levels or respond to alarms. Carers frequently feel helpless watching a loved one suffer sudden collapses or confusion, and many describe living “on alert” at all times. The emotional toll is significant, compounded by the rarity of the condition, which leaves families searching for specialist knowledge, support, and reassurance.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers are grateful when insulinomas are recognised and treated successfully on the NHS, particularly where skilled surgical teams and specialist endocrinology services are involved. Surgery remains the only curative treatment, and for many it is life-changing. However, access to experienced specialists is inconsistent, and long waiting times for diagnosis and treatment are common. Patients often feel their symptoms are dismissed or misdiagnosed, leading to delayed care and prolonged suffering. Medical therapies are seen as limited and, in some cases, poorly tolerated. There is a strong sense among patients and carers that suitable, long-term treatment options are lacking, particularly for those with malignant or recurrent disease. Carers highlight the burden of navigating complex care pathways and the frustration of limited follow-up or coordinated support. Many families describe feeling left on their own once the immediate crisis of diagnosis or surgery has passed, with insufficient psychological, nutritional, or long-term management support. Overall, while there is deep appreciation for the NHS and the expertise of dedicated clinicians, patients and carers consistently express that treatments and care for insulinomas are fragmented, under-resourced, and in urgent need of improvement.
8. Is there an unmet need for patients with this condition?	Yes, there is a significant unmet need for patients with an insulinoma. Many face long delays in diagnosis, such as the 72-hour fast, often being misdiagnosed with anxiety, epilepsy, or psychiatric conditions before the true cause is recognised. Even after diagnosis, access to specialist centres and consistent expertise across the NHS is uneven, meaning not all patients receive the same standard of care. Treatment options are limited. Surgery can be curative, but not all patients are suitable candidates, and those with malignant or recurrent disease face very few effective alternatives. Current medical therapies can be difficult to tolerate, and long-term management remains uncertain. Beyond treatment, there is little structured psychological, nutritional, or social support, leaving patients and carers isolated and struggling with daily challenges. Insulinoma Charity UK helps to address some of these gaps by providing medically verified information, peer support groups, advocacy, and funding pioneering research into the lived experience of insulinoma. However, there remains an urgent need for greater awareness among healthcare professionals, improved pathways to specialist care, and more investment in developing effective treatments.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients and carers strongly value technologies that improve safety, quality of life, and treatment outcomes. Continuous Glucose Monitors (CGMs) are seen as essential. They give real-time glucose readings, alerts for hypoglycaemia, and reassurance for both patients and carers. CGMs reduce fear, improve independence, and allow better-informed clinical decisions. Many patients believe CGMs should be approved and available to everyone suspected of or diagnosed with an insulinoma. Advances in surgical technology, particularly robotic-assisted surgery, are also seen as highly advantageous. Robotic surgery can offer greater precision, reduced risk of complications, shorter recovery times, and better preservation of pancreatic function, all of which matter deeply to patients. For those with malignant or recurrent disease, Radiofrequency Ablation (RFA) provides an important option where surgery is not possible. Patients appreciate that RFA can reduce tumour burden, stabilise disease, and help manage symptoms, offering hope where treatment choices are limited. Overall, patients and carers view these technologies as transformative, giving them safer care, better outcomes, and a stronger sense of security in daily life.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	While patients and carers recognise the benefits of new technologies, they also identify several disadvantages and challenges. For Continuous Glucose Monitors (CGMs), the main concerns are cost and availability. At present, CGMs are not routinely provided to patients with an insulinoma, leaving many to self-fund or go without. Some patients also report issues with accuracy during extreme hypoglycaemia, device discomfort, or the anxiety of constant monitoring alarms. Robotic-assisted surgery, although highly precise, is not widely available in all NHS centres. Patients highlight that access depends heavily on postcode and referral pathways, creating inequality of care. In addition, the technology requires specialist training and can carry higher costs. For Radiofrequency Ablation (RFA), the disadvantages include limited long-term data on outcomes in insulinoma, the potential need for repeat procedures, and restricted access to centres that offer it. Patients also note that RFA is not curative but palliative, which can be difficult emotionally. Overall, patients and carers are frustrated that life-changing technologies exist but are often difficult to access, inconsistently provided, or not tailored specifically to an insulinoma.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Yes. Patients and carers believe that certain groups may benefit more from these technologies than others. Continuous Glucose Monitors (CGMs): These are particularly valuable for patients with frequent or unpredictable hypoglycaemic episodes, those living alone, or carers who need reassurance and safety alerts. They are also highly beneficial for children and young adults, where independence, school attendance, and parental peace of mind are major concerns. Robotic-assisted surgery: This offers the greatest benefit to patients with localised, surgically resectable tumours. The precision and reduced risk of complications make it especially important for younger patients who need to preserve pancreatic function long term. However, those with widespread or inoperable disease may not benefit. Radiofrequency Ablation (RFA): This is most valuable for patients with malignant, recurrent, or inoperable insulinoma, where curative surgery is not possible. It provides symptom control and stabilisation, though patients with small, resectable tumours may not require it. In summary, while all groups benefit to some extent, patients with severe, complex, or high-risk disease gain the most from access to these technologies, whereas those with early-stage, easily resectable tumours may benefit less.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Yes. Patients and carers believe there are several important equality issues that need to be considered: Access to specialist care: Insulinoma is rare and expertise is concentrated in a small number of centres. Patients living in rural areas or outside major cities often face longer waiting times, greater travel costs, and less consistent access to advanced treatments such as robotic surgery or RFA. Access to technology: Continuous Glucose Monitors (CGMs) are not routinely funded for insulinoma patients. This creates inequality, as those who can afford to self-fund have improved safety and quality of life, while others go without. Age-related differences: Younger patients, especially children and young adults, may face additional challenges around independence, education, and safeguarding. CGMs in particular are critical for these groups, yet access is inconsistent. Socioeconomic factors: Patients and carers from lower-income backgrounds are disproportionately disadvantaged by travel, time off work, and self-funded devices or treatments. Awareness among clinicians: Some patients experience delayed diagnosis due to lack of awareness of insulinoma among frontline healthcare professionals, which disproportionately affects those without resources to seek multiple opinions. Addressing these issues is essential to ensure equitable access to diagnosis, treatment, and technology for all patients, regardless of geography, age, or financial situation.

Other issues

13. Are there any other issues that you would like the committee to consider?	Patients and carers consistently raise concerns about access and funding for advanced diagnostic and treatment options in the UK. Specialised scans, such as ⁶⁸Ga-DOTATATE PET/CT, are critical for accurately locating insulinomas, especially when tumours are small, multiple, or difficult to detect with standard imaging. However, access is limited and inconsistent, leaving some patients without the best available diagnostic tools. Similarly, Peptide Receptor Radionuclide Therapy (PRRT) is viewed by patients with malignant or recurrent insulinomas as a vital treatment option, yet availability and funding remain highly restricted within the NHS. Families often describe the stress of being told these treatments exist but are not accessible to them. Improving equitable access to specialised scans and PRRT would address a significant unmet need and offer patients real hope in otherwise limited treatment pathways.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Insulinoma is a rare and often misdiagnosed neuroendocrine tumour, with long delays in diagnosis and inconsistent access to specialist care across the NHS. • Current treatments are limited: surgery can be curative, but many patients face recurrence, malignant disease, or unsuitable treatment options, leaving significant unmet needs. • Patients and carers strongly support wider access to Continuous Glucose Monitors (CGMs), robotic surgery, Radiofrequency Ablation (RFA), specialised scans, and PRRT, which improve safety, quality of life, and outcomes. • There are major equality issues: postcode variation, limited funding, socioeconomic barriers, and lack of awareness among clinicians all affect fair access to care. • The Insulinoma Support Network and Insulinoma Charity UK plays a vital role in bridging gaps by providing trusted information, peer support, and patient advocacy, but systemic improvements in access, treatment, and research are urgently needed.

Thank you for your time.

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Single Technology Appraisal

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

Patient Organisation Submission

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- Your response should not be longer than 10 pages.

About you

1. Your name	
2. Name of organisation	Neuroendocrine Cancer UK
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	Neuroendocrine Cancer UK was founded with the vision of providing support, raising awareness, and driving research for those affected by neuroendocrine cancer: advocate for improved care, diagnosis, and treatment, while supporting the community through information, resources, and fundraising. NCUK is a donation-dependent patient organisation, that receives no central government or other funding: we do receive occasional unrestricted grant funding to support patient-centric projects. We have a staff of 11 (only 3 are full-time) and serve a population of > 5,000 people/yr (approx. 16% of the neuroendocrine cancer population).
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	No

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Helpline, support group and online forum thematic analysis – and discussion. We have both patient-centric and family & friend support groups and forums, as well as group therapy programmes. Combined with a literature review of reported experiences and related research/clinical trial publications.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	All grades of neuroendocrine cancer—including G1NET (neuroendocrine tumour)—retain the potential for metastasis and/or accelerated growth. This often necessitates one or more lines of therapy as the disease inevitably progresses Patients with functioning NETs—tumours that secrete excess hormones—face additional challenges. Hormonal hypersecretion can lead to significant clinical symptoms and, if uncontrolled, may become life-limiting. Managing these effects often requires complex, multidisciplinary care. Patient accounts consistently highlight delays in receiving an accurate diagnosis, with an average time to diagnosis of around four years. These delays are often followed by further challenges in accessing specialist expertise, timely treatment, reliable information, and appropriate support. Many patients report feeling dismissed, unseen, and unheard—experiences echoed by their families and carers. These barriers contribute to poorer outcomes and diminished quality of life. Patients and their families describe living with NETs as facing an uncertain and unpredictable future – and having to deal with the pervasive nature of this diagnosis on daily life. The disease necessitates lifelong medical appointments, invasive tests, and complex treatment regimens. Symptoms can fluctuate daily, impacting personal plans, reliability, self-confidence, health and overall well-being. The short- and long-term effects of both the disease and its treatments are common, varied in manifestation and often debilitating. These include physical disability, emotional distress, anxiety, and depression. The impact on daily living is profound, affecting relationships, employment, and social engagement. Supporting a loved one with NETs can be overwhelming. Family members and carers frequently report emotional fatigue, guilt, resentment, and burnout. Financial strain, social isolation, role reversals, and loss of identity are common. The stress of caregiving can test relationships—some adapt and grow stronger, while others struggle or break down, compounding the emotional toll.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	There are several therapies available for neuroendocrine tumours (NETs), but not all are suitable for every individual – and not everyone will receive treatment in the same sequence as another – expert clinical judgement and guidance (MDT) is required. Treatment decisions depend on factors such as the site, stage, grade, and functionality of the disease, as well as the patient's overall health, co-morbidities, eligibility criteria, and treatment availability. Many side-effects, such as those attributed to Cabozantinib, can mimic symptoms of their disease. Patients will have experience of other treatments such as somatostatin analogues, interventional procedures and / or medications such as Everolimus or Sunitinib – Cabozantinib offers an alternative or further treatment for those who need this consideration. While patients and families often accept this complexity—many having become their own disease experts—variations in access across regions (both within and outside the UK) can feel unfair and inequitable. Nonetheless, many patients express understanding of the financial and logistical constraints faced by healthcare systems. Perceptions of NHS care and treatment often depend on individual experiences: what therapies were offered, how well they were tolerated, the benefits or side effects encountered, and how accessible they were. Factors such as geographical distance, personal costs, and NHS funding all influence these views. Many patients are willing to travel for treatment, provided they are well enough to do so. As highlighted in answer 6, delays in receiving an accurate diagnosis and timely access to expertise, information, treatment, and support can significantly impact patients' perceptions of care. However, these experiences often shift positively when patients engage with disease experts or specialist multidisciplinary teams (MDTs). <i>One of the most common recommendations to improve NEN diagnosis and management given by NEN patients and healthcare professionals around the world is “better access to NET experts/specialist centers.” Kolarova & Bouvier 2021</i> The relief of speaking with professionals who understand their condition and are skilled in delivering appropriate clinical interventions is profound and should not be underestimated. Patients, and their families, also have contact with the global patient community: they share lived experiences. Treatments that support independence and well-being are viewed more positively, although the hope for a cure remains ever-present.

	For those, particularly of working age, maintaining physical, mental, and cognitive independence is a priority. In the context of an incurable, progressive disease, progression-free survival and quality of life are often valued more than survival at any cost. A treatment seen as more tolerable than current alternatives – that can maintain or even improve quality of life (as published) offers benefit.
8. Is there an unmet need for patients with this condition?	Current treatments for neuroendocrine tumours (NETs) remain limited to select patient groups: • Lutetium (177Lu) oxodotreotide is NICE-approved for adults with unresectable or metastatic, progressive, well-differentiated (grade 1 or 2), somatostatin receptor-positive gastroenteropancreatic NETs. This excludes patients with primary NETs outside the gastroenteropancreatic system. • Everolimus and sunitinib are recommended, within their marketing authorisations, for well- or moderately differentiated, unresectable or metastatic pancreatic NETs in adults with progressive disease—excluding non-pancreatic primaries. • Everolimus is also approved for well-differentiated (grade 1 or 2), non-functional, unresectable or metastatic NETs of gastrointestinal or lung origin in adults with progressive disease. Patients with functional disease are excluded. These limitations leave individuals with inoperable, locally advanced or metastatic non-pancreatic and/or functional NETs at a disadvantage. There is a clear unmet need for more inclusive and accessible therapeutic options. Furthermore, patients who progress despite these treatments often face limited or no alternative beyond supportive care.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	From the patient's perspective, there is significant variability in how expectations align with actual treatment experiences. They have to navigate the reality of living with cancer while striving to maintain hope. Peer support plays a crucial role in shaping how treatments are perceived. Patients often place immense value on the information and emotional support shared within their community: <i>"Finding the neuroendocrine cancer community was like being pulled to safety by the lifeboat crew when being lost in a storm. Not only did they understand the fears generated by the complexity of my disease, but they have also provided continual help and support, to help me navigate my way through all the twists and turns generated by my journey."</i> — Kath, Functional small bowel primary diagnosed 2015 Cabozantinib trials for neuroendocrine tumors have primarily taken place in the United States and parts of Europe, but not in the UK for this indication. Despite this, national and global online forums and support groups enable discussions among patients, fostering shared understanding of emerging treatments. Published outcomes show that Cabozantinib significantly improves progression-free survival in patients with previously treated, progressive advanced pancreatic and extra-pancreatic neuroendocrine tumors. While side effects are consistent with its known safety profile, overall, Health-Related Quality of Life (HRQoL) is maintained. Reported side effects—such as diarrhoea, constipation, appetite changes, nausea, and fatigue—are similar to those experienced with other treatments or the disease itself. Notably, some patients previously treated with other TKIs (e.g., Everolimus) have found Cabozantinib more tolerable and note quality of life is maintained or improved.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients' concerns vary depending on their disease status and treatment history: • Asymptomatic patients worry about the trade-off between potential side effects and maintaining current well-being. • Symptomatic patients express concerns, as related to other treatments, about whether treatment will exacerbate or alleviate existing symptoms. • Patients with limited treatment options, or where prior treatments have failed, view Cabozantinib as a source of renewed hope. All patients share a common concern: the fear the treatment not being approved or made available.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients with inoperable, locally advanced or metastatic non-pancreatic and/or functional NETs and those who have progressive disease despite approved treatments often face limited / no alternative beyond supportive care.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Not as defined by appraisal criteria.

Other issues

13. Are there any other issues that you would like the committee to consider?	While patients and families often accept the complexity in policy and decision-making and appreciate limited healthcare funding availability — variations in access across regions (both within and outside the UK) can feel unfair and inequitable. Cabozantinib is a potential treatment option that has been approved by both the FDA and European Commission <i>“making it the first and only systemic therapy to be approved in the European Union for previously treated unresectable or metastatic NETs, regardless of tumour site, grade, or previous non–somatostatin analogue–based systemic therapy”</i>. (multiple sources July 2025) Patients in the UK, would appreciate an equitable opportunity in access and availability.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	A) Meets an identified currently unmet need, especially for those with limited / no alternative treatment options beyond supportive care alone. B) Meets an identified need for those who have progressed through and/or following currently available treatment options C) Maintained HRQoL – a key priority for patients & their families D) Reported significant PFS benefit – another important priority for patients and their families E) From patient's perspective, approval would confer parity in treatment, with non-UK peers.

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Professional organisation submission

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- Your response should not be longer than 13 pages.

About you

1. Your name	[REDACTED]
2. Name of organisation	UKINETS
3. Job title or position	Consultant medical oncologist specialising in Neuroendocrine tumours and GI cancers and [REDACTED]
4. Are you (please select Yes or No):	A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes
5a. Brief description of the organisation (including who funds it).	UK and Ireland Neuroendocrine Tumour Society (UKINETS) represents scientists, nurses, allied health workers and clinicians involved in the care of patients with neuroendocrine tumours. Its aims include standardising practise, improving standards of NET services, promoting education, collaboration and research.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Ipsen Ltd provides sponsorship to UKINETS for its annual conference and annual training day. Funding received in last 12 months: £35,000
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Neuroendocrine tumours (NETs) are a heterogenous group of tumours. They most often arise in the gastrointestinal tract or lung but can originate from other sites. They can be classified according to the primary site, whether they are functional or non functional, the stage, grade and differentiation of the tumour. This information is used to determine treatment options for patients, which are made by a multi-disciplinary team with experience in managing NETs. Patients with advanced disease have limited treatment options after progression on 1 or 2 lines of systemic therapy. In advanced disease, the aim of systemic therapy in NETs is to control symptoms and delay tumour progression.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In the CABINET trial, the median progression free survival (PFS) in patients with extra pancreatic NETs with cabozantinib was 8.4 months versus 3.9 months with placebo (stratified hazard ratio for progression or death, 0.38; 95% confidence interval [CI], 0.25 to 0.59; P<0.001). In patients with pancreatic NETs, median PFS was 13.8 months with cabozantinib versus 4.4 months with placebo (stratified hazard ratio, 0.23; 95% CI, 0.12 to 0.42; P<0.001). This is clinically significant for patients with both pancreatic and extra pancreatic NETs.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Treatment of advanced well differentiated NETs is based on patient factors such as comorbidities and performance status, pathological features such as proliferation/grade, whether the tumour is functional, the primary tumour site and the somatostatin receptor status. ENETS or ESMO guidelines are most often followed by clinicians in the NHS. Systemic options include somatostatin analogues, peptide receptor radionuclide

	therapy, everolimus, sunitinib (pancreatic NETs) and chemotherapy. Often these treatments are used sequentially.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Most UK clinicians treating neuroendocrine tumours would use the European Neuroendocrine Tumour Society or the European Society for Medical Oncology guidelines (ESMO clinical practice guidelines: Endocrine and Neuroendocrine cancers. Ann Oncol 2020;31(7):844-60).
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is variability in the pathway of care for patients with NETs in the UK as access to multidisciplinary care and expert centres can vary. An ideal patient care pathway has been developed to address this. With the use of ENETs and ESMO guidelines, alongside MDTs, variability amongst professionals should be reduced.
9c. What impact would the technology have on the current pathway of care?	It would provide a needed additional systemic treatment option for patients with advanced pancreatic and extra pancreatic well or moderately differentiated NETs.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Cabozantinib is currently used in the treatment of renal cell carcinoma, hepatocellular carcinoma and differentiated thyroid carcinoma.
10a. How does healthcare resource use differ between the technology and current care?	
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	In secondary care, prescribed by a specialist trained in the use of systemic anticancer therapy and treatment of neuroendocrine neoplasms.

10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Other than the cost of cabozantinib there should not be a significant cost for additional resources if this were to be approved. These patients would likely already be managed in specialist outpatient clinics.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, it provides an additional or alternate option to currently available systemic therapy.
11a. Do you expect the technology to increase length of life more than current care?	No overall survival difference was observed in the CABINET trial but the data was not mature at the time of publication. Given the crossover allowed within the trial following the amendment and a high number of patients receiving subsequent therapies, overall survival may be affected by these.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Full analysis of the quality of life data in CABINET has yet to be published but note this will be compared to placebo.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with grade 1-3 pancreatic and extra pancreatic neuroendocrine tumours, functioning or non functioning were included in the trial. They had to have progressive disease following at least one line of therapy and of Performance status 0-2. This would be the population I would anticipate its use in.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are	Other options for systemic therapy for this group of patients currently includes everolimus, sunitinib and chemotherapy and patients requiring these treatments are managed in outpatient clinics by oncologists experienced in prescribing and managing systemic anticancer therapy. This will apply to patients recommended cabozantinib.

there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	To continue until disease progression, unacceptable toxicity or patient choice.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	It would provide an additional option for systemic treatment for this group of patients.

16a. Is the technology a 'step-change' in the management of the condition?	
16b. Does the use of the technology address any particular unmet need of the patient population?	There is an unmet need for additional treatment options to delay disease progression.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Reported toxicity was consistent with the known side effect profile for cabozantinib and managed by dose reductions and interruptions.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The CABINET trial used placebo as the control arm. It is usual practice to sequence the available systemic therapies on progression after 1 or 2 lines of treatment (available therapies would include PRRT, everolimus, sunitinib for pancreatic NET and chemotherapy). There is little trial data on sequencing and often this is a clinical decision based on tumour and patient factors.
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Progression free survival and quality of life are important outcomes in this group of patients. PFS was the primary endpoint.

18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Progression free survival was the primary endpoint. The 2021 Consensus report of the National Cancer Institute NET clinical trials planning meeting (J Natl Cancer Inst 2023 May 31;115(9):1001–1010) recommended that PFS is the recommended primary end point for phase III studies in well differentiated neuroendocrine tumours. There was crossover in the trial and many of these patients will be treated with subsequent systemic therapies so overall survival data will be affected by this.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Adverse effects in the CABINET trial were consistent with the known safety profile of cabozantinib
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA449] and [TA539]	No
21. How do data on real-world experience compare with the trial data?	

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Cabozantinib improved progression free survival in patients with pancreatic and extrapancreatic neuroendocrine tumours which is clinically significant • Adverse events in the CABINET trial were consistent with the known safety profile of cabozantinib • Outside of the cost of the drug, there is no anticipated additional infrastructure/staffing cost •

Thank you for your time.

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Single Technology Appraisal

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

Clinical expert statement

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Clinical expert statement

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

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The deadline for your response is **5pm on Wednesday 6 August 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating advanced neuroendocrine tumours and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Charlotte Fribbens
2. Name of organisation	
3. Job title or position	Consultant medical oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with advanced neuroendocrine tumours? ☐ A specialist in the clinical evidence base for advanced neuroendocrine tumours or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
8. What is the main aim of treatment for advanced neuroendocrine tumours?	

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Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

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(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	
10. In your view, is there an unmet need for patients and healthcare professionals in advanced neuroendocrine tumours?	
11. How is advanced neuroendocrine tumours currently treated in the NHS? - Are any clinical guidelines used in the treatment of the condition, and if so, which? - Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) - What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? - How does healthcare resource use differ between the technology and current care? - In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) - What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	

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13. Do you expect the technology to provide clinically meaningful benefits compared with current care? - Do you expect the technology to increase length of life more than current care? - Do you expect the technology to increase health-related quality of life more than current care?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	

Clinical expert statement

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
20. Do the clinical trials on the technology reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials? - If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? - Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA449, TA539]?	

Clinical expert statement

23. How do data on real-world experience compare with the trial data?	
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Clinical expert statement

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

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Single Technology Appraisal

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

Clinical expert statement

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Clinical expert statement

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

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Part 1: Treating advanced neuroendocrine tumours and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Debashis Sarker
2. Name of organisation	King's College London
3. Job title or position	Consultant Medical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with advanced neuroendocrine tumours? ☒ A specialist in the clinical evidence base for advanced neuroendocrine tumours or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
8. What is the main aim of treatment for advanced neuroendocrine tumours?	To stop progression, thereby improving life expectancy and quality of life

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Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

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(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A doubling of progression free survival compared to placebo would indicate a clinically significant benefit of a new therapy in advanced neuroendocrine tumours
10. In your view, is there an unmet need for patients and healthcare professionals in advanced neuroendocrine tumours?	Patients with advanced neuroendocrine cancers have incurable disease, often associated with poor survival and limited effective treatment options (in particular for patients with extrapancreatic neuroendocrine tumours). There is therefore a significant unmet need for effective therapies to improve outcomes across the whole spectrum of patients with advanced neuroendocrine tumours.
11. How is advanced neuroendocrine tumours currently treated in the NHS? - Are any clinical guidelines used in the treatment of the condition, and if so, which? - Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) - What impact would the technology have on the current pathway of care?	Clinical guidelines for the diagnosis and management of neuroendocrine cancers most commonly used in NHS practice include: -UK and Ireland NET Society (UKINETS: https://www.ukinets.org/net-clinics-clinical-practice/) -European NET Society (ENETS: https://www.enets.org/guidelines.html) -European Society of Medical Oncology (ESMO: https://www.esmo.org/guidelines/esmo-clinical-practice-guidelines-endocrine-and-neuroendocrine-cancers) Pathways of care for neuroendocrine cancer are highly variable across the NHS. Whilst the NHS has a number of NET specialist centre (as evidenced by 13 units having formal designation as ENETS Centres of Excellence: https://www.enets.org/coe.html), overall care for people with NETs is challenging due to low disease awareness, missed detection opportunities, delays in diagnosis, barriers in access to appropriate treatments and, crucially, the absence of a national care pathway. This has been highlighted in a recent major campaign by Neuroendocrine Cancer UK to implement a dedicated

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Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

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	neuroendocrine cancer pathway into NHS England: https://www.healthpolicypartnership.com/app/uploads/Neuroendocrine-cancer-an-ideal-patient-care-pathway.pdf ; https://www.neuroendocrinecancer.org.uk/wp-content/uploads/2024/03/Neuroendocrine-neoplasms-Consensus-on-a-patient-care-pathway.pdf With regards the proposed technology, as this is a systemic therapy given in the second line or beyond setting (after therapies such as chemotherapy, everolimus and peptide receptor radionuclide therapy), most patients will already be under the care of an established neuroendocrine team experienced in management of NETs. The pathway of care is therefore unlikely to be impacted with the introduction of cabozantinib. The results of the CABINET trial showed benefit for cabozantinib in patients with both advanced pancreatic (PNET) and extrapancreatic NET (EP-NET). One of the potential issues around the pathway for implementation are around the more heterogenous group of clinicians who are potentially involved in the management of extrapancreatic NETs (EP-NET). This includes patients with lung NETs who are often treated by site-specific specialists, such as respiratory physicians and lung oncologists as well as nuclear medicine physicians and lung cancer nurse specialists.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	Cabozantinib will be used in a similar way to other systemic therapies currently given on the NHS for management of advanced neuroendocrine cancers. Systemic therapy for NETs is usually given in either specialist NET centres (broadly aligning to the ENETS Centres of Excellence) or in secondary care settings by site-specific teams (eg lung or gastrointestinal oncologists). As this is an oral systemic therapy, there are likely to be minimal implications around further investment needed for implementation. The toxicity profile of cabozantinib is typical of a multi-targeted tyrosine kinase inhibitor (such as

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What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	sunitinib, which is already used for advanced pancreatic NET) and is therefore familiar to oncologists and therefore will not require extra investment for training.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? - Do you expect the technology to increase length of life more than current care? - Do you expect the technology to increase health-related quality of life more than current care?	As per the CABINET trial, cabozantinib was evaluated in patients with advanced pancreatic (PNET) and extrapancreatic NET (EP-NET). Primary endpoint was progression-free survival, with secondary endpoints of confirmed objective response rate, overall survival, and safety. For patients with extra-pancreatic NET, median progression-free survival with cabozantinib was 8.4 months compared to 3.9 months with placebo (stratified hazard ratio [HR], 0.38; 95% confidence interval [CI] 0.25–0.59, $p < 0.001$). Confirmed objective response rates with cabozantinib was 5% compared to 0% with placebo. Median survival follow-up time was 24.2 months, with median overall survival of 21.9 months with cabozantinib versus 19.7 months with placebo (HR= 0.86; 95% CI: 0.56–1.31; Figure 1B). In patients with pancreatic NET, median progression-free survival was 13.8 months compared to 4.4 months with placebo (stratified HR, 0.23; 95% CI 0.12–0.42, $p < 0.001$); confirmed objective response rates with cabozantinib was 19% compared to 0% with placebo. Median survival follow-up was 23.1 months, with median overall survival 40 months with cabozantinib versus 31.1 months with placebo (HR= 0.95; 95% CI: 0.45 to 2.00). Reviewing this data in the context of other standard of care systemic therapies for both advanced PNET and EP-NET, cabozantinib provides clinically meaningful improvements in progression-free survival whose disease has progressed after at least one other line of therapy for their disease. Although no improvement in overall survival has been demonstrated to date, this is likely to be related to a relatively short period of survival follow up, use of subsequent

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Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

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	therapies and potential crossover. When compared with existing systemic therapies, the improvements in PFS are similar to what has been achieved with other systemic therapies used in these settings such as everolimus, sunitinib and cytotoxic chemotherapy. This is particularly of importance for patients with EP-NET, who have more limited systemic therapy options compared to patients with PNET. Overall health related quality of life (HRQL) remained stable over time and was similar in both arms. As expected, Grade 3 or higher adverse events were higher in patients treated with cabozantinib (62–65%) of compared to placebo (23–27%). When compared with existing systemic therapies, toxicity profile is similar to established drug therapies such as sunitinib, everolimus and cytotoxic chemotherapy. I would therefore anticipate that use of cabozantinib will allow maintenance of health related quality of life similar to other systemic therapies.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Based on the subgroup analysis from the CABINET trial, efficacy of cabozantinib appears to be consistent in efficacy across clinically relevant subgroups.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Cabozantinib is already a standard of care therapy for patients with advanced renal cell carcinoma and hepatocellular carcinoma. Protocols for cabozantinib are therefore already in use across the NHS. Management of cabozantinib related toxicities are also well recognised with clearly established associated supportive care protocols. (eg for diarrhoea, rash, hypertension). I therefore do not envisage any issues around ease of use with cabozantinib and with no differences compared to other oral systemic therapies routinely used for NETs such as everolimus, sunitinib and capecitabine-temozolomide chemotherapy.

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Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

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16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting and stopping of cabozantinib will be done according to established clinical pathways for patients with NETs, ie starting of therapy on progression or intolerance of previous line of treatment; stopping on clinical or radiological progression or if intolerant of cabozantinib
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	QALY is sufficient to capture the health-related benefits of cabozantinib
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	Whilst the mechanism of action of Cabozantinib is not novel (sunitinib is another multitargeted TKI which is approved for PNET), cabozantinib the potential to provide significant, clinically meaningful health related benefits for patients with advanced NETs. Treatment options for patients with NETs are relatively limited (especially patients with EP-NET) and the addition of cabozantinib to the therapeutic armamentarium is likely to provide improvements in survival and maintenance of health-related quality of life which are substantial.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects of cabozantinib reported in the CABINET trial are typical of this class of drug and those previously reported when used in other cancer types. The majority of patients require dose reduction or interruption with Grade 3 or higher adverse events noted in 62–65% of patients, compared to 23–27% with placebo. Common grade 3 or higher treatment-related adverse events included hypertension, fatigue, diarrhea, and thromboembolic events. Despite these side effects, global health related quality of life is maintained, with a higher proportion of patients receiving cabozantinib reporting improved overall status.

Clinical expert statement

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

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20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The pivotal CABINET trial is broadly reflective of current UK clinical practice. I have previously outlined the primary and secondary outcomes and results earlier in my statement. Progression free survival is an established primary endpoint in NET trials and has been demonstrated to be an appropriate surrogate for overall survival (OS) in NET trials, as studies show a statistically significant correlation between the two endpoints (Imaoka H et al, Endocr Relat Cancer. 2017; Ter-Minassian M, et al. Oncologist. 2017). There are no new toxicity signals of concern around use of cabozantinib.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No, I'm not aware of any other relevant evidence
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA449, TA539]?	There is no new evidence for the comparator treatment
23. How do data on real-world experience compare with the trial data?	I am not aware of any published real world evidence of cabozantinib for advanced NETs. FDA approval of cabozantinib only occurred in March 2025.
24. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil	I do not think there are any equality issues of concern related to use of cabozantinib.

Clinical expert statement

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

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partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.

Please state if you think this evaluation could

- exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation
- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

Clinical expert statement

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Advanced NETs are an incurable malignancy, with many subgroups associated with poor prognosis and limited treatment options. Cabozantinib has shown clinically meaningful improvements in progression free survival in patients with both pancreatic and extra-pancreatic NETs, which is likely to provide improvements in survival which are substantial.

Cabozantinib causes a high incidence of toxicities leading to the majority of patients requiring dose reductions consistent with its known safety profile; however global quality of life was maintained, with a higher proportion of patients reporting improved overall status.

Cabozantinib is an important new treatment option for patients with advanced NETs, not limited by site of origin o

Click or tap here to enter text.

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Clinical expert statement

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

Single Technology Appraisal

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on Wednesday 6 August 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating advanced neuroendocrine tumours and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	
2. Name of organisation	Christie NHS Foundation Trust
3. Job title or position	
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with advanced neuroendocrine tumours? ☒ A specialist in the clinical evidence base for advanced neuroendocrine tumours or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for advanced neuroendocrine tumours?	Improve survivability by improving overall survival and/ or progression free survival

Clinical expert statement

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	For patients with well differentiated NETs the most important clinically significant treatment response has to be an improvement in survival. Response rates in these cancer which generally grow slowly is less important and sometimes misleading. An improvement in PFS or OS associated with a HR> 0.7 would be considered a good response. With respect to an agent being used post pRRT or everolimus then a PFS delta of >3months would be considered a clinically meaningful and significant treatment response.
10. In your view, is there an unmet need for patients and healthcare professionals in advanced neuroendocrine tumours?	Yes. This is especially true for the bronchial NETs which only have one line of NICE approved / commissioned therapy (everolimus) but account for approximately 30% of all well differentiated NETs presenting in the UK.
11. How is advanced neuroendocrine tumours currently treated in the NHS? - Are any clinical guidelines used in the treatment of the condition, and if so, which? - Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) - What impact would the technology have on the current pathway of care?	Currently, the management advanced NETs is roughly split into one pathway for the management of bowel and pancreatic NETs and a separate pathway for the bronchial NETs. The former pathway is better defined and more organised with respect to both the diagnostic and treatment pathway. The bronchial NET pathway is more variable depending on where in the country a patient presents. Over the last 5 years, UKINETS has put a lot of effort into developing UK specific guidelines for all these NETS. These have helped to homogenise the bronchial NET pathways although it is accepted that further work needs to be done. Approval of this technology would help improve structure the management pathway and reduced the national variation in care. The disease group that would most benefit in this way would be the bronchial NET pathway. This was observed when everolimus was approved. Cabozantinib has to be given in sequence following other drugs. This will help reduce variation in practice.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes

Clinical expert statement

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Currently, chemotherapy is being used with pancreatic or bowel NETs which tend to have low levels of evidence (level 3 or higher). For bronchial NETs most units would refer to best supportive care. Therefore, length of life will increase. HR QOL should improve especially with the bronchial NETs as they only receive BSC at this stage.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Bronchial NETs patients have the largest unmet need as they have the least treatments currently available to them.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	No special requirements needed with this oral medication. It might therefore be easier for patients as the current active treatment choice is chemotherapy which may require extra hospital visits etc.

Clinical expert statement

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Clinical and radiological responses will be assessed
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	Yes, currently for bronchial NETs there is an unmet need at this stage of the pathway. Therefore, by definition, this is a step wise change in management.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Reasonably well tolerated therefore not expecting AEs to adversely affect management.
20. Do the clinical trials on the technology reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials?	Yes As stated previously, PFS or OS are the most important outcomes. PFS was the primary end point in the trial.

Clinical expert statement

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA449, TA539]?	No
23. How do data on real-world experience compare with the trial data?	No survival data improvements recorded in real world data.
24. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	Bronchial NET patients are often poorly represented in such appraisals either because there were not enough patients representing them in the trial being appraised or because it is an inherently less responsive condition than the pancreatic or small bowel NETs. They therefore get adverse outcomes from appraisal.

Clinical expert statement

- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The primary end point of the trials is most relevant to these disease groups

The demonstrated benefits in primary end point are clinically meaningful

Bronchial NETs are well represented and in proportion to real world experience

The PFS benefits for the bronchial NETs is clinically meaningful

Large unmet need certainly for the bronchial NETs

Thank you for your time.

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Single Technology Appraisal

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with advanced neuroendocrine tumours or caring for a patient with advanced neuroendocrine tumours. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Patient expert statement

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **<insert deadline>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Patient expert statement

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

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Part 1: Living with this condition or caring for a patient with advanced neuroendocrine tumours

Table 1 About you, advanced neuroendocrine tumours, current treatments and equality

1. Your name	Enola Wright
2. Are you (please tick all that apply)	☒ A patient with advanced neuroendocrine tumours? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with advanced neuroendocrine tumours? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Insulinoma Support Network (Insulinoma Charity UK)
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☒ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: I am

Patient expert statement

	drawing on others' experiences. As Founder of the Insulinoma Support Network, established, in 2007, and Insulinoma Charity UK, established 2023, I have extensive contact with patients and carers through moderated peer groups and one to one support. ☒ I have completed part 2 of the statement after attending the expert engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with advanced neuroendocrine tumours? If you are a carer (for someone with advanced neuroendocrine tumours) please share your experience of caring for them	I was diagnosed with metastatic insulinoma in 2007. Insulinoma is a functional neuroendocrine tumour that releases insulin inappropriately and causes hypoglycaemia. My daily life has been shaped by the fear and unpredictability of hypoglycaemic episodes, alongside the long-term consequences of investigations, surgery, and medical therapy. Before diagnosis I experienced episodes of confusion, visual disturbance, tremor, and loss of awareness, with significant risk to personal safety. After treatment the constant concern is recurrence and the possibility of further progression. The condition affects diet, work, social life, sleep, and independence. Planning revolves around access to glucose, alarms, and support. I have learned to live with constant vigilance while trying to maintain a normal life.
7a. What do you think of the current treatments and care available for advanced neuroendocrine tumours on the NHS?	7a. From my experience as a metastatic insulinoma patient, and from what I see and hear daily through our Insulinoma peer support groups [1.2k members in the Diagnosed Insulinoma group, 1.5k in the Suspected group, 100 in the Malignant group, and 38 in the NIPHS group], NHS care can be excellent when patients reach a recognised NET Centre of Excellence with

Patient expert statement

7b. How do your views on these current treatments compare to those of other people that you may be aware of?

access to a multidisciplinary team. The combined expertise of surgical, endocrinology, and oncology specialists is highly valued. However, for metastatic insulinoma, access to this level of care is inconsistent, and many treatments recommended in international guidance are delayed, unevenly available, or restricted by geography and funding, leaving patients vulnerable to gaps in care. For example:

- Initial symptom management. Diazoxide and somatostatin analogues are used to control hypoglycaemia, but access to diazoxide can be difficult in some regions and side effects are significant with little or no support. Nutritional support is not consistently offered, for how to manage hypoglycaemia, particularly overnight, the role of carbohydrates and the need to eat small frequent meals to prevent hypos.
- Surgery. Surgical resection is potentially curative, and minimally invasive or robotic techniques reduce complications. Yet access depends on referral to high-volume centres, and not all patients are offered cytoreductive surgery when it could improve symptom control. The last three people to die in the metastatic group died, despite their efforts, no surgery was forthcoming.
- Somatostatin analogues and Everolimus. These treatments are available, but patients often face delays in escalation. Everolimus is approved for progressive Pan-NETs, but not all metastatic insulinoma patients are able to access it promptly. We lost one member due to side effects of Everolimus. She received little or no surveillance such as blood tests and scans and died from leukaemia induced by Everolimus. Another is experiencing kidney failure.
- PRRT (e.g. ¹⁷⁷Lu-DOTATATE). This is highly effective for advanced disease, but NHS funding and capacity are limited. Many patients report being told it is not available to them, despite evidence of benefit. There is currently one 35 year old mother of three young children who has been refused PRRT. She is trying to raise the funds privately to access PRRT.

Patient expert statement

	• Chemotherapy. Regimens such as streptozotocin-based therapy or CAPTEM can be offered, but access to CAPTEM is variable and sometimes limited by local protocols. There is no evidence in the group that chemotherapy stops or helps insulinoma patients. In the advanced aggressive disease, it didn't prolong or enhance life. • Liver-directed therapies (RFA, TACE, TARE). These can be important for patients with liver metastases, yet availability is patchy and often limited to specialist centres. Patients frequently feel excluded because they live far away or are not referred early enough. Evidence from the group supports RFA, TACE and TARE are a positive and effective treatment but difficult to access in the UK. One member financed the treatment privately and travelled to a specialist centre in Germany. • Monitoring and follow-up. Advanced imaging (CT, MRI, PET/CT) is essential, but PET/CT availability, particularly ⁶⁸Ga-DOTATATE PET, is inconsistent. Patients are often left waiting months for scans, adding to anxiety and risking delayed decisions. The Exendin PET scan targets the GLP-1 receptor with ⁶⁸Ga-labelled Exendin-4, delivering highly sensitive functional imaging for locating insulinomas. However, availability remains very limited. I am not aware of anyone with the advanced disease having access to it. • Palliative care. Symptom control is highly valued, but structured psychological support, end-of-life planning, and access to specialist hypoglycaemia rescue plans are non-existent inconsistent across the NHS. No guidance is offered or given. Following the death of a much loved member of the group, his hospice wrote and produced a guide "Withdrawal of life sustaining treatment in advanced metastatic insulinoma." It includes reflections and key learning. The guideline is available for download on the insulinoma website and in the group. In summary, patients are grateful for the dedication of individual clinicians, but current NHS treatments and care fall short in consistency, equity, and

Patient expert statement

	timeliness. The key challenges are limited treatment options after progression, variation in access to advanced therapies such as PRRT, RFA, and CAPTEM, and surgery, a lack of integrated support for the daily realities of living with a metastatic insulinoma, particularly the constant management of severe hypoglycaemia. 7b. My views reflect what I hear from many others living with advanced insulinoma diagnosis. While patients value the expertise of NHS specialists, there is widespread frustration that effective options are so limited once the disease has progressed. Access to surgery is not always offered, even when certain procedures might help with symptom control. Surveillance is often poor, with long intervals between scans or delays in obtaining specialist imaging, which adds to anxiety and can delay decisions about treatment. Management of metastatic insulinoma is inconsistent, with significant variation in whether patients are considered for PRRT, CAPTEM, or liver-directed therapies. Alongside this, there is no structured psychological support for patients or carers who are coping with both the physical challenges of hypoglycaemia and the constant fear of recurrence and progression. These concerns are shared widely within the community and mirror my own experiences.
8. If there are disadvantages for patients of current NHS treatments for advanced neuroendocrine tumours (for example, how they are given or taken, side effects of treatment, and any others) please describe these	• Limited options after progression. After first systemic treatment, there are few effective choices for some • Toxicity and burden. Side effects from systemic therapy can be significant and may worsen fatigue, for example mouth sores, digestive problems, diarrhoea, and the recognised toxicities of Everolimus and chemotherapy.

Patient expert statement

	• Impact on hypoglycaemia management. Treatments that reduce appetite, cause nausea, or cause diarrhoea can make hypoglycaemia harder to manage, especially for those who rely on regular carbohydrate intake. • Travel and logistics. Repeated hospital visits for infusions, imaging, and monitoring are challenging, particularly for those who live far from specialist centres or have caring responsibilities. • Psychological load. Anxiety about progression or recurrence is constant. Structured psychological support is not consistently available. Includes no support for family or carers.
9a. If there are advantages of cabozantinib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does cabozantinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	9a. Cabozantinib offers important advantages over current NHS treatments. It provides an additional option after progression, with evidence of longer disease control and stable quality of life. Being an oral treatment, it reduces the need for hospital visits, which makes it easier to continue working, studying, and managing family responsibilities. For patients with functional tumours such as metastatic insulinoma, controlling tumour growth may also reduce hormone-related symptoms, making daily life more predictable and safer. Overall, Cabozantinib supports independence, self-care, and the ability to care for others while living with advanced disease. 9b. The most important advantage is that Cabozantinib offers an effective option after progression, when very few treatments remain on the NHS. Almost as important is that it is taken orally, reducing hospital visits and allowing patients to continue working, caring for family, and maintaining independence with less disruption to daily life. 9c. Cabozantinib directly addresses one of the greatest disadvantages of current NHS treatment, which is the lack of effective options after progression. It provides

Patient expert statement

	an additional line of therapy when choices are otherwise very limited. Its oral administration also reduces the burden of frequent hospital visits, which eases the strain of travel and logistics for patients and carers, particularly those living far from specialist NET centres. For metastatic insulinomas, controlling tumour growth has the potential to lessen the severity and frequency of hypoglycaemic episodes, which makes daily life safer and more predictable. This can reduce the constant vigilance required by both patients and carers. In addition, having access to another active treatment option can ease the psychological load by reducing anxiety about progression or recurrence, and by giving families more hope and security. While Cabozantinib does have side effects, proactive monitoring and dose adjustments can make it more manageable than some existing systemic treatments.
10. If there are disadvantages of cabozantinib over current treatments on the NHS please describe these. For example, are there any risks with cabozantinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Cabozantinib has disadvantages, mainly related to side effects such as fatigue, high blood pressure, diarrhoea, mouth soreness, skin changes, and weight loss. These can be particularly difficult for patients with an insulinoma, as reduced appetite or diarrhoea make hypoglycaemia harder to manage. There are also risks of blood clots, bleeding, and impaired wound healing, which require careful monitoring. While dose adjustments can help, some patients may find the side effects outweigh the benefits.
11. Are there any groups of patients who might benefit more from cabozantinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Patients who may benefit more include those with advanced disease after progression, people living far from or who have no access to specialist NET centres who need an oral option, and those where tumour control may reduce hypoglycaemia. Patients who may benefit less include those with uncontrolled hypertension, severe gastrointestinal or nutritional problems, or difficulties with mobility, or understanding, as side effects and self-management could be harder to cope with.
12. Are there any potential equality issues that should be taken into account when considering advanced neuroendocrine tumours and cabozantinib? Please explain if you think any groups of people with this condition are particularly disadvantage	People may experience inequalities linked to age, disability, mobility, financial circumstances, or geographical distance from specialist NET centres. Management at local non-specialist NHS is at best precarious. Cabozantinib, as an oral therapy, has the potential to ease some of these barriers by reducing reliance on hospital-based care, but equitable access and consistent support are critical. Additional

Patient expert statement

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	differences arise from language and culture, may limit comprehension of treatment and side effect management, and women of childbearing age may require specific counselling regarding pregnancy-related risks. A further and significant concern is that patients at the end of life are often not offered any additional NHS treatment once progression has occurred. This results in inequity, as individuals without private means are left with no therapeutic options. Addressing such gaps is essential to ensure that access to treatment does not exclude patients either on the basis of vulnerability or solely due to their stage of disease.
13. Are there any other issues that you would like the committee to consider?	Consistency of care is a major issue, particularly for metastatic insulinomas. Management varies greatly between centres, and patients cared for in local hospitals that are not recognised NET Centres of Excellence often do not receive the same investigations, treatments, or timely referrals. A lack of clear national pathways leads to delays, missed opportunities, uncertainty and sometimes death. The committee should consider how to ensure that every patient, regardless of where they are first seen, has equitable access to specialist review, advanced imaging, and the full range of available treatments. All patients diagnosed with metastatic insulinoma should be referred to a recognised ENETS Centre of Excellence in the UK for specialist multidisciplinary care. A small number of people who complete the diagnosis process for an insulinoma are diagnosed with related conditions: • Insulinomatosis: multiple insulinomas including micro-insulinomas

Patient expert statement

- Proinsulinoma: neuroendocrine tumour which produces proinsulin
- Noninsulinoma pancreatogenous hypoglycaemia syndrome (NIPHS): beta cells in the pancreas produce excess insulin without forming a tumour

Will Cabozantinib be evaluated or considered within the NHS as a potential treatment option for patients diagnosed with non-insulinoma pancreatogenous hypoglycaemia syndrome (NIPHS)? This is important because patients with NIPHS experience severe and unpredictable hypoglycaemia, yet currently have very limited treatment options and no clearly defined NHS pathway. We also have a dedicated peer support group for NIPHS patients, which highlights the urgent need for better recognition and treatment options within this community.

Patient expert statement

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

11 of

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- I was diagnosed with metastatic insulinoma in 2007 and speak from my own personal lived experience and as founder of the Insulinoma Support Network and Insulinoma Charity UK, representing patients and carers.
- NHS care for metastatic insulinomas lacks consistent pathways, management varies widely between centres of excellence and local NHS hospitals and no national protocol exists, leading to delays, missed treatments, uncertainty and on occasions, death.
- Current treatments are limited, toxic, and disruptive, while structured support for hypoglycaemia and psychological well-being is notably absent.
- Cabozantinib adds a vital treatment option after progression. As an oral therapy, it reduces hospital visits, helps maintain work, self-care, and family care, and offers hope when others have failed.
- Equity of access must be guaranteed so that every patient, including those at the end of life and receive the same standard of care, regardless of where they are treated. Related conditions such as NIPHS should be considered for evaluation and inclusion.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Patient expert statement

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Patient expert statement

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

STA Report

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List of Abbreviations

1L/2L	First line/second line
¹⁷⁷ Lu-dotatate	¹⁷⁷ Lutetium-dotatate
5-FU	5-fluorouracil
ADTTE	Analysis of Delayed Time-to-Event
AE	Adverse event
AIC	Akaike Information Criterion
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BIC	Bayesian Information Criterion
BIRC	Blinded Independent Review Committee
BNF	British National Formulary
BOR	Best overall response
BSA	Body surface area
BSC	Best supportive care
CAP	Capecitabine
CAPTEM	Capecitabine and temozolomide
CCT	Concomitant therapy
CE	Conformité Européenne
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Cycle length
CMH	Cochran–Mantel–Haenszel
CR	Complete response
CRF	Case report form
CS	Company submission
CS	Carcinoid syndrome
CSR	Clinical study report
CT	Computed tomography
DCO	Data cut-off
DCR	Disease control rate
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSMB	Data and Safety Monitoring Board
DSU	Decision support unit
DTC	Differentiated thyroid cancer
EAG	External assessment group
ECOG	Eastern Cooperative Oncology Group

EDC	Electronic data capture
EMA	European Medicines Agency
ENETS	European Neuroendocrine Tumor Society
EORTC	European Organisation for Research and Treatment of Cancer
pNET	Extra-pancreatic neuroendocrine tumour
EQ-5D	EuroQol-5 dimension
ESMO	European Society for Medical Oncology
ETM	Event to monitor
FDA	Food and Drug Administration
FOLFOX	Folinic Acid, Fluorouracil, and Oxaliplatin
G	Grade
GEP NET	Gastroenteropancreatic neuroendocrine tumour
GI	Gastrointestinal
GI NET	Gastrointestinal neuroendocrine tumour
HCC	Hepatocellular carcinoma
HCRU	Healthcare and resource use
HPF	High-power field
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HSE	Health Survey England
ICER	Incremental cost-effectiveness ratio
IFN- α	Interferon alpha
IM	Intramuscular
INHB	Incremental net health benefit
IP	Investigational product
IPCW	Inverse probability of censoring weights
IPD	Individual patient data
IQR	Interquartile range
IRP	International Recognition Procedure
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IWRS	Interactive web response system
IxRS	Interactive voice/web response system
KM	Kaplan-Meier
LAR	Long-acting release
LCNEC	Large cell neuroendocrine carcinoma
LMWH	Low molecular weight heparin
LR	Log-rank test
LYG	Life-years gained

MAIC	Matching-adjusted indirect comparison
MET	Mesenchymal-epithelial transition
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
NA	Not applicable
NCI	National Cancer Institute
NCRAS	National Cancer Registration and Analysis Service
NEC	Neuroendocrine carcinoma
NEN	Neuroendocrine neoplasm
NET	Neuroendocrine tumour
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
NPACT	Non-protocol anticancer therapy
NSCLC	Non-small cell lung cancer
ONS	Office for National Statistics
OPEN	Oncology Patient Enrollment Network
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressed disease
PF	Progression-free
PFS	Progression-free survival
PGIC	Patient Global Impression of Change
PH	Proportional hazards
PICO	Population, intervention, comparator, outcome
pNET	Pancreatic neuroendocrine tumour
PPE	Palmar-plantar erythrodysesthesia
PPS	Post-progression survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROs	Patient reported outcomes
PRRT	Peptide receptor radionuclide therapy
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal social services
PSSRU	Personal social services research unit
QALE	Quality-adjusted life expectancy

QALY	Quality-adjusted life year
QD	Once daily
QLQ	Quality of Life Questionnaire
QoL	Quality of life
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response evaluation criteria in solid tumors
RET	Rearranged during transfection
RoB	Risk-of-bias
RPSFTM	Rank preserving structural failure time model
RTK	Receptor tyrosine kinase
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SCLC	Small cell lung cancer
SD	Stable disease
SD	Standard deviation
SEER	Surveillance, epidemiology, and end results
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SOC	Standard of care
SSA	Somatostatin analogue
SSTR	Somatostatin receptor
STA	Single technology appraisal
STM	State transition model
STZ	Streptozotocin
TA	Technology appraisal
TEM	Temozolomide
TH	Time horizon
TKI	Tyrosine kinase inhibitor
TLR	Targeted literature review
TNM	Tumour, node, metastasis
ToT	Time on treatment
TRAE	Treatment-related adverse event
TSD	Technical support document
TTD	Time to treatment discontinuation
TTO	Time trade-off
VEGF	Vascular endothelial growth factor

VEGFR	Vascular endothelial growth factor receptor
WBC	White blood cell
WHO	World Health Organization
WTP	Willingness to pay

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 presents a summary of the EAG's key issues on the evidence submitted on the clinical and cost effectiveness of cabozantinib for treating people with advanced neuroendocrine tumours (NETs) which have progressed after at least one systemic treatment.

Table 1. Summary of key issues

ID	Summary of issue	Report sections
1	The company's analysis does not represent the entire population considered in the company's marketing authorisation and excludes key comparators of interest	2.3.1, 2.3.3 and 3.4
2	The site-agnostic approach for the epNET cohort is unjustified. Specifically, it does not appropriately capture the different prognosis and treatment response in lung NET patients compared to other epNET patients	2.3.1, 3.2, 3.3.1.1, 3.3.2.1.1 and 3.4.2
3	The company's base case does not use the most recent OS data cut	2.3.4, 3.3.1.1 and 3.3.2
4	The EAG disagrees with the company's modelling approach for PFS	4.2.3.1.2 and 4.2.3.1.3
5	The EAG disagrees with the company's modelling approach for OS	4.2.3.2.1.3
6	Uncertainty around the survival benefit for cabozantinib	3.2 and 4.2.3.2.1
7	The EAG disagrees with the company's HSUV used in the model	2.3.4, 3.3.3 and 4.2.5.1
8	The EAG considers that the company's approach to modelling concomitant treatment duration with SSAs in the model is inappropriate	4.2.6.2
9	The EAG considers that the company's approach to modelling subsequent treatments in the model is inappropriate	4.2.6.3

Abbreviations: CS, company submission; EAG, External Assessment Group; eNET, extra-pancreatic neuroendocrine tumours; HRQoL, health-related quality of life; HSUV, Health State Utility Values; OS, overall survival; pNET, pancreatic neuroendocrine tumours; PFS, progression-free survival; PH, proportional hazards

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the choice of relevant comparators for cabozantinib; the approach to modelling the epNET subgroup as a site-agnostic population; the choice of data set to model overall survival; the choice of HSUVs and the approach to modelling concomitant SSAs.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Delaying disease progression;
- Increasing survival.

Overall, the technology is modelled to affect costs by:

- It has higher total costs than current treatments.

The modelling assumptions that have the greatest effect on the ICER are:

- Inclusion of sunitinib and everolimus as comparators in the model;
- Use of the OS latest data cut-off from CABINET;
- The assumption that the OS HRs for BSC vs cabozantinib cannot exceed 1, when using the latest OS data available from CABINET;
- Separating the epNET subgroup into lung NET and epNET without lung;
- The approach taken to modelling subsequent treatment.

1.3 The decision problem: summary of the EAG's key issues

Table 2. Issue 1. The company's analysis does not represent the entire population considered in the company's marketing authorisation and excludes key comparators of interest

Report section	2.3.1, 2.3.3 and 3.4
Description of issue and why the EAG has identified it as important	The anticipated marketing authorisation for cabozantinib is for the treatment of [REDACTED] [REDACTED] [REDACTED]

	<u>The company's analysis considered BSC to be the only relevant comparator in the analysis.</u> The clinical evidence presented by the company is based on the CABINET population, which was heavily pretreated. Patients in the pNET cohort of CABINET had a mean number of 3 prior systemic treatments, excluding SSAs (2.7 and 2.6 in the cabozantinib and placebo arms, respectively), while patients in the epNET cohort had received a mean number of 2 prior treatments, excluding SSAs, (1.9 and 1.8, excluding SSAs in the cabozantinib and placebo arms, respectively). The EAG considered two populations in its assessment. The first directly reflects the mean CABINET population, where the EAG agrees that the main comparator of interest is BSC. These patients are heavily pretreated and at a late stage in the treatment pathway. The second population reflects the less heavily pretreated population, including patients who are at an earlier stage in the treatment pathway and may have cabozantinib as a second line systemic treatment option. This population is represented in CABINET by the subgroup of patients who had only received one prior systemic treatment other than an SSA. The EAG notes that 27% of cabozantinib patients and 32% of placebo patients in the pNET population in CABINET had received only one prior systemic therapy, while in the epNET population, 44% of cabozantinib patients and 48% of placebo patients had received one prior systemic treatment. These patients are not at the stage where the only available option would be BSC as many may also be eligible for other systemic treatments in the UK NHS, such as PRRT, everolimus or sunitinib. The EAG notes that even though the analyses for these two populations have been considered separately in the EAG report, it is the combined CABINET and less heavily pretreated populations that constitute the overall population eligible to receive cabozantinib. Comparisons of effectiveness with PRRT, sunitinib and everolimus were not provided by the company, with the company citing concerns about the heterogeneous nature of the disease resulting in no clear or consistent treatment pathway. While the EAG agrees that treatment for NETs can vary depending on a range of clinical factors, it considers that this is not a good rationale for excluding relevant comparators to cabozantinib.
What alternative approach has the EAG suggested?	The EAG conducted exploratory Bucher ITCs to compare the effect estimates from CABINET with studies identified from previously published NICE TAs for sunitinib and everolimus in NETs patients (evidence for the effectiveness of PRRT was not available from previous TAs to be used in the ITC). Although these comparisons required a simplification of the treatment pathway, the EAG considers them to be crucial to assess the cost-effectiveness of cabozantinib against all relevant systemic treatments. The EAG caveats the results of its exploratory ITC by the fact that there were marked differences in trial populations and in the number of previous treatments received across the different trials included in the ITCs, which the EAG was unable to address with the available data (but which the company could attempt to resolve – see below). The EAG could not use the subgroup

	of patients from CABINET who had only received one prior systemic treatment as these data were not available. The company presented a feasibility study around conducting an ITC (which led the company to the decision of not conducting the analysis - Appendix A of clarification responses). Nonetheless, the EAG considers that conducting an ITC would be of paramount importance in order to account for all relevant comparators to cabozantinib, albeit with an acknowledgement of the limitations of the analysis.
What is the expected effect on the cost-effectiveness estimates?	In the EAG's exploratory ITC, for PFS and OS, there were no statistically significant differences between cabozantinib and either everolimus or sunitinib for any group, with cabozantinib showing a numerical PFS advantage against the treatments and a numerical disadvantage for OS. The EAG considered external evidence to help resolve the apparent discrepancy in the direction of the PFS and OS results in its exploratory analysis. While the EAG appreciates that assumptions across different disease areas should be interpreted with caution, the external evidence shows that cabozantinib has a statistically significant survival advantage over everolimus in previously treated advanced renal cell carcinoma (METEOR trial) and a numerical but not statistically significant OS benefit against sunitinib (CABOSUN trial). After consideration of the evidence, the EAG concluded that assuming a PFS benefit for cabozantinib (i.e., using the Bucher exploratory HRs) and assuming equal survival for cabozantinib, everolimus and sunitinib in the economic model reflected a more clinically plausible approach, while still reflecting the uncertainty around the survival benefits for cabozantinib. This was supported by the views of the EAG's clinical experts that, with no evidence of a significant deterioration in quality of life, or a greater number of treatment-related deaths with cabozantinib, it would be unlikely that PFS would be better, while OS would be worse, with cabozantinib than BSC or other systemic treatments. The resulting ICERs against everolimus and sunitinib are █████ and █████ in pNET, █████ against everolimus in lung NETs and █████ in epNET without lung. The ICERs are all higher when the EAG base case assumptions are used.
What additional evidence or analyses might help to resolve this key issue?	The EAG notes that its ITC analysis is exploratory and should be interpreted with caution. The EAG considers that more advanced methods (such as matching-adjusted indirect comparisons - MAICs) could provide a more robust method of analysis for comparisons between cabozantinib and everolimus or sunitinib, taking into account differences in trial populations. MAICs would enable the CABINET population to be adjusted to more closely align with the populations from other trials, focusing on those patients who had fewer prior systemic treatments. Further analyses may also provide the opportunity to compare cabozantinib against PRRT, for which no relevant evidence was identified in the NICE TAs used for the EAG's exploratory analyses. Crucially, the EAG considers that the company should use the subgroup of patients from CABINET who have received one previous systemic treatment (other than SSAs) to more closely align the populations in CABINET and in the comparator studies and increase the robustness of any future ITCs conducted.

	The EAG considers that the company should provide ITC results (potentially using MAICs) for PFS and OS (and TTD whenever possible) for: • pNET patients, with comparisons against PRRT, sunitinib and everolimus; • epNET patients (without lung NETs), with comparisons against PRRT (for patients with functional epNETs who received prior chemotherapy) and everolimus (for patients with non-functional epNETs); • lung NET patients (for patients with non-functional tumours who received prior chemotherapy), with comparisons against everolimus. These additional analyses could reduce some of the uncertainties associated with the EAG's exploratory ITCs, particularly around OS. These could provide a more robust assessment with which to compare the effects of cabozantinib and other systemic treatments for patients included in the company's marketing authorisation.
Abbreviations: BSC, best supportive care; CS, company submission; CE, cost-effectiveness; EAG, External Assessment Group; eNET, extra-pancreatic neuroendocrine tumours; ITC, indirect treatment comparison; MAIC, matched-adjusted indirect comparison; OS, overall survival; pNET, pancreatic neuroendocrine tumours; PFS, progression-free survival; PH, proportional hazards; PRRT, Peptide receptor radionuclide therapy; TTD, time to treatment discontinuation	

Table 3. Issue 2. The site-agnostic approach for the epNET cohort is unjustified and does not appropriately capture the different prognosis and treatment response in lung NET patients

Report section	2.3.1, 3.2, 3.3.1.1, 3.3.2.1.1 and 3.4.2
Description of issue and why the EAG has identified it as important	The company used a site-agnostic approach for the analysis of the epNET population, combining the analysis for patients with GI NETs, lung NETs and other types of epNETs. The EAG's clinical experts highlighted that lung NET patients have a worse prognosis and fewer treatment options than other epNET patients. The EAG is, therefore, concerned that the grouping of epNET patients may not be appropriate and could mask differences in treatment response between lung NET patients and those with other types of epNETs.
What alternative approach has the EAG suggested?	The EAG requested that the company provide separate analyses for the CABINET patients with lung NETs and patients with other types of epNETs (without lung NETs included). The company provided PFS and OS results for both groups, and these were included in the EAG's assessment of clinical and cost-effectiveness. The company highlighted concerns about the limitations of the lung NET analysis, particularly in relation to the small number of lung NET patients in the trial, and the fact that the lung NET subgroup was not prespecified in the trial. The company also noted the differences in baseline characteristics between cabozantinib and placebo, particularly for race, mean disease duration, proportion of Grade 1 tumours and proportion of patients with functional disease. The company highlighted similar concerns for the epNETs (without lung) subgroup, although the EAG has fewer concerns about this group, due to greater patient numbers and less pronounced differences in baseline characteristics. The EAG acknowledges the uncertainty in these <i>post-hoc</i> analyses and the fact that there is a marked difference in baseline characteristics of patients in the cabozantinib and the placebo arms for the lung NET subgroup. These

	differences could potentially bias the results in favour of cabozantinib, as they appear to be indicative of a worse prognosis in the placebo group: [REDACTED] [REDACTED] [REDACTED] [REDACTED]. Nonetheless, the EAG considers this to be a crucial subgroup, given the expected difference in clinical outcomes for lung NETs when compared to the other epNETs.
What is the expected effect on the cost-effectiveness estimates?	The <i>post-hoc</i> analysis of the lung NET PFS and OS data from CABINET shows that cabozantinib is likely to have PFS benefits for all epNET patients (although of a much higher magnitude for lung NETs) and that while cabozantinib might not demonstrate a survival benefit in the pooled epNET population, it does show a statistically significant benefit for patients with lung NETs, when compared to placebo. The EAG cautions the results of the <i>post-hoc</i> analysis by the imbalance in the baseline characteristics in the lung NETs subgroup and notes, again, the likely bias in results in favour of cabozantinib. The EAG's preferred ICERs for the lung NETs subgroup were [REDACTED] vs BSC and [REDACTED] vs everolimus. In the epNET without lung population it was [REDACTED] vs BSC and [REDACTED] vs everolimus. Even with the company base case assumptions but using independent HRs for lung and epNET without lung, the ICER is dominated vs BSC for epNET without lung patients. It is important to note that only a small subset of lung NET patients would be eligible for everolimus.
What additional evidence or analyses might help to resolve this key issue?	The additional analyses suggested by the EAG in Key Issue 1 (more complex ITCs for PFS, OS and TTD) could be conducted for patients with lung NETs and those with epNETs (without lung). This could provide a more robust comparison with which to assess any differences in treatment response between the two populations.
Abbreviations: EAG, External Assessment Group; eNET, extra-pancreatic neuroendocrine tumours; GI, gastrointestinal; ITC, indirect treatment comparison; MAIC, matched-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation	

Table 4. Issue 3. The company's base case does not use the most recent OS data cut

Report section	2.3.4, 3.3.1.1 and 3.3.2
Description of issue and why the EAG has identified it as important	The company's base case uses the first OS DCO of the CABINET trial, which reported data until the CABINET trial was terminated in August 2023. During clarification, the company reported the results from an unplanned OS data sweep (updated DCO) that provided an additional 12 months of data. The company preferred the data from the first DCO. This was due to concerns around imbalances in prognostic factors having a greater impact on the updated DCO than in the first DCO ; a higher proportion of censored events; and a higher proportion of patients in the placebo arm who received subsequent treatments. The EAG does not consider that the impact of the imbalances in prognostic factors are an issue related to using a more mature OS data cut. It also notes that the OS data from the first DCO was immature, particularly for the pNET cohort, where the number of events for the final analysis was not

	achieved and median OS exceeded the median follow-up time (median OS: █ months for cabozantinib and █ months for placebo; median follow-up: 23.2 months for cabozantinib and 25.2 months for placebo). Concerns about the maturity of OS data was therefore an additional factor in the EAG's use of the updated DCO for OS analysis. The EAG acknowledges that the number of patients crossing over in CABINET is small, but they represent a substantial proportion of patients at risk of an OS event. Consequently, OS results with different adjustment methods are uncertain. This might have been accentuated in the updated DCO due to the convergence of the cabozantinib and placebo OS curves; thus, the estimated HR is closer to 1, making it more challenging to robustly adjust for crossover. Nonetheless, the EAG's preference is to use the latest OS data available, and notes that 12 months of additional OS trial data should not be ignored (as is the company's preference in their base case).
What alternative approach has the EAG suggested?	The EAG has used the updated OS DCO in their analysis. Given the company's concerns about the updated DCO, scenario analyses using the primary DCO were also included with the EAG's preferred assumption in an appendix.
What is the expected effect on the cost-effectiveness estimates?	The impact on the company's base case was large, with an increase in ICERs (vs BSC) from: █ to dominated in pNET, █ to █ in lung NET and █ to dominated in epNET without lung. In the lung NET/epNET without lung subgroups, these individual scenarios used the company assumption of applying the total epNET HR for OS and PFS to both subgroups.
What additional evidence or analyses might help to resolve this key issue?	Additional information could be provided by the company about the median treatment duration, median follow-up and baseline characteristics for the population included in the updated DCO.
Abbreviations: CS, company submission; DCO, data cutoff; EAG, External Assessment Group; OS, overall survival	

Table 5. Issue 4. The EAG disagrees with the company's modelling approach of PFS

Report section	4.2.3.1.2 and 4.2.3.1.3
Description of issue and why the EAG has identified it as important	The EAG disagrees with the company's assumption of PHs for PFS in CABINET and therefore disagrees with the use of a HR to estimate the BSC PFS curve in the model. Furthermore, the EAG is concerned that the company's choice of a lognormal PFS curve overpredicts PFS with cabozantinib between approximately 18 and 28 months.
What alternative approach has the EAG suggested?	The company provided a scenario analysis where the cabozantinib and BSC curves were independently fitted with lognormal curves in both populations. The EAG's preference is to use the Weibull model for the cabozantinib curves for both the pNET and epNET populations. Even though the AIC and BIC for this model is higher than the company's base case loglogistic choice, though not meaningfully (≥ 5), it provides a more conservative fit to the underlying PFS KM data. The EAG acknowledges the uncertainty around the tails of the KM curves due to a low number of patients at risk, however, notes that this further justifies taking the more conservative approach based on the Weibull curve.

	The EAG's preference to estimate the BSC arm is to use the lognormal curve, as it provides the best statistical fit. The EAG acknowledges the difference in distributions used for cabozantinib and BSC, however, considers that the use of the most conservative Weibull curve for cabozantinib (given the uncertainty around PFS estimates) and the best fitting curve for the placebo data in the trial is appropriate. The EAG also notes that cabozantinib is an active treatment (as opposed to placebo), which provides a clinical rationale for considering the appropriateness of different distributions for each curve.
What is the expected effect on the cost-effectiveness estimates?	The impact on the company's base case was modest, with a change in ICERs (vs BSC) from: [REDACTED] to [REDACTED] for pNET, [REDACTED] to [REDACTED] in lung NETs and [REDACTED] to [REDACTED] in epNET without lung.
What additional evidence or analyses might help to resolve this key issue?	No additional evidence is required, the EAG base case addresses this issue.
Abbreviations: BSC, best supportive care; EAG, External Assessment Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; PHs, proportional hazards	

Table 6. Issue 5. The EAG disagrees with the company's modelling approach for OS

Report section	Section 4.2.3.2.1.3
Description of issue and why the EAG has identified it as important	The EAG has some concerns with the company's selected loglogistic curves for the OS updated DCO. The latter are not compatible with using fixed hazard ratios as loglogistic curves imply time varying hazards. Given the minimal difference in AIC and BIC values, the EAG has selected the best fitting survival curves which are compatible with using a HR in the model. This was the exponential in the pNET population and the Weibull in the epNET population. In the lung NET population, the Weibull was also the best fitting and HR-compatible curve and the exponential provides the better fit in the epNET without lung group (for a HR-compatible curve). Both these curves have AICs/BICs within 1 of the best fitting curves. Furthermore, given the small number of patients crossing over in CABINET ([REDACTED] of patients in the pNET cohort [n=[REDACTED]] and [REDACTED] in the epNET cohort [n=[REDACTED]]), paired with a high percentage of crossover, the EAG considered that the RPSFTM approach provides a step in the right direction for adjusting the OS data from CABINET, when compared to the IPCW and the unadjusted ITT analysis. Nonetheless, the EAG notes that the RPSFTM method is still likely to produce uncertain estimates of survival given the small number of patients who crossed over.
What alternative approach has the EAG suggested?	The EAG has used RPSFTM HRs for lung NET patients. The EAG notes that for pNETs and epNETs without lung, the HRs were assumed to be 1 (see Key Issue 6 below).
What is the expected effect on the cost-effectiveness estimates?	In the cumulative modelling assumptions analysis; using EAG PFS assumptions, the latest DCO and independent HRs for lung NETs/epNET without lung (all other assumptions in line with company base case), the ICER for pNET changed from dominated to [REDACTED], in lung NET from [REDACTED] to [REDACTED] and in epNET without lung from dominated to [REDACTED].
What additional evidence or analyses might help to resolve this key issue?	Considering that each method of crossover adjustment is associated with limitations, results of the ITT analysis are also presented in the EAG's critique, as recommended by NICE DSU TSD 16.
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; CS, company submission; DCO, data cutoff; EAG, External Assessment Group; epNET, extra-pancreatic neuroendocrine tumour OS, overall survival; HRs,	

Table 7. Issue 6. Uncertainty around the survival benefit for cabozantinib

Report section	Section 3.2 and 4.2.3.2.1
Description of issue and why the EAG has identified it as important	The interim analysis methods used for the CABINET trial resulted in fewer patients being recruited than originally planned. This was particularly evident in the pNET cohort, where only half of the target number of patients were recruited (95 of the target 185), in comparison to 203 of the target 210 epNET patients. In addition to the small number of patients, the duration of trial follow-up was not likely to be long enough to observe statistically significant OS differences, with the company noting that OS data at the time of the first DCO was immature (discussed in Key issue 3). For the first OS DCO in CABINET, effect estimates numerically favoured cabozantinib vs placebo for OS, but differences were non-statistically significant in the ITT; IPCW and the RPSFTM methods in both NET cohorts. The lack of statistical significance in the OS results may be related to the maturity of the OS data, with ■■■ of patients experiencing an OS event during the first DCO. Furthermore, for the updated DCO, effect estimates numerically favoured placebo, but differences were not statistically significant for the ITT; IPCW (except for epNETs) and the RPSFTM methods. The updated DCO data may have similar limitations relating to data immaturity as the first DCO, although the OS data sweep had an additional 12-month follow-up. The EAG notes that the trials included in TA449 and TA539 for NETs (RADIANT-3 and RADIANT-4 for everolimus vs BSC and Raymond <i>et al.</i> 2011 for sunitinib vs BSC) also showed numerically advantageous but non-statistically significant HRs (both ITT and RPSFTM) for OS for the respective treatments vs placebo. The follow-up period across all the NET trials (including CABINET) was not dissimilar (approximately 23 months in CABINET, compared to 17 and 21 months for the comparator trials), which may be an indication of follow-up being too short to capture an observable survival benefit in NETs. In the EAG's exploratory ITC against everolimus and sunitinib, for both the original and the updated DCO, results numerically favoured survival for the comparators but were not statistically significant (for both the pNET and epNET cohorts). Overall, the EAG notes a paramount level of uncertainty around the relative effectiveness of cabozantinib vs BSC; everolimus and sunitinib on OS.
What alternative approach has the EAG suggested?	The EAG's preferred ICERs have used HRs of 1 for OS between cabozantinib and BSC; everolimus and sunitinib. The exceptions to this were the following scenarios: - lung NETs; where for CABINET the HR was statistically significant and favoured cabozantinib; - first DCO for the overall pNET and epNET cohorts; where the HRs favoured cabozantinib but were not statistically significant.
What is the expected effect	The impact of using HRs of 1 is incorporated as part of EAG OS preferences

on the cost-effectiveness estimates?	(listed in key issue 5 above). It is the primary driver of the significantly decreased ICER from EAG OS preferences for the updated DCO.
What additional evidence or analyses might help to resolve this key issue?	Longer follow-up data for cabozantinib on OS.

Abbreviations: BSC, best supportive care; DCO, data cutoff; EAG, external assessment group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPCW, Inverse probability of censoring weights; ITC indirect treatment comparison; ITT, intention to treat; OS, overall survival; RPSFTM, rank preserving structural failure time model; TA, technology appraisal

Table 8. Issue 7. The EAG disagrees with the company's HSUV used in the model

Report section	Section 2.3.4, 3.3.3 and 4.2.5.1
Description of issue and why the EAG has identified it as important	In the company's base case, the HSUVs used for the progression-free health state in the economic model were derived from a regression analysis of the HRQoL sub-study of the CABINET trial. The company initially fitted two linear MMRMs to the HRQoL sub-study data for both the pNETs and epNETs populations, one including only fixed effect terms (the 'simplified' model) and one including additional fixed effect terms corresponding to key prognostic factors (the 'full' model). The company ultimately decided that the simplified model was more appropriate. The EAG has concerns about the quality of the HRQoL sub-study, particularly in relation to recruitment methods and low patient numbers (discussed in Sections 2.3.4 and 3.3.3). There are also several concerns about the methodology used to derive the utility values used in the model, as follows: • Insufficient justification was given for the use of a linear MMRM structure, which does not give appropriate constraints for the value of HSUVs; • The company did not provide the utility values for the full model, either in the CS or the economic model; • The company did not provide fitted coefficients or p-value estimates for either model; • The EAG has not seen any evidence that a systematic approach was used to select the fixed effect terms for inclusion in either model; • Both models neglected to include key terms which would be likely to affect patient quality of life, including whether the patient was receiving treatment with cabozantinib, and whether the patient was experiencing AEs.
What alternative approach has the EAG suggested?	The EAG considers that until the EAG's concerns around the HRQoL data and analysis are mitigated by the company, it is not appropriate to use HSUVs derived from the CABINET HRQoL sub-study in the economic model. The EAG has used alternative sources to parametrise the HSUV for the progression-free health state in the EAG base case (RADIANT-4 for the epNETs population and Swinburn <i>et al.</i> 2012 for the pNETs population). Utility values for the progressed disease health state were informed by the same sources as for the progression-free health state for both populations. The progression-free and progressed disease utility values for the pNET populations were 0.771 and 0.612, respectively, in the EAG analysis; while for the epNET population were 0.807 and 0.725, respectively. Although the EAG acknowledges the limitations of Swinburn <i>et al.</i> 2012, it considers that this is still a preferable source to the CABINET HRQoL sub-study, and no more appropriate alternative was identified for the pNETs

	population.
What is the expected effect on the cost-effectiveness estimates?	The impact of using the EAG preferred HSUV changes the company base case ICER from [REDACTED] to [REDACTED] in pNET patients, [REDACTED] to [REDACTED] in lung NET and [REDACTED] to [REDACTED] in epNET without lung patients. The epNET health state utility increases and the pNET utility decreases in the EAG base case compared to the company's base case. As such, any benefit from remaining progression free or through overall survival is increased in epNET and decreased in pNET compared to the company's base case.
What additional evidence or analyses might help to resolve this key issue?	The EAG's preference would be to use the CABINET HRQoL sub-study to parametrise the HSUV for the progression-free health state, if the following information is provided: • Details for the rationale for drop-out and missing data from the HRQoL sub-study; • Updated regression analyses including fixed effect terms for treatment and/or AEs; • Fitted coefficients, estimated p-values, goodness-of-fit statistics, and diagnostic plots for the updated regression analyses; • Full justification for the selection of terms for inclusion in the full regression model; • Justification for use of a linear MMRM rather than a generalised model.
Abbreviations: AE, adverse event; CS, company submission; EAG, External Assessment Group; epNETs, extra-pancreatic neuroendocrine tumours; HRQoL, health-related quality of life; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; MMRM, mixed model for repeated measures; pNETs, pancreatic neuroendocrine tumours.	

Table 9. Issue 8. The EAG considers that the company's approach to modelling concomitant treatment duration in the model is inappropriate

Report section	4.2.6.2
Description of issue and why the EAG has identified it as important	In the company's base case, a proportion of patients was assumed to receive treatment with concomitant SSAs alongside cabozantinib or BSC from baseline. The duration of treatment with SSAs was assumed to align with TTD from the CABINET trial; in particular, duration of treatment with SSAs in the BSC arm was aligned with TTD for placebo in the CABINET trial. Costs for acquisition and administration of SSAs were applied up until treatment discontinuation for the relevant proportion of patients. Separately, a proportion of patients incurred costs for subsequent treatment with SSAs, applied when patients entered the progressed disease health state. The EAG considers that the company's approach is inconsistent with both the EAG's and the company's clinical advisors' description of the use of concomitant treatment with SSAs in UK clinical practice. In particular, patients receiving concomitant treatment with SSAs would be expected to continue receiving treatment indefinitely, as SSAs would be used to manage symptoms of functional NETs, regardless of which (if any) systemic treatment was being used. There is no reason why a patient would be expected to discontinue treatment with concomitant SSAs at the point of discontinuing the primary systemic treatment, and there is also no rationale for reintroducing concomitant SSA as a subsequent treatment after disease progression.

	Furthermore, the EAG disagrees with the company's approach of assuming that the proportion of patients receiving concomitant SSAs in the model could be informed by the proportion of patients being treated with SSAs at baseline in the CABINET trial. The EAG's clinical experts stated that, in UK clinical practice, the majority of patients receiving systemic treatment with SSAs would discontinue treatment upon starting another systemic treatment. The EAG identified a table entitled '<i>Concomitant Medications</i>' for both the epNETs and pNETs populations in the CSR (Tables 14.3.1.2.1.a and 14.3.1.2.1.b), including SSAs but at clarification the company stated that these tables in fact represented '<i>subsequent treatment only</i>'. The EAG is still unclear if the CSR data reported concomitant SSA use. Due to the relatively high costs of SSAs, the approach to modelling discontinuation of SSAs has a major effect on the cost-effectiveness of cabozantinib.
What alternative approach has the EAG suggested?	The EAG's preferred approach is to assume that patients receiving concomitant SSAs would continue to do so from baseline until death, accruing acquisition and administration costs accordingly. The EAG acknowledges that in some cases, patients would discontinue treatment with concomitant SSAs before death, so this approach may overestimate the cost of concomitant SSAs in all treatment arms; however, the EAG considers that this approach is a more appropriate representation of UK clinical practice than the company's preferred approach. As an alternative, the EAG also considered a scenario in which patients were assumed to receive concomitant SSAs up to progression rather than treatment discontinuation; thereafter, concomitant SSA use was modelled as a subsequent treatment, as in the company's base case. The EAG also explored a scenario in which the proportion of patients receiving concomitant treatment with SSAs was aligned with the proportion of patients with functional NETs in the CABINET trial, pooled between treatment arms (████ in the epNETs population and █████ in the pNETs population; lung NETs and non-lung epNETs were not considered separately due to lack of data).
What is the expected effect on the cost-effectiveness estimates?	The impact of using the EAG preferred concomitant treatment assumption (linked to OS) changed the company's base case ICER from █████ to █████ in pNET patients, █████ to █████ in lung NET and █████ to █████ in epNET without lung patients. The EAG scenario for patients receiving treatment up to progression changed the EAG base case ICER from █████ to █████ in pNET patients, █████ to █████ in lung NET and █████ to █████ in epNET without lung patients. The reason the effect differs for lung, pNET and epNET without lung is that the OS is assumed to be equal for cabozantinib and BSC in the latter subgroups with PFS being for cabozantinib being superior to BSC. As such, discontinuations will occur relatively later in patients receiving BSC. Lung NETs have an OS and PFS benefit in the base case, so there is already a higher concomitant treatment cost for cabozantinib when discontinuation is linked to OS, so changing it to discontinuation on progression results in relatively lower costs.
What additional evidence or analyses might help to	The company should clarify if the table entitled '<i>Concomitant Medications</i>' for both the epNETs and pNETs populations in the CSR (Tables 14.3.1.2.1.a

resolve this key issue?	and 14.3.1.2.1.b), including SSAs, is in fact for concomitant treatments received in the trial.
Abbreviations: BSC, best supportive care; EAG, External Assessment Group; NETs, neuroendocrine tumours; PFS, progression-free survival; SSA, somatostatin analogue; TTD, time to treatment discontinuation.	

Table 10. Issue 9. The EAG considers that the company's approach to modelling subsequent treatments in the model is inappropriate

Report section	4.2.6.3
Description of issue and why the EAG has identified it as important	Subsequent treatment costs in the model were applied as a one-off cost to the proportion of patients entering the progressed disease health state each cycle, estimated as the difference in occupancy of this health state between cycles. This one-off cost was informed by the proportion of patients receiving individual subsequent treatments, sourced from the CABINET trial, and rescaled to sum to 100% of the patients receiving any subsequent treatment. The EAG has two concerns with the company's approach to modelling subsequent treatment, as follows: • The company's approach of applying the one-off subsequent treatment costs to the difference in the proportion of patients occupying the progressed disease health state in consecutive cycles does not account for the fact that as well as entering the progressed disease health state from the progression-free health state, patients are also leaving to the death state each cycle. Thus, the difference between health state occupancy is less than the proportion of patients progressing each cycle. The company's approach, therefore, is likely to considerably underestimate subsequent treatment costs. • The company's approach of rescaling the proportion of patients receiving individual subsequent treatments implicitly assumes that patients would receive at most one subsequent treatment; however, the EAG's clinical experts stated that many patients would be expected to receive multiple lines of subsequent treatment. Together, these issues have a major impact on the resulting ICER for cabozantinib.
What alternative approach has the EAG suggested?	For the CABINET trial population, the EAG updated the implementation of subsequent treatment by applying the subsequent treatment cost to patients leaving the progression-free health state, rather than patients entering the progressed disease health state. To account for patients moving to the death state instead of the progressed disease state from the progression-free state, the proportions of patients receiving subsequent treatment were taken as proportions of the whole patient population, rather than the proportions of patients surviving to progression. This is a simplification, as it assumes that the ratio of patients dying to patients progressing when leaving the progression-free health state is constant over time, but the EAG considers that this is still preferable to the company's approach. For the CABINET population, the EAG also allowed for patients to receive more than 1 subsequent treatment in the model. The distribution of subsequent treatments received was taken from CABINET. For the exploratory analysis of the less heavily pretreated population, the

	EAG chose to exclude subsequent treatments altogether (i.e., after cabozantinib, everolimus or sunitinib), as the EAG was unable to identify appropriate data to parametrise the proportion of patients receiving subsequent treatments for sunitinib and everolimus. This was also the approach taken in TA449 and TA539. ^{1, 2}
What is the expected effect on the cost-effectiveness estimates?	The impact of using the EAG preferred subsequent treatments for the CABINET population changed the company's base case ICER vs BSC from [REDACTED] to [REDACTED] in pNET patients, [REDACTED] to [REDACTED] in lung NET and [REDACTED] to [REDACTED] in epNET without lung patients. The impact of using the EAG preferred assumed no subsequent treatment in the less heavily pretreated population changed the ICER vs everolimus and sunitinib from [REDACTED] and [REDACTED] to [REDACTED] and [REDACTED] in the pNET population. In the lung NET population the ICER vs everolimus changed from [REDACTED] to [REDACTED]. In the epNET without lung population the ICER vs everolimus changed from [REDACTED] to [REDACTED].
What additional evidence or analyses might help to resolve this key issue?	The availability of more survival data (for example, post-progression survival) would remove the need for assumptions to calculate proportion of patients incurring subsequent treatment costs each cycle. Data to inform the proportion of patients expected to receive subsequent treatments after cabozantinib (at an earlier line); sunitinib; or everolimus would allow subsequent treatment costs to be included in the less heavily pretreated population analysis.
Abbreviations: EAG, External Assessment Group	

1.4 Other key issues: summary of the EAG's view

The EAG identified some secondary issues that had minimal impact on the ICER but were considered to be more appropriate than the company's base case approach. These are as follows:

1. TTD for cabozantinib should be modelled by KM curve, section 4.2.3.2.3;
2. AEs incorrectly applied in the model 4.2.4.1;
3. EAG identified more appropriate alternative disutilities for hypertension, small intestinal obstruction and embolism 4.2.5.2.1;
4. The EAG does not consider the dose hold is appropriate 4.2.6.1.1;
5. The EAG has identified more appropriate alternative disease management costs 4.2.6.5.1;
6. The PSSRU data should be taken from the latest available costs source and should be corrected to more accurately reflect administration times. 4.2.6.5.

1.5 Summary of EAG's preferred assumptions and resulting ICER

The resulting deterministic ICERs from the cumulative EAG preferences are listed in Table 11, Table 12 and Table 13 below for pNET, lung NET and epNET without lung, respectively. Probabilistic ICERs are reported in Section 6.

Table 11. EAG's preferred model assumptions pNET (deterministic results)

Preferred assumption	Key issue/secondary issue number	Cumulative ICER vs Sunitinib (£)	Cumulative ICER vs Everolimus (£)	Cumulative ICER vs BSC (£)
Company base case	—	████	████	████
Independently modelled PFS BSC curve + EAG choice of cabozantinib PFS curve (Weibull)	Key issue 5	████	████	████
Latest DCO (Loglogistic)	Key issue 3	████	████	████████████████ ████████
EAG choice of OS curves (Weibull) Cap OS HRs for BSC at 1 RPSFTM	Key issue 5 Key issue 6	████	████	████
TTD KM curve	Secondary issue 1	████	████	████
Concomitant treatment duration	Key issue 8	████	████	████
AEs applied 1st cycle	Secondary issue 2	████	████	████
EAG HSUV	Key issue 7	████	████	████
Alternate AE disutilities	Secondary issue 3	████	████	████
Dose hold removed	Secondary issue 4	████	████	████
PSSRU 2024+correction	Secondary issue 5	████	████	████

EAG alternate disease management costs	Secondary issue 6	████	████	████
Exclude subsequent treatments (less heavily pretreated population only)	Key issue 9	████	████	NA
EAG preferred subsequent treatment (CABINET population)	Key issue 9	NA	NA	████

* BSC dominates as using the latest DCO implies using a HR for OS which favours BSC vs cabozantinib, the EAG base case caps the OS HR for cabo vs BSC at 1.

Abbreviations: AE, adverse events; BSC, best supportive care; DCO, data cut-off; EAG, economic assessment group; HSUV, health state utility; ICER, incremental cost-effectiveness ratio; IPCW, inverse probability of censoring weights; NA, not available; NMB, net monetary benefit; PSSRU, personal social services research unit; QALY, quality adjusted life years; RPSFTM, rank preserving structural failure time model; WTP, willingness to pay.

Table 12. EAG's preferred model assumptions lung NETs (deterministic results)

Preferred assumption	Key issue/secondary issue number	Cumulative ICER vs Everolimus (£)	Cumulative ICER vs BSC (£)
Company base case	—	████	████
Independent BSC HR for epNETs without lung	Key issue 2	████	████
EAG choice of cabozantinib PFS curve (Weibull)	Key issue 5	████	████
Latest DCO OS (Gompertz)	Key issue 3	████	████
EAG choice of OS curves (Weibull) RPSFTM	Key issue 5 Key issue 6	████	████
TTD KM curve	Secondary issue 1	████	████
Concomitant treatment duration	Key issue 8	████	████
AEs applied 1st cycle	Secondary issue 2	████	████
EAG HSUV	Key issue 7	████	████
Alternate AE disutilities	Secondary issue 3	████	████
Dose hold removed	Secondary issue 4	████	████
PSSRU 2024+correction	Secondary issue 5	████	████

EAG alternate disease management costs	Secondary issue 4	████	████
Exclude subsequent treatments (less heavily pretreated population only)	Key issue 9	████	NA
EAG preferred subsequent treatment (CABINET population)	Key issue 9	NA	████

Abbreviations: AE, adverse events; BSC, best supportive care; DCO, data cut-off; EAG, economic assessment group; HSUV, health state utility; ICER, incremental cost-effectiveness ratio; IPCW, inverse probability of censoring weights; NA, not available; NMB, net monetary benefit; PSSRU, personal social services research unit; QALY, quality adjusted life years; RPSFTM, rank preserving structural failure time model; WTP, willingness to pay.

Table 13. EAG's preferred model assumptions epNETs without lung (deterministic results)

Preferred assumption	Key issue/secondary issue number	Cumulative ICER vs Everolimus (£)	Cumulative ICER vs BSC (£)
Company base case	—	████	████
Independent BSC HR for epNETs without lung	Key issue 2	████	████████████████ ██████
EAG choice of cabozantinib PFS curve (Weibull)	Key issue 5	████	████████████████ ██████
Latest DCO OS (Loglogistic)	Key issue 3	████	████████████████ ██████
EAG choice of OS curves (exponential) Cap OS HRs for BSC at 1 (RPSFTM)	Key issue 5 Key issue 6	████	████
TTD KM curve	Secondary issue 1	████	████
Concomitant treatment duration	Key issue 8	██████	████
AEs applied 1st cycle	Secondary issue 2	██████	████
EAG HSUV	Key issue 7	██████	████

Alternate AE disutilities	Secondary issue 3	██████	██████
Dose hold removed	Secondary issue 4	██████	██████
PSSRU 2024+correction	Secondary issue 5	██████	██████
EAG alternate disease management costs	Secondary issue 4	██████	██████
Exclude subsequent treatments (less heavily pretreated population only)	Key issue 9	██████	NA
EAG preferred subsequent treatment (CABINET population)	Key issue 9	NA	██████

* BSC dominates as the HR for epNET without lung for OS favours BSC vs cabozantinib, the EAG base case caps the OS HR for cabo vs BSC at 1.

Abbreviations: AE, adverse events; BSC, best supportive care; DCO, data cut-off; EAG, economic assessment group; HSUV, health state utility; ICER, incremental cost-effectiveness ratio; IPCW, inverse probability of censoring weights; NA, not available; NMB, net monetary benefit; PSSRU, personal social services research unit; QALY, quality adjusted life years; RPSFTM, rank preserving structural failure time model; WTP, willingness to pay.

For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6 of the report.

2 Introduction and background

2.1 Introduction

This report contains the External Assessment Group (EAG)'s critique of the clinical and cost-effectiveness evidence submitted for the Single Technology Appraisal (STA) of cabozantinib (Ipsen) for the treatment of people with advanced neuroendocrine tumours (NETs) which have progressed after at least one systemic treatment. The anticipated marketing authorisation for cabozantinib in this indication is “ [REDACTED]

[REDACTED]

[REDACTED]

2.2 Background

The company submission (CS) provides an overview of NETs, including the aetiology, symptoms, prevalence, disease classification, diagnosis and symptom burden (Section 1.3 of the CS). It also provides a description of cabozantinib, its mechanism of action, current indications, and methods of administration and dosage (Section 1.2 of the CS). Included below is the EAG's summary of the key background information presented in the CS, supplemented by information provided by the EAG's clinical experts.

Well-differentiated NETs contain cancerous cells that mimic normal body cells and have a prolonged course of disease. While these can develop in most organs, they are mainly common in the gastrointestinal (GI) tract, lungs, and pancreas. Advanced NETs can be grouped into categories based on whether the location of the primary tumour site is in the pancreas (pNET) or any other location outside of the pancreas (epNET). The epNET category includes a broad range of tumours, including those located in the gastrointestinal (GI) tract or the lung. Tumours in the lung tend to be considered separately to those in the GI tract, and GI tumours can be categorised based on whether they are in the midgut (jejunum, ileum and cecum) or non-midgut. Common risk factors for the development of NETs include a family history of cancer as well as body mass index, diabetes, smoking and alcohol consumption.

In the early stages of disease, NETs produce a range of symptoms which vary depending on tumour location. The associated non-specific symptoms often result in delays in diagnosis, with a 2018 survey of UK patients with NETs reporting that the time from first symptom to diagnosis was an average of 53.8 months.⁴ Patients with NETs, therefore, tend to be older, with a median age in

England of 62 years (Interquartile range [IQR]63-73), and at a more advanced stage of the disease when diagnosed, at which point many have a poor prognosis.⁵

Disease classification of NETs is complex and based on a range of factors including primary tumour site (pNETs or epNETs), histological characteristics, tumour stage and functional status. Diagnosis is based on a combination of tests, the choice of which depends on the patient's symptoms, and can include endoscopic procedures, radiological or radionuclide scans, biochemical testing and histopathologic assessments. The combined results from these tests are used to determine the most appropriate treatment pathway for each patient.

Patients diagnosed with advanced NETs have a poor prognosis, with the CS reporting that five-year survival for patients with Stage IV NETs is below 50% for all tumour sites. At 5 years, survival rates are lowest for patients with primary tumour sites in the lung (12%), colon (18%), stomach (21%), rectum (22%) and pancreas (26%).⁵ NETs can also have a major impact on health-related quality of life (HRQoL), with the greatest effects seen in patients who have either functional disease (approximately 30% to 40% of pNET patients and 70% of epNET patients) or progressive disease.

2.2.1 Current treatment pathway

Current UK management of NETs is based on the guidelines provided by the European Neuroendocrine Tumor Society (ENETS, 2023) and the European Society for Medical Oncology (ESMO 2020 and 2021).⁶⁻¹¹ Treatment for unresectable or metastatic NETs aims to control symptoms, slow tumour growth and delay disease progression. The treatment pathway varies depending on a range of factors, such as primary tumour site and functional status, as discussed in Section 2.2.

For most patients who have advanced disease, first-line systemic treatment options are somatostatin analogues (SSAs), such as lanreotide. If disease continues to progress despite treatment with an SSA, patients can then be prescribed other systemic treatments, including:

- peptide receptor radionuclide therapy (PRRT): ¹⁷⁷Lutetium-DOTATATE octreotide;
- mammalian target of rapamycin (mTOR) inhibitor: everolimus;
- tyrosine kinase inhibitor (TKI): sunitinib; or
- chemotherapy: Folinic Acid, Fluorouracil, and Oxaliplatin (FOLFOX), Capecitabine and temozolomide (CAPTEM), Streptozotocin (STZ), 5-fluorouracil (5-FU).

If patients progress despite the above treatment options, they will be offered best supportive care (BSC). This is generally considered the final line in the treatment pathway and does not involve any further systemic therapies or chemotherapy. Instead, it aims to help control the symptoms of the disease, through the provision of treatments such as antibiotics and pain relief.

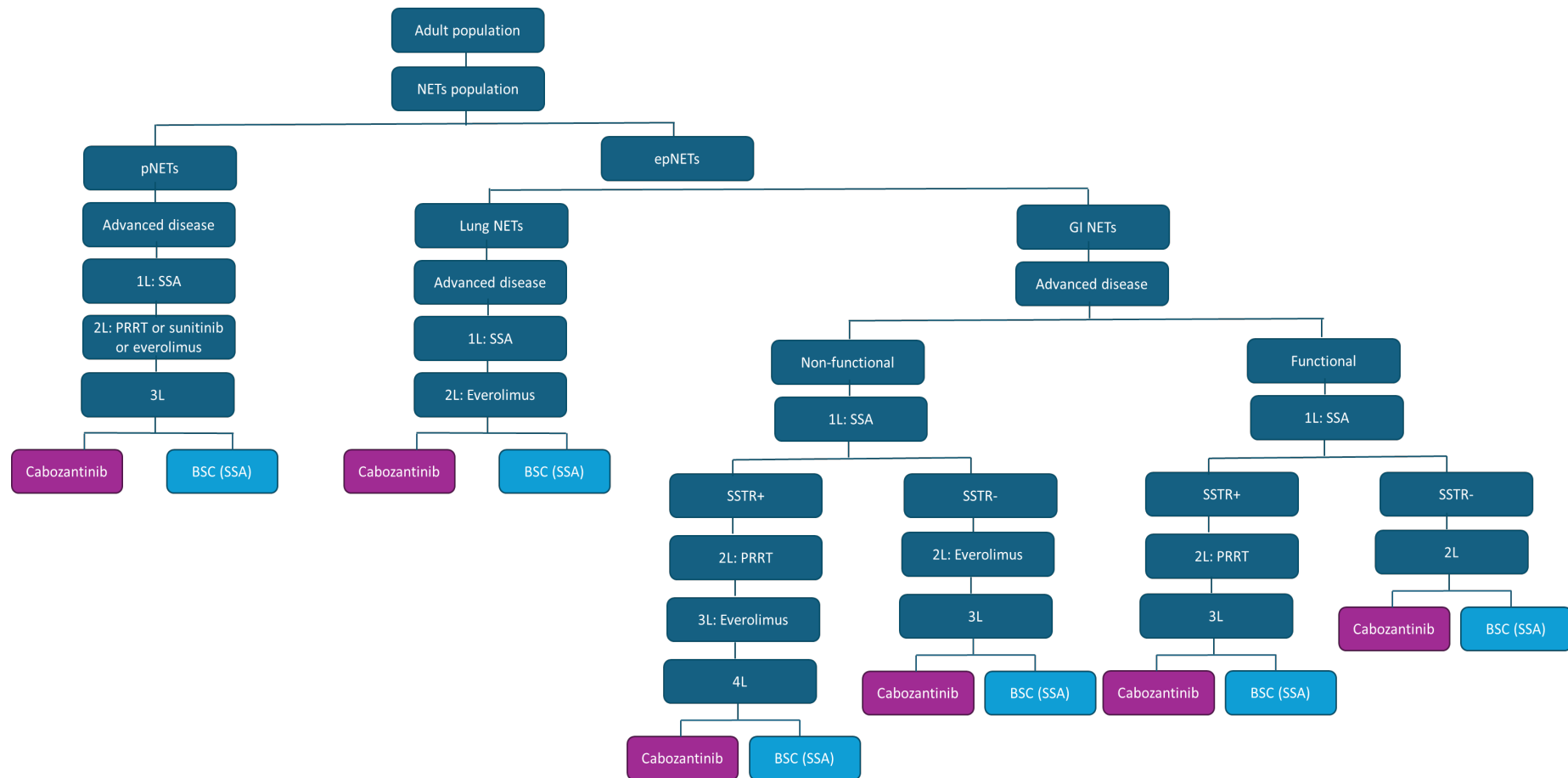
The company provided a diagram of the treatment pathway (Figure 4 of the CS), with separate pathways detailed for patients in the pNET and epNET cohorts. While the EAG's clinical experts broadly agreed with the company's summary of the treatment pathway, they noted that some key aspects of the disease that affect treatment eligibility, such as functional status, were not considered. They also noted that, for epNETs, the treatment pathway should differentiate between lung and GI tumours. The company provided an additional diagram of the treatment pathway used in the budget impact model (Figure 1), which the EAG considers to be a more accurate representation of the treatment pathway for NETs in NHS clinical practice. As discussed in Section 2.2, treatment for pNETs and epNETs varies between patients, and disease characteristics, however, the EAG considers that Figure 1 reflects the current treatment pathway for most patients in the NHS.

While the EAG considers that Figure 1 is a reasonable reflection of the current treatment pathway, it disagrees with the company's proposed positioning of cabozantinib in the pathway, when considering its anticipated marketing authorisation (**Key issue 1**). Given the company's positioning of cabozantinib as a second (or further) line systemic treatment option (excluding previous SSAs), cabozantinib could offer an alternative treatment to either PRRT, everolimus or sunitinib (depending on which treatment was given first and the type of tumour). For instance, under the current treatment pathway, a pNET patient could be eligible for PRRT, sunitinib, or everolimus as a first line systemic treatment (excluding prior SSA). Upon progression, the patient would be eligible to receive any of the alternative treatments (subject to their specific disease characteristics), including cabozantinib. For example, a patient who initially received PRRT and progressed while on treatment, would then be eligible to receive either sunitinib, everolimus or cabozantinib, assuming their disease characteristics permit the use of each of these treatment options. BSC is likely to only be considered later in the pathway, after the patient had exhausted all active treatment options, or when patients need a temporary break from active treatment.

While most pNET patients are eligible for multiple systemic therapies, other groups have fewer treatment options available to them. However, the EAG considers that even some of these patients are eligible for more treatments than solely BSC. For instance, patients with non-functional lung NETs who have chemotherapy will then be eligible for either cabozantinib or everolimus. As such,

while the EAG acknowledges that there are some populations where cabozantinib may be considered an alternative to BSC (such as for patients with functional GI NETs or functional lung NETs), it notes that PRRT, everolimus and sunitinib are also relevant comparators to cabozantinib. The EAG considers the company's representation of cabozantinib in the treatment pathway, and crucially, the choice of comparator for cabozantinib in the company's submission, to be an oversimplification of the decision problem (**Key issue 1**). This forms a key discussion point throughout the EAG's critique and is discussed in more detail in Sections 2.3.1 and 2.3.3.

Figure 1. Current treatment pathway for pNETs and epNETs and the company's proposed positioning of cabozantinib. Reproduced from the budget impact model in the CS



Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line ; 4L, 4th line ; BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; GI NETs, gastrointestinal neuroendocrine tumours; pNETs, pancreatic neuroendocrine tumours; PRRT, peptide receptor radionuclide therapy; SSA, Somatostatin analogue; SSTR+, Somatostatin receptor positive ; SSTR-, Somatostatin receptor negative

2.3 Critique of the company's definition of the decision problem

The company provided a summary of the final scope issued by the National Institute for Health and Care Excellence (NICE), together with the rationale for any deviations from the decision problem. The company has presented evidence that aligns with the intervention and outcomes defined in the NICE final scope. However, there are fundamental differences between the NICE final scope and the CS in relation to the population and the comparators, which may impair the decision-making process for the full NETs patient population. These differences are highlighted in more detail in Table 14, along with a summary of the final scope issued by NICE and the decision problem addressed in the CS. Further detail about the EAG's critique is provided in Sections 2.3.1 to 2.3.5.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	Adults with advanced pancreatic or extra-pancreatic neuroendocrine tumours (pNETs or epNETs) that have progressed after systemic treatment	As per the NICE final scope	N/A	The anticipated marketing authorisation for cabozantinib is “ [REDACTED] ” [REDACTED] [REDACTED] [REDACTED] [REDACTED] The EAG notes that the population in CABINET was heavily pretreated. Patients in the pNET group had received a mean number of three previous systemic treatments, excluding SSAs, in the cabozantinib and placebo arms (2.7 and 2.6, respectively), while patients in the epNET cohort had received a mean number of two systemic treatments, excluding SSAs (1.9 and 1.8, respectively). Therefore, patients were at a late stage in the treatment pathway, where the only remaining option for most patients in the NHS would be BSC. In contrast, the marketing authorisation positions cabozantinib as a second (or further) systemic treatment line (other than previous treatment with an SSA), at which stage other systemic therapies are treatment options in the NHS. Therefore, the EAG considers that there are two populations of interest for this appraisal:

				1. The population, and the evidence, included in the CABINET trial, which are most appropriate to inform a scenario where cabozantinib is given as a fourth (or further) line of systemic treatment for pNET patients (excluding previous SSAs); and as a third (or further) line of systemic treatment for epNET patients, excluding previous SSAs. In this context, the EAG agrees that the main comparator of interest is BSC. Equally, for functional lung NETs, BSC is the most relevant comparator, as chemotherapy is the only available systemic treatment (excluding SSAs) which would be given before cabozantinib. 2. The less heavily pretreated population. The evidence for this analysis is sourced from the EAG's exploratory indirect treatment comparison (ITC), and all the results presented are part of an exploratory analysis, as discussed in Section 3.4. The appropriate comparators in this scenario are everolimus, sunitinib and PRRT; depending on tumour location; functional status and SSTR status.
Intervention	Cabozantinib	As per the NICE final scope	N/A	N/A

Comparator(s)	Established clinical management without cabozantinib, including but not limited to: • Best supportive care (BSC) • Chemotherapy • Other systemic treatments	Best supportive care	The company did not consider chemotherapy or other systemic treatments to be appropriate comparators. The CS states that systemic therapies are not relevant comparators due to the heterogeneous nature of the disease and the resulting narrow labels for systemic treatment options, resulting in no clear or consistent treatment pathway. The company highlighted how chemotherapy regimens can be considered for off-label use but noted that there is a limited evidence base and that chemotherapy is not commonly used for well-differentiated NETs, for which cabozantinib is indicated. Finally, the company highlighted a lack of relevant RCTs identified in the company's SLR which evaluated other	The EAG's clinical experts agreed that treatment for NETs varies depending on a range of factors, such as tumour location, functional status and disease severity. However, while the treatment pathway may vary, there are similarities regarding which treatment options are available, primarily dependent on whether a tumour is classed as a pNET, epNET or lung NET. As discussed in Sections 2.3.3 and 3.4, the EAG's clinical experts agreed that the use of chemotherapy is relatively limited and generally reserved for patients with higher grade disease, aggressive tumours, or those with few treatment options available. The EAG therefore considers the exclusion of chemotherapy as a comparator to be a reasonable decision. However, it considers that PRRT, sunitinib and everolimus should have been included for the population to reflect the company's anticipated marketing authorisation. Finally, as discussed in Sections 2.3.3, 3.1 and 3.4, the EAG is concerned that the company's rationale for excluding RCTs where less than 70% of patients received one relevant prior systemic treatment, and results were not stratified by patients having received at least one prior systemic therapy, as this

			systemic treatments. Although there were RCTs investigating other systemic treatments in the UK, these were excluded from the review as less than 70% of patients received a relevant prior line of therapy. The company did not consider these patients to be comparable to the patients in the CABINET trial.	might have led to relevant comparator data being missed.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • symptom control • adverse effects of treatment • health-related quality of life	As per the NICE final scope	N/A	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs out	• The cost-effectiveness of cabozantinib versus BSC has been evaluated, in line with the NICE reference case • The time horizon for assessing costs was set to a lifetime horizon, which is sufficiently long to capture the majority of costs and benefits associated with the use of cabozantinib • Costs were considered from an NHS and PSS perspective	N/A	N/A

	outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services (PSS) perspective.	• A patient access scheme (PAS) for cabozantinib was included in the analysis		
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Pancreatic NETs • Extra-pancreatic NETs (including by tumour location) • Other characteristics of NETs (for example, functioning status, differentiation status, Ki-67 index and somatostatin receptor expression)	The following subgroups are considered in the economic model, informed by the randomised, ITT cohorts of the CABINET trial: • Pancreatic NETs • Extra-pancreatic NETs Prespecified subgroup analyses for PFS are presented for key patients characteristics, including primary tumour site in epNETs (midgut GI/unknown versus non-midgut GI/lung/other), tumour grade and differentiation status. Post-hoc subgroup analyses are presented for PFS by specific tumour location in epNETs (i.e. lung, GI tract or other) for completeness but are not sufficiently robust to inform decision-making. Subgroup analysis by other characteristics of NETs (functional status, Ki-67 index and somatostatin receptor expression)	The company considered pNET and epNET groups separately throughout the submission. The other characteristics in the NICE final scope (functioning status, differentiation status, Ki-67 index and somatostatin receptor expression) were not included as subgroups because this information was not available from the CABINET trial.	The company's separation of tumours into pNETs and epNETs is in line with the NICE final scope and supports the views of the EAG's clinical experts about fundamental differences between the two groups, including tumour location, prognosis and treatment options. The company also gave some consideration to the primary tumour location of epNETs by providing a subgroup analysis for PFS, separated by patients with midgut GI and non-midgut GI tumours. OS results for this subgroup were also provided by the company in response to clarification questions. Nonetheless, the EAG's clinical experts considered that lung NETs should have been considered separately from other epNETs, as lung NETs have a worse prognosis and fewer treatment options. In response to clarification questions, the company provided separate analyses of PFS, OS and TTD for lung NETs and epNETs (without lung NETs). The EAG's clinical experts also highlighted that hormonal-dependent cancers (such as ovarian or prostate cancer) were not reported

		were not pre-specified and are not available.		in the CS. However, the company noted that these cancers are rare and that prostate cancer was not included in the CABINET trial. While information on these patients would have aided decision-making, the EAG does not consider the exclusion of patients with hormonal-dependent cancers to be a major limitation to the analysis. Subgroup analysis by functional status, Ki-67 index and somatostatin receptor expression would have been useful as these can inform treatment options. However, as this information was not available from the CABINET trial, the exclusion of these subgroups is unavoidable. The absence of this analysis, should however, be considered when interpreting the trial results.
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	The company did not consider there to be any equality concerns related to this appraisal. Cabozantinib does not present any issues to the NICE's commitment of promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.	N/A	N/A

Abbreviations: BSC, best supportive care; EAG, External Assessment Group; epNET, extra-pancreatic neuroendocrine tumour; GI, gastrointestinal; ITC, indirect treatment comparison; ITT, intention to treat; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PAS, patient access scheme; PFS,

progression-free survival; pNET, pancreatic neuroendocrine tumour; PRRT, Peptide receptor radionuclide therapy; PSS, Personal Social Services Perspective; RCT, randomised controlled trial; SLR, systematic literature review; SSA, somatostatin analogue; TTD, time to treatment discontinuation

2.3.1 Population

The NICE scope includes adults with advanced pancreatic or extra-pancreatic neuroendocrine tumours (pNETs or epNETs) who have progressed after systemic treatment. This aligns with the anticipated extension of the marketing authorisation for cabozantinib, [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED].³

Although the company stated that the population included in the clinical and economic analysis aligned with the anticipated marketing authorisation, the EAG notes that the results presented in the CABINET trial are for heavily pretreated patients. The high mean number of prior systemic treatments for patients in the CABINET trial (Table 15) raises concerns for the EAG about the applicability of the trial results to those patients who may receive cabozantinib at an earlier stage in the treatment pathway and are eligible to receive other systemic treatments prior to BSC (**Key issue 1**). Patients in the pNET group received a mean number of three previous systemic treatments, excluding SSAs, in the cabozantinib and placebo arms (2.7 and 2.6, respectively), while patients in the epNET cohort had received a mean number of two systemic treatments, excluding SSAs (1.9 and 1.8, respectively). Importantly, more than half of the pNET patients in the cabozantinib arm had received more than three previous systemic treatments (excluding previous SSAs).

In contrast to the CABINET trial, the marketing authorisation positions cabozantinib as a second (or further) systemic treatment line (other than previous treatment with an SSA). Although the EAG acknowledges a lack of direct evidence for cabozantinib in this population, it considers that indirect treatment comparisons (ITCs) could have been explored by the company to provide an insight into the effects of cabozantinib in a less pretreated population.

Crucially, the EAG notes that 27% of cabozantinib patients and 32% of placebo patients in the pNET population in CABINET had received only one prior systemic therapy (other than SSAs), while in the epNET population, 44% of cabozantinib patients and 48% of placebo patients had received one prior systemic treatment. Although it is unclear if any of these patients would have been eligible for alternative systemic treatments (or whether these are patients who would only be eligible for BSC), the EAG considers this subgroup of patients to be the key population of interest from CABINET to conduct the ITC.

Table 15. Number of prior systemic treatments in the CABINET trial, excluding SSAs (reproduced from Table 10 of the CS)

	pNET cohort		epNET cohort	
	Cabozantinib (n=64)	Placebo (n=31)	Cabozantinib (n=134)	Placebo (n=69)
Mean (SD)	2.7 (1.54)	2.6 (1.74)	1.9 (1.04)	1.8 (1.07)
Median (Range)	3.0 (1–8)	2.0 (1–7)	2.0 (1–5)	2.0 (1–6)
Number of patients receiving ≥3 treatments (%)	33 (52%)	12 (39%)	35 (26%)	15 (22%)
Abbreviations: epNET, extra-pancreatic neuroendocrine tumour; pNET, pancreatic neuroendocrine tumour; SD, standard deviation				

Given the concerns outlined above, the EAG considers there to be two main populations of interest:

1. The CABINET population, who are heavily pretreated, and reflect NHS patients who may receive cabozantinib as a fourth (or further) line of systemic treatment for pNETs (excluding prior SSAs); or epNET patients who may receive cabozantinib as a third (or further) line of systemic treatment, excluding prior SSAs. BSC is an appropriate comparator for this group, with direct evidence provided from the CABINET trial; and
2. The less heavily pretreated population, who are not at the stage where the only available option would be BSC, and may receive cabozantinib earlier in the treatment pathway, as a second (or further) systemic treatment line (excluding prior SSAs). The appropriate comparators for this group would be PRRT, everolimus or sunitinib, depending on tumour location, functional status and SSTR status. No direct evidence is available to inform the cost-effectiveness of cabozantinib for this group, but exploratory ITC analyses have been performed by the EAG to help with the decision-making process for this group of patients. Further details about the ITCs are provided in Section 2.3.3.

The company's analysis, based on the CABINET trial, separated patients into cohorts based on tumour location (pNETs or epNETs). The separation of patients with pNET or epNET tumours appears to be an important distinction, based on the different treatments available and the different prognosis for each cohort. However, the EAG's clinical experts also highlighted the importance of considering patients with lung NETs separately to other epNET patients (**Key issue 2**). There are currently fewer treatment options available for lung NETs, and the clinical experts noted that these patients have a worse prognosis than other epNET patients.

Previous studies have also noted the worse prognosis associated with lung NETs, with RADIANT-4 including a stratification factor based on NETs with better or worse prognosis. Lung NETs were included as one of the NETs with the worst prognosis, alongside stomach, rectum, and colon (excluding cecum).¹²

Given the above concerns, and the potential for different treatment effects for cabozantinib in the lung NET population, the EAG requested a separate analysis of the CABINET trial data for patients with lung epNETs. The company provided the baseline characteristics for patients with lung NETs, and for patients with epNETs (excluding lung NETs), along with analyses for PFS, OS and TTD. The company noted that lung NETs were not a stratification factor for randomisation of the CABINET trial and highlighted their concerns about the limitations of this analysis. These limitations are acknowledged in the EAG's critique of the results for this subgroup (Section 3.3).

The EAG's clinical experts also noted that hormonal-dependent cancers (such as ovarian or prostate cancer) were not reported in the CS. The company noted that prostate cancer was not included in the CABINET trial due to it being a rare and aggressive type of disease which is more commonly a neuroendocrine carcinoma than a NET. While ovarian cancer was not excluded from the CABINET trial, the company stated that it is extremely rare and therefore the recruitment of patients with this type of NET into the trial was statistically unlikely. As such, the EAG does not consider the exclusion of patients with hormonal-dependent cancers to be a major limitation to the analysis but notes that the lack of evidence for treatment effectiveness in these groups should be considered when interpreting the results.

The EAG notes that no sufficient justification (according to Murphy *et al.* 2021¹³) was provided for the company's use of a site-agnostic approach for the epNET population (**Key issue 2**). In response to clarification questions, the company stated that the pre-specified subgroup analyses of epNET primary tumour location demonstrated a relatively consistent benefit for PFS of midgut GI/unknown versus non-midgut GI/lung/other:

- Midgut GI/unknown: HR 0.33 (95% CIs: 0.19 to 0.57);
- Non-midgut GI/lung/other HR 0.57 (95% CIs: 0.24 to 1.29).

The EAG disagrees that the results above show a consistent benefit, given that the HRs are considerably different in magnitude, and crucially that the HR for the non-midgut GI/lung/other group is non-statistically significant. These concerns are considered in more detail in the EAG's

assessment of results for the lung NET population (Section 3.3.1.1) and the subgroup analyses (Section 3.3.4).

The inclusion criteria for CABINET were discussed with the EAG's clinical experts. This included patients with:

- Well or moderately differentiated pNETs or epNETs;
- Locally advanced/unresectable or metastatic disease;
- WHO tumour grades of 1 to 3;
- Any primary tumour site;
- Evidence of disease progression within 12 months prior to study registration, as assessed by RECIST 1.1 criteria;
- ECOG status 0 to 2;
- Disease progression or unacceptable side-effects leading to discontinuation after at least one systemic therapy (excluding SSAs). Prior lines of therapy included:
 - pNET: everolimus, sunitinib, or PRRT
 - GI NET: everolimus or PRRT
 - Lung NET: everolimus

Patients with either functional or non-functional tumours were included in the study and concurrent use of somatostatin analogues (SSAs) was allowed during the trial if the dose had been stable for a minimum of two months prior to enrolment. The EAG's clinical experts noted that the percentage of functional tumours was slightly higher than they would expect to see in practice (Table 16), but they did not consider this difference sufficient to cause any major concerns about the applicability of the trial to NHS practice. Although CABINET was a US-based trial, the EAG's clinical experts were not aware of any major differences in practice that would be likely to impact the results and, as the baseline characteristics reflected what would be expected in clinical practice in the NHS, the location of the trial does not appear to be a major concern.

Table 16. Cancer history and baseline disease characteristics of the CABINET trial. Reproduced from Table 10 of CS

	pNET cohort		epNET cohort	
	Cabozantinib (n=64)	Placebo (n=31)	Cabozantinib (n=134)	Placebo (n=69)
Tumour type, n (%)				
pNET	62 (97%)	30 (97%)	4 (3.0%)	3 (4.3%)

epNET	2 (3.1%)	1 (3.2%)	130 (97%)	66 (96%)
Histologic type				
Carcinoid tumour	1 (1.6%)	1 (3.2%)	85 (63%)	54 (78%)
Atypical carcinoid tumour	0	0	26 (19%)	11 (16%)
Not specified	1 (1.6%)	0	19 (14%)	1 (1.4%)
Time from initial diagnosis of the primary tumour to randomisation (months)				
Mean (SD)	85.7 (48.38)	86.1 (53.85)	89.7 (77.15)	90.5 (63.40)
Median (Range)	71.3 (18–214)	73.6 (18–230)	64.7 (9–489)	75.9 (14–340)
Primary tumour site, n (%)				
Pancreas	62 (97%)	30 (97%)	4 (3.0%)	3 (4.3%)
Lung	0	0	27 (20%)	12 (17%)
Stomach	1 (1.6%)	0	3 (2.2%)	2 (2.9%)
Small bowel (including duodenum, jejunum, ileum)	1 (1.6%) ^b	0	37 (28%)	29 (42%)
Appendix	0	0	1 (0.7%)	0
Caecum	0	1 (3.2%)	3 (2.2%)	0
Non-caecum colon	0	0	2 (1.5%)	0
Rectum	0	0	5 (3.7%)	6 (8.7%)
Thymus	0	0	6 (4.5%)	4 (5.8%)
Unknown	0	0	22 (16%)	2 (2.9%)
Other	0	0	24 (18%)	11 (16%)
Functional (hormone secretion) status, n (%)				
Functional tumour	11 (17%)	5 (16%)	41 (31%)	25 (36%)
Non-functional tumour	48 (75%)	22 (71%)	75 (56%)	34 (49%)
Unknown	5 (7.8%)	4 (13%)	18 (13%)	10 (14%)
Tumour grade, n (%)				
G1	14 (22%)	7 (23%)	37 (28%)	15 (22%)
G2	39 (61%)	19 (61%)	86 (64%)	48 (70%)
G3	8 (13%)	3 (9.7%)	8 (6.0%)	5 (7.2%)
Unknown	3 (4.7%)	2 (6.5%)	3 (2.2%)	1 (1.4%)
Histologic differentiation, n (%)				
Well differentiated	59 (92%)	30 (97%)	118 (88%)	61 (88%)
Moderately differentiated	4 (6.3%)	0	6 (4.5%)	5 (7.2%)
Poorly differentiated	0	0	0	0
Not specified	1 (1.6%)	1 (3.2%)	10 (7.5%)	3 (4.3%)
Extent of disease, n (%)				
Locally advanced	1 (1.6%)	2 (6.5%)	0	0
Metastatic	63 (98%)	29 (94%)	134 (100%)	69 (100%)
Number of prior systemic anticancer regimens				

Prior SSA use, n (%)	63 (98%)	30 (97%)	124 (93%)	64 (93%)
Mean (SD)	2.7 (1.54)	2.6 (1.74)	1.9 (1.04)	1.8 (1.07)
Median (Range)	3.0 (1–8)	2.0 (1–7)	2.0 (1–5)	2.0 (1–6)
≥3	33 (52%)	12 (39%)	35 (26%)	15 (22%)
Types of prior systemic anti-cancer regimens (excluding SSAs)				
Everolimus, n (%)	51 (80%)	25 (81%)	96 (72%)	44 (64%)
PRRT, n (%)	38 (59%)	18 (58%)	81 (60%)	41 (59%)
Anti-VEGFR TKI	19 (30%)	8 (26%)	7 (5.2%)	6 (8.7%)
Sunitinib	18 (28%)	7 (23%)	4 (3.0%)	1 (1.4%)
Other anti-VEGFR TKI	1 (1.6%)	1 (3.2%)	3 (2.2%)	5 (7.2%)
Cytotoxic chemotherapy regimens	44 (69%)	18 (58%)	51 (38%)	23 (33%)
Other	6 (9.4%)	3 (9.7%)	10 (7.5%)	2 (2.9%)
Abbreviations: epNET, extra-pancreatic neuroendocrine tumour; G, Grade; ITT, intent-to-treat; OPEN, Oncology Patient Enrolment Network; pNET, pancreatic neuroendocrine tumour, PRRT, peptide receptor radionuclide therapy; SD, standard deviation; SSA, somatostatin analogue; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor				

The EAG notes that while the clinical experts considered the inclusion criteria and the trial baseline characteristics to be a reasonable reflection of the patients seen in clinical practice, this was in relation to the heavily pretreated population included in CABINET, rather than as a reflection of the patients who may receive cabozantinib earlier in the treatment pathway, such as a second line systemic therapy (excluding prior SSAs). The EAG's clinical experts also added that, currently, they would not want to prescribe cabozantinib as an earlier treatment line than that reflected in the CABINET trial, as no evidence is available for treatment effectiveness in that setting.

2.3.2 Intervention

The intervention matches that stated in the NICE final scope. Cabozantinib is a third-generation small molecule that inhibits the enzymatic activity of multiple tyrosine kinases by targeting receptor tyrosine kinases (RTKs) including VEGFR2, RET, MET, and AXL. The inhibition of these RTKs has been demonstrated as an effective treatment method for advanced NETs.^{14, 15} By targeting multiple signalling pathways, cabozantinib may provide greater anti-tumour effects, and reduce the risk of disease progression, compared to other existing treatments which only target single pathways.

Patients in the CABINET trial were randomised to either cabozantinib, using the recommended dose of a 60 mg tablet taken once daily, or placebo. Patients in both trial arms also received BSC. Patients were assessed every 12 weeks until they experienced progression or began a new anticancer

therapy, after which they were monitored for survival every six months until either eight years after trial registration or death. The EAG's clinical experts considered this to be a reasonable method and time period over which to assess response to treatment. Given that the dose, method of administration and assessment time points reflect what the clinical experts would expect in practice, the intervention used in the trial appears suitable to address the decision problem.

2.3.3 Comparators

The CS presents placebo as the sole comparator for cabozantinib. The CS stated that placebo could be considered as a proxy for BSC, and the EAG's clinical experts confirmed that the care outlined for the placebo arm accurately reflected what would be provided in clinical practice.

As discussed in Section 2.3.1, the evidence from the CABINET trial reflects heavily pretreated patients who may receive cabozantinib as a fourth (or further) line of systemic treatment for pNETs (excluding prior SSAs); or as a third (or further) line of systemic treatment for epNETs, excluding prior SSAs. The EAG considers that BSC is an appropriate comparator for this group, and the EAG's clinical experts confirmed that the population included in the CABINET trial accurately reflects the average patient in the NHS who would be treated with BSC.

The NICE final scope also includes chemotherapy and other systemic treatments as potential comparators, but the company did not consider these relevant to the decision problem (**Key issue 1**). The primary reasons the company presented for the exclusion of these comparators were:

- The heterogeneous nature of the disease and the narrow labels for systemic treatment options, resulting in no clear or consistent treatment pathway;
- The limited evidence base for chemotherapy, and its limited use in clinical practice for well-differentiated NETs;
- Similarities between the anticipated marketing authorisation for cabozantinib and the CABINET trial; and
- A lack of relevant RCTs for other systemic therapies used in the NHS.

The EAG discussed the treatment pathway and positioning of cabozantinib with its clinical experts. While the experts agreed that there was variation in the treatment pathway for patients with NETs, they noted that there were some common treatment options, the use of which is dependent on a range of factors, including tumour location, functional status and SSTR status. The EAG's clinical

experts agreed with the company's statements that the use of chemotherapy is relatively limited and generally reserved for patients with higher grade disease, aggressive tumours, or those with few treatment options available, such as patients who have lung NETs.

Based on the above discussions, and the information on the current treatment pathway presented in the CS (summarised in Section 2.2), the EAG considers the exclusion of chemotherapy to be a reasonable decision as it is likely to be used for a small number of patients with very specific disease criteria. In the case of lung NETs, the EAG considers the exclusion of chemotherapy appropriate, as it would most often be given as a first-line systemic treatment, before patients would be eligible to receive cabozantinib. For these lung NET patients, everolimus is the appropriate comparator to cabozantinib.

While the EAG agrees with the exclusion of chemotherapy, it disagrees with the exclusion of other systemic treatments as comparators when considering the anticipated marketing authorisation for cabozantinib (**Key issue 1**). Instead, the EAG considers the treatments below to be relevant comparators in patients who may receive cabozantinib as a second systemic treatment line (excluding prior SSAs):

- The pNET population: Everolimus, sunitinib and PRRT, respectively;
- The epNET population (without lung NETs): Everolimus, PRRT, and BSC respectively; and
- The epNET population (lung NETs): Everolimus and BSC, respectively.

While the EAG accepts this is a simplification of the treatment pathway, with additional treatment decisions based on functional status and disease severity, it considers these to be the treatment options available to most patients in each of the three populations. The EAG's clinical experts discussed how there is a move towards PRRT as the first systemic treatment option for pNETs and most epNETs, apart from lung NETs. However, as there is still variation in treatment across the NHS, the EAG accepts that any of the treatments in the list above could currently be used in the same position as that reflected in the marketing authorisation for cabozantinib.

Given the concerns outlined above and in Section 2.3.1, the EAG requested clarification from the company about their proposed positioning of cabozantinib. The company responded that cabozantinib was being positioned in line with the full marketing authorisation, informed by the population in the CABINET trial. They noted that the proposed positioning of cabozantinib is not exclusively as a second line systemic treatment, citing the views of their clinical experts that the

number of prior treatments varies depending on individual patient characteristics. They discussed how the requirement for at least one prior systemic therapy means that, while some patients may have only had one prior treatment, others may have had multiple treatments. The EAG agrees that individual patient characteristics will affect the number of treatments that a patient receives prior to cabozantinib, but does not consider the company's argument outlined above to be a reasonable justification for only assessing the cost-effectiveness of cabozantinib against BSC, thereby missing relevant comparators.

The EAG requested additional analyses from the company to incorporate the other relevant comparators into the analysis. Although no direct comparisons were available between cabozantinib and the other systemic therapies, the EAG noted that ITCs could be used as an exploratory analysis to assess the relative treatment effectiveness of cabozantinib. However, based on a feasibility assessment, the company concluded that robust ITCs could not be performed (as discussed in Section 3.4), and so the requested analyses were not provided (**Key issue 1**). Therefore the EAG has performed its own exploratory analyses for the additional comparators (see Section 3.4).

2.3.4 Outcomes

The outcomes in the CS match those in the NICE final scope (see Table 14). The primary endpoint of the CABINET trial was progression-free survival (PFS), which the EAG's clinical experts confirmed was a key outcome in clinical practice when determining if a patient is responding to treatment.

Overall survival (OS) was also considered, although the CS notes that data were immature at the time of study termination. In response to clarification questions, the company provided analyses for an additional year of OS data, based on an OS data sweep requested by the regulator. The company had a number of concerns about using the unplanned OS data sweep and has not included it in the company's base case analysis (**Key issue 3**). Nonetheless, the EAG considers the more mature OS data to be the most relevant data for decision-making, and these are considered further in Section 3.3.2.1.

The OS results were also impacted by the use of a cross-over design in the CABINET trial, with patients in the placebo arm allowed to switch to cabozantinib when they experienced disease progression. The impact of this cross-over design and the choice of the most appropriate method to analyse OS is discussed in more detail in Section 3.3.2.1.

Health-related quality of life (HRQoL) was reported as an additional endpoint in the trial. HRQoL was not assessed as part of the primary CABINET trial but was reported in a separate sub-study (A021602-HO1) in which participation was optional (**Key issue 7**). The optional aspect of the sub-study meant that data were available for fewer patients than the wider CABINET trial and also resulted in a breaking of randomisation. The potential impact of the design of the sub-study on HRQoL is discussed in more detail in Section 3.3.3.

For safety outcomes, the company provided information on patients with adverse events (AEs), serious adverse events (SAEs), treatment emergent adverse events (TEAEs), treatment discontinuation due to AEs and deaths. The EAG's clinical experts did not identify any additional adverse events that would commonly be seen in patients with NETs that were not covered by the CS.

The EAG's clinical experts did not identify any additional outcomes or alternative assessment methods that would be more relevant to clinical practice. The outcomes reported in the CABINET trial, and those selected by the company to address the NICE final scope, therefore appear appropriate to answer the decision problem.

2.3.5 Subgroups

Two subgroups in the NICE final scope were based on tumour location (pNETs or epNETs). As discussed in Section 2.3.1, results were presented separately for these two groups throughout the CS. Separating pNETs from epNETs is appropriate, although, as previously mentioned, the EAG considers that lung NETs should have been considered separately from the other epNETs.

Subgroup analysis for tumour grade, differentiation status and epNET primary tumour site (midgut and non-midgut GI) were provided, as specified by the NICE scope. Although these subgroup results were initially only provided for the primary endpoint of PFS, the company also provided the results for OS following a clarification request from the EAG. Additional subgroup analyses for PFS were reported, beyond those specified in the NICE final scope, including:

- Age: <65 / ≥65;
- Sex: Male/Female;
- Race: White/Other;
- ECOG status: 0/1/2;
- Concurrent SSA at randomisation: Yes/No;

- Prior sunitinib therapy (pNETs): Yes/No;
- Number of prior systemic therapies: 1/2/>3;
- Prior everolimus: Yes/No;
- Prior 177Lu-dotatate (PRRT): Yes/No; and
- Histologic type (epNETs): Atypical carcinoid tumour/Carcinoid tumour/Not specified.

The CS reports the results of a *post-hoc* subgroup analysis based on specific tumour location for epNETs (lung, GI tract or other). The company highlighted that these subgroups were not stratification factors at randomisation, and so it did not consider these analyses sufficiently robust for decision-making. The results of these subgroups are included in the EAG's critique, alongside an acknowledgment of these limitations and their potential impact on decision-making (Section 2.3.5).

As discussed in Section 2.3.1, based on feedback from its clinical experts, the EAG requested more detailed results for the subgroup of patients with lung NETs (**Key issue 2**). The interpretation of the results for this subgroup, along with the associated limitations of the analysis highlighted by the company, are discussed in Sections 3.3.1.1, 3.3.2.1.1 and 3.4.

The company could not provide analyses for some of the subgroups in the NICE final scope, including functional status, Ki-67 index and somatostatin receptor expression, as this information was not available from the CABINET trial. While this information would have been useful to identify any differences in treatment response, their exclusion appears to be unavoidable. However, the lack of information about these characteristics should lead to caution when interpreting the results. No additional characteristics were identified by the EAG's clinical experts as likely to affect a patient's response to treatment and so the choice of subgroups appears reasonable.

3 Clinical effectiveness

3.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify RCTs which reported on the clinical efficacy and safety of treatments for adults with either pNETs or epNETs. Studies were included if results were stratified by prior line of treatment. For any study where results were not stratified by prior line of therapy (i.e. a mixed population), only those where $\geq 70\%$ of patients had received a relevant prior line of therapy were included. Systemic therapies considered relevant to the review included everolimus, sunitinib, lu-dotatate, capecitabine and temozolomide (CAPTEM), streptozocin and 5-fluorouracil (STZ/5-FU), folinic acid, fluorouracil and oxaliplatin (FOLFOX) and interferon-alpha (IFN- α).

Methods used for the SLR are summarised in Table 17. The SLR was updated in January 2025, three months prior to the submission, and so is unlikely to have missed any substantial, more recent, evidence. The EAG considers the methods used to be largely appropriate, however, is concerned with the company's decision to exclude studies where fewer than 70% of patients had a prior relevant systemic therapy and the results were not stratified by prior line of treatment. No information is provided on the percentage of patients who did receive prior systemic therapies in these studies and could, therefore, be relevant to the decision problem, and there is no justification for the choice of the 70% threshold. Without this additional information, it is not possible to determine whether relevant evidence has been overlooked in the SLR. This is discussed in more detail in Section 3.4.

Table 17. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant this appraisal

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	CS Appendix B, Section B1.1	Appropriate The following databases were searched: • MEDLINE; • Embase; • The Cochrane Library, including the Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL); • The University of York Centre for Reviews and Dissemination (CRD) platform, including Database of Abstracts of Reviews of Effects (DARE).

		The following clinical trial registries were searched: • ClinicalTrials.gov. The following conference proceedings were searched: • American Society of Clinical Oncology (ASCO): 2022, 2023 and 2024; • ASCO Gastrointestinal Cancer Symposium (ASCO-GI): 2022, 2023, 2024 and 2025; • European Neuroendocrine Tumor Society (ENETS): 2022, 2023 and 2024; • European Society for Medical Oncology (ESMO): 2022, 2023 and 2024; • ESMO Gastrointestinal Cancers Congress (ESMO-GI): 2022, 2023 and 2024; • North American Neuroendocrine Tumor Society (NANETS): 2022, 2023 and 2024. Manual searches of the bibliographies of all relevant SLRs and NMAs identified during abstract screening were also performed.
Search strategies	CS Appendix B, Section B1.1	Appropriate Searches included systemic therapies that matched the NICE final scope and included the relevant population, interventions and study designs. The initial search was performed in May 2024, followed by an update search in January 2025. This was 3 months prior to submission and so the likelihood of missing key references is low. The main trial in the CS was identified in the SLR.
Inclusion criteria	CS Appendix B, Section B1.2	Serious concerns The population, intervention and comparators match those in the NICE final scope and decision problem. However, the restriction of the studies which did not stratify by prior line of therapy to only those where $\geq 70\%$ of patients received a relevant prior line of therapy resulted in the exclusion of relevant UK-based RCT evidence. Without further information it is unclear why the 70% threshold was chosen, or what percentage of patients in each of the excluded studies did receive a relevant prior therapy.
Screening	CS Appendix B, Section B1.2	Appropriate Abstract and full-text screening was completed by two independent investigators, with discrepancies resolved by a third reviewer.
Data extraction	CS Appendix B, Section B1.3	Appropriate Data were extracted by a single reviewer in an Excel-based data extraction workbook. All extracted data were validated by a second reviewer, with discrepancies resolved by a third reviewer.
Tool for quality assessment of included study or studies	CS Appendix B, Section B1.3	Some concerns The Cochrane Risk of Bias Assessment Tool 2.0 was used for the quality assessment of RCTs which is appropriate. The EAG performed its own quality assessment of the key trial from the CS (CABINET). While it broadly agrees with the company's assessment, there are some concerns about the interim analysis methods which are not reflected in the company's risk of bias assessment. Details of the EAG's assessment of the CABINET trial are described in Section 3.2.

Abbreviations: CS, company submission; EAG, External Assessment Group; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; RCT, randomised controlled trial; SLR, systematic literature review

The SLR identified 2,416 novel records in the initial searches with an additional 82 identified in the updated search (Figure 1 and Figure 2, CS Appendix B). A total of 448 full-text articles were screened, with 19 identified as relevant. An additional 23 relevant records were identified through supplementary searches. Of these, ten were deprioritised for data extraction due to the provision of individual patient data or only presenting graphical results. The final analysis included 32 publications covering 16 studies. The studies considered a range of treatments (Table 8, CS Appendix B), which the company reported by population:

- pNETs only: 5 studies (1 RCT, 4 non-RCTs);
- epNETs only: 5 studies (1 RCT, 4 non-RCTs); and
- Non-stratified NETs: 6 studies (1 RCT, 5 non-RCTs).

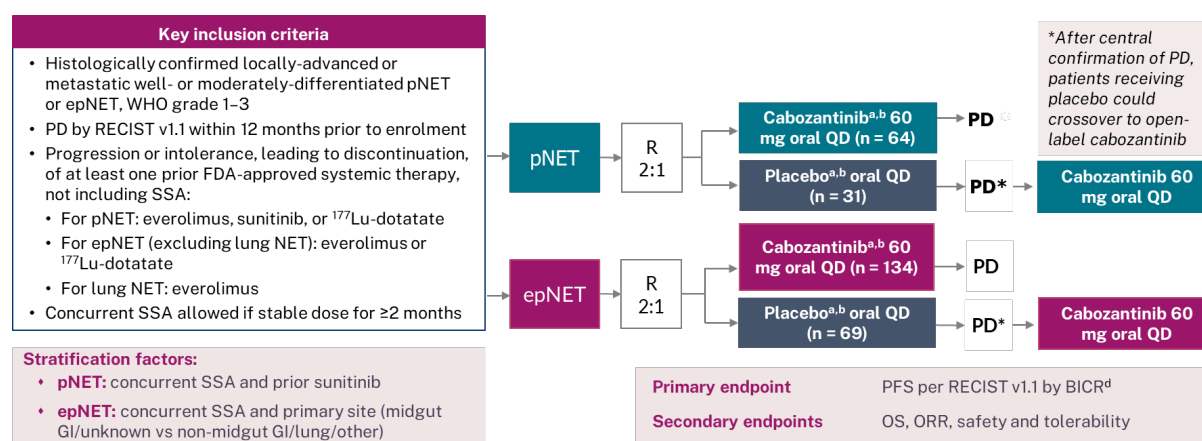
While 16 studies reported on treatment in the population specified in the decision problem, only three were RCTs. Of these, two were China-based studies which assessed the effects of surufatinib, which is not recommended for treatment in the NHS. The third RCT was the CABINET trial, which forms the basis of the company's submission.

The company reported that the CABINET trial was the only relevant trial which met the inclusion criteria for the review. However, as discussed above, the company excluded other RCTs which included systemic treatments used in clinical practice based on the exclusion criteria that fewer than 70% of patients received a relevant prior line of therapy, and results were not stratified by prior line of therapy. The EAG considers these studies to be potentially important sources of evidence for relevant comparators to cabozantinib. As such, while the methods used in the SLR for searching, screening and data extraction appear appropriate, the criteria to only include those studies where $\geq 70\%$ of patients received a relevant prior line of therapy may have limited the comparisons in the CS.

3.2 Critique of trials of the technology of interest

One RCT relating to cabozantinib was identified in the company's SLR (Section 3.1). CABINET (NCT03375320) was a phase III, US-based, multicentre, randomised, double-blind, placebo-controlled trial. Participants were randomised to either 60 mg cabozantinib or placebo (Figure 2), with patients in the placebo arm eligible to cross-over to cabozantinib if they had confirmed disease progression.

Figure 2. Study design of the CABINET trial. Reproduced from Figure 5 of the CS



^a Interruptions and dose reductions for cabozantinib (40 mg, then 20 mg) and placebo were specified for adverse event management. ^b Blinded treatment continued until PD, unacceptable toxicity or withdrawal of consent. ^c If investigator assessments of PD were confirmed by blinded real-time central review, patients were unblinded to treatment assignment. ^d Patients were evaluated every 12 weeks by radiographic imaging for tumour response and progression.

Abbreviations: BIRC: blinded independent review committee; epNET: extra-pancreatic neuroendocrine tumour; GI: gastrointestinal; ¹⁷⁷Lu-dotatate: ¹⁷⁷Lutetium-dotatate; mg: milligram; NET: neuroendocrine tumour; ORR: objective response rate; OS: overall survival; PD: progressed disease; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour; QD: once daily; R: randomised; RECIST: Response Evaluation Criteria in Solid Tumours; SSA: somatostatin analogue; WHO: World Health Organization.

The CABINET trial used an interim design, with two analyses planned during the trial (when 33% and 66% of the projected number of PFS events had occurred, respectively), followed by a final analysis when 100% of the projected number of PFS events had occurred (149 PFS events in the pNET cohort and 164 PFS events for epNETs). However, the company reported that the interim analyses demonstrated compelling efficacy for PFS in both pNET and epNET patients and so termination of patient recruitment was recommended and the final analysis was not conducted. At the point of trial termination, 203 of the target 210 epNET patients and 95 of the target 185 pNET patients had been enrolled, and 38.2% of the planned PFS events in the pNET cohort and 67.7% of the planned PFS event in the epNET cohort had occurred. This aligned with the first planned interim analysis (33%) for pNETs and the second planned interim analysis (66%) for epNETs. Interim analyses can be useful in indications such as NETs, which the company noted is an area with high unmet clinical need. However, these can have drawbacks including uncertainty in the results and the potential overestimation of treatment effects, which should be considered when interpreting the results of CABINET. These considerations appear to be most important for the pNET cohort, where the number of patients enrolled prior to trial termination was half the number that was originally planned (**Key issue 6**).

The CABINET trial allocated patients to one of two cohorts depending on whether their tumour was a pNET or epNET. As discussed in Section 2.3.1, this is an important distinction given the different treatments available for each group and the different prognosis of the two cohorts. However, there was limited additional distinction between tumour locations, with the exception of a planned subgroup analysis by epNET primary tumour site (midgut vs non-midgut GI). For the midgut analysis, patients were separated into groups based on whether they had a midgut NET (jejunum, ileum, cecum, ascending colon, hepatic flexure/unknown tumour location), or a non-midgut GI NET (stomach, duodenum, transverse colon, splenic flexure, descending colon, sigmoid colon/lung). The company also conducted a *post-hoc* analysis of epNET primary site (GI vs lung/thymus vs unknown/other) for PFS outcomes.

The EAG's clinical experts noted that the distinction between midgut and non-midgut NETs tends to be a stratification factor in clinical trials, but that the majority of patients in these groups are not treated differently in clinical practice. The exception is the lung NETs subgroup, which should be considered separately to the other tumour sites to avoid masking important differences in prognostic factors and treatment response (see Section 2.3.1). Due to this, during clarification, the EAG requested that the company provided an additional analysis, separating patients with lung NETs from those who had any other type of epNET (**Key issue 2**). The results of these additional analyses are discussed in Section 3.3.

Table 18. EAG's summary of the design, conduct and analysis of the CABINET trial.

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique*
Randomisation	2.3.1 in CS	CABINET trial: Appropriate Patients were randomised in a 2:1 ratio to receive either cabozantinib (60 mg once daily) or placebo (60 mg once daily) administered orally, every 28 days, using the permuted blocks method with a block of six. Randomisation was stratified by key clinical variables including concurrent SSA use and receipt of prior sunitinib therapy in the pNET cohort and primary tumour site (midgut GI/unknown versus non-midgut GI/lung/other) and concurrent SSA use in the epNET cohort. A021602-HO1 sub-study (HRQoL): Some concerns While the sub-study was conducted alongside the CABINET trial, participation was optional. This led to breaking of the randomisation that was achieved in the main trial and led to differences in the

		baseline characteristics of the cabozantinib and placebo arms of each cohort.
Concealment of treatment allocation	2.3.1 in CS	CABINET trial and A021602-HO1 sub-study: Appropriate Randomisation was centrally implemented via an Interactive Web Response System (IWRS) and the web-based Oncology Patient Enrolment Network (OPEN) system, ensuring appropriate concealment of treatment allocation and minimisation of selection bias. The double-blind study design further reinforces the internal validity of the trial.
Eligibility criteria	2.3.2 in CS	CABINET trial: Appropriate Full details of the eligibility criteria for CABINET overall trial population are available in the CS Table 7. The EAG's clinical experts confirmed the eligibility criteria were broad and consistent with UK clinical practice. The trial included adults with WHO grade 1-3 well or moderately differentiated pNETS or epNETS, with progressive disease following at least one prior systemic therapy (excluding SSA-only regimens). A021602-HO1 sub-study (HRQoL): Some concerns All patients in the CABINET trial were eligible for the HRQoL sub-study but participation was optional. Limited information is provided in CS about how well the patients who chose to take part reflect the full CABINET cohort.
Blinding	2.3.1 in CS	CABINET trial and A021602-HO1 sub-study: Appropriate CABINET was a double-blind placebo-controlled RCT with participants and assessors masked to the treatment assignment. Given the efficacy of the drug in terms of PFS observed during interim analyses, if disease progression was confirmed by blinded real-time central review, the study was unblinded to allow crossover for patients in the placebo arm to receive open-label cabozantinib treatment. While this introduces potential confounding in OS estimation, the use of ITT principles and supportive sensitivity analyses help to mitigate this risk.
Baseline characteristics	2.3.3 in CS	CABINET trial: Appropriate for a subset of the population who are heavily pretreated The EAG notes that the trial population included patients with a high disease burden and who were heavily pretreated (mean number of previous systemic treatments, excluding SSAs, in the cabozantinib and placebo arms of 2.7 and 2.6 respectively in the pNET cohort and 1.9 and 1.8 in the epNET cohort, respectively), with high use of previous everolimus (approximately 60% to 80%) and PRRT (approximately 60%). The EAG's clinical experts noted that patients in CABINET had slightly better ECOG performance status than is often seen in UK clinical practice and that the pNET cohort had a lower proportion of functional tumours than expected, but this was not expected to have a major impact on the applicability of the results to clinical practice. They also noted that small bowel tumours, which typically have a better prognosis than other epNETs, were more common in the placebo than cabozantinib arm (42% vs 28%). However, if this

		imbalance has any impact on the results, it is likely to be in a conservative direction. The EAG notes that in the epNET cohort, 20% of patients in the cabozantinib arm and 17% in the placebo arm had lung as their primary tumour site. The EAG's clinical experts noted this reflected a higher proportion than expected in clinical practice, noting lung NETs tend to be less common, and this could reflect histopathological diagnostic variability. Clinical experts also noted that lung NETs have a worse prognosis and often fewer treatment options, as PRRT is not available in lung NETs in the UK. Following clarification questions, the company provided additional analyses which assessed lung NETS separately to the wider epNET cohort. This analysis is considered in the EAG's critique. A021602-HO1 sub-study (HRQoL): Some concerns Some differences were evident between trial arms for both cohorts, such as the percentage of patients with Grade 3 tumours in the pNET cohort and the percentage of patients with 3 or more prior systemic treatments (excluding SSAs) in both cohorts. Some of these differences may be treatment effect modifiers and may therefore influence patient-reported HRQoL outcomes. As for the main CABINET trial, these results are only applicable for a subset of the population who are heavily pretreated.
Dropouts	2.3.4	CABINET trial: Appropriate In the pNET cohort, the median follow-up times were 23.2 months in the cabozantinib arm and 25.2 months in the placebo arm. Few participants withdrew from the trial (5 for cabozantinib, 4 for placebo). Treatment discontinuation was primarily due to disease progression and adverse events. In the epNET cohort, median follow-up times were 23.3 months in the cabozantinib arm and 23.0 months in the placebo arm. Few participants withdrew from the trial (7 for cabozantinib, 4 for placebo). Treatment discontinuation was primarily due to disease progression and adverse events. A021602-HO1 sub-study (HRQoL): Concerns The percentage of patients who completed each assessment were less than the expected rate at each time point. There is limited explanation for the lower than expected response rates, and whether this was related to dropouts, patients being censored on disease progression, or whether some patients completed assessments at some of the time points, and not others. With the exception of baseline, the percentage of patients who responded at each timepoint was lower in the placebo arm than the cabozantinib arm for both cohorts.
Statistical analysis		
Sample size and power	2.4 in CS	CABINET trial: Appropriate for the overall trial population but early stopping may limit the power of the analyses for the pNET cohort and the robustness of the OS analyses.

		The trial planned to enrol approximately 185 patients in the pNET cohort and 210 patients in the epNET cohort, to provide 90% power to detect a HR of 0.583 between the two treatment arms. The EAG notes the trial was powered separately for the pNET and epNET cohorts based on the primary endpoint of PFS, and both cohorts were analysed independently (i.e. not pooled). The EAG considers this to be methodologically reasonable. Early stopping The trial recruitment was stopped early following interim analyses that showed compelling efficacy for PFS, leading to early unblinding of patients and crossover, especially in the epNET cohort. The EAG notes that while early stopping may suggest a strong treatment effect, it can also result in an overestimation of the treatment effect. An early stop can also potentially compromise the ability to fully assess longer-term endpoints like OS and HRQoL, particularly given that crossover was allowed from placebo to cabozantinib, which could dilute OS differences by reducing the number of events, making statistical comparisons less robust. Following the early stop, 203 of the target 210 epNET patients and 95 of the target 185 pNET patients had been enrolled and 38.2% of the planned PFS events in the pNET cohort and 67.7% of the planned PFS event in the epNET cohort had occurred. The EAG has few concerns about the difference between the planned and included number of patients in the epNET cohort (10 patients) but notes that the pNET cohort was close to half the number that was originally planned. This may reduce the statistical power for the pNET analyses, with the sample size originally chosen to provide the study with 90% power to detect a HR of 0.583 between the two treatment arms. A021602-HO1 sub-study (HRQoL): Serious concerns 85% of the patients in the CABINET trial were enrolled in the HRQoL sub-study. However, the response rate was highly variable for each time point, and considerably lower in the placebo than cabozantinib arms for both cohorts. In the pNET cohort response rates ranged between 60% and 76% at each time point for cabozantinib, compared to between 0 and 59% for placebo. For epNETs, responses ranged from 42% to 72% for cabozantinib, compared to 31% to 64% for placebo.
Handling of missing data	2.4 in CS	CABINET trial: Appropriate The company stated that missing data was not imputed and was treated as missing. The percentage missing data was relatively low in both arms and not expected to have a major impact on the results. A021602-HO1 sub-study (HRQoL): Unclear High percentage of missing data in the HRQoL sub-study and limited information provided about the handling of this missing data. Small

		sample sizes were reported towards the end of the study which limits the robustness of comparisons.
Outcome assessment	2.3.2 in CS	CABINET trial and A021602-HO1 sub-study: Appropriate Efficacy analyses of the primary endpoints were performed in the intention to treat populations (ITT), with patients grouped based on their assigned treatment at randomisation. The primary endpoint was PFS, assessed by a blinded independent review committee (BIRC) using RECIST 1.1 criteria, with secondary outcomes including OS, ORR, DOR, DCR, safety, and HRQoL. These are relevant and appropriately defined outcomes. The trial also conducted multiple pre-planned subgroup analyses based on stratification and prognostic factors; however, <i>post-hoc</i> analyses by tumour site (GI vs lung/thymus vs unknown/other) were not pre-specified and may be underpowered. The EAG notes the small sample size limits the robustness of subgroup analyses, especially for tumour-site-specific responses or for stratified variables such as prior PRRT or ECOG 2 patients. The HRQoL sub-study assessed patient-reported outcomes using EORTC, QLQ-C30, GINET21, and PGIC. These are considered relevant methods of assessing patient-centred outcomes in relation to cabozantinib. Patients in the placebo arm were permitted to crossover to cabozantinib following disease progression. The ITT analysis therefore produced a conservative estimate of the effects of cabozantinib on OS. The company therefore explored the use of crossover adjustment methods. Although ITT results were presented in the CS, the results of each adjustment method were reported in Appendix L.
Abbreviations: BIRC, blinded independent review committee; CS, company submission; DCR, disease control rate; DOR, duration of response; EAG, External Assessment Group; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; epNET, extra-pancreatic neuroendocrine tumour; GINET21, Quality of Life Questionnaire – GI NET; HR, hazard ratio; HRQoL, health-related quality of life; ITT, intention to treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PGIC, Patient Global Impression of Change; pNET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; QLQ-C30, Quality of Life Questionnaire; RCT, randomised controlled trial; SSA, somatostatin analogue; WHO, World Health Organisation		

The EAG considers CABINET to be a generally well-conducted trial, however, some aspects of the trial should be considered when interpreting its results. These include:

- The trial population was heavily pretreated (**Key issue 1**). Therefore, the EAG considers that CABINET is most appropriate to inform a scenario where cabozantinib is given as a fourth (or further) line of systemic treatment for pNET patients (excluding previous SSAs); and as a third (or further) line of systemic treatment for epNET patients, excluding previous SSAs.

- The interim analysis methods introduced uncertainty in the trial results and may result in an overestimation of treatment effectiveness for cabozantinib (**Key issue 6**). The early stop to the trial resulted in the recruitment of fewer participants than originally planned which could impact the power of the analyses. This may not be a major concern for the epNET cohort but should be considered when interpreting results for the pNET cohort where only half the number of intended patients were recruited;
- There are serious concerns about the quality of results from the HRQoL sub-study (**Key issue 7**). Participation in the sub-study was optional, and the results are therefore subject to the breaking of randomisation. The EAG considers that this limits the confidence in the conclusions drawn from the HRQoL sub-study.

Each of the concerns outlined above are considered in more detail in the discussion of the decision problem (Sections 2.3.1 and 2.3.3) and the critique of the results (Sections 3.3 and 3.4).

3.3 Critique of the clinical effectiveness analysis and interpretation

A summary of the results of the CABINET trial are presented in the CS (Section 2.6), while the sections below focus on the results most relevant to the NICE final scope.

3.3.1 Primary outcome

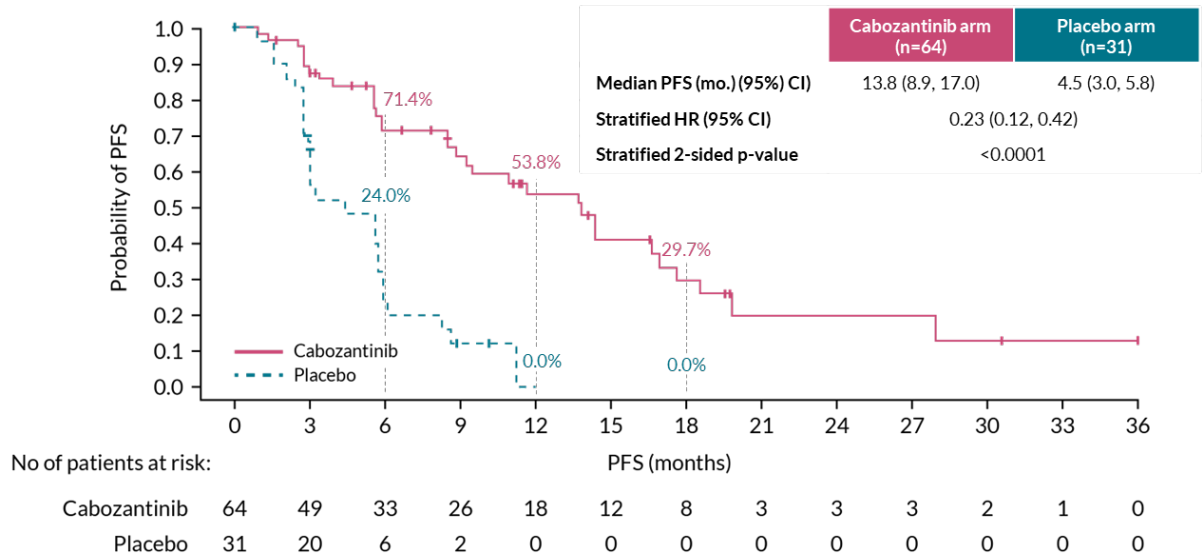
The primary outcome of the trial was PFS. Fewer progression events were reported with cabozantinib than placebo for both the pNET and epNET cohorts, with the company reporting statistically significant improvements in PFS with cabozantinib (Table 19).

Table 19. PFS from the CABINET trial for pNET and epNET cohorts (reproduced from Table 14 of CS).

PFS	pNET		epNET	
	Cabozantinib (n=64)	Placebo (n=31)	Cabozantinib (n=134)	Placebo (n=69)
Number of events, n (%)	32 (50)	25 (81)	71 (53)	40 (58)
Median PFS (months)	13.83	4.47	8.48	3.98
HR (95% CI)	0.23 (0.12 to 0.42)		0.38 (0.25 to 0.58)	
Stratified 2-sided p-value	<0.0001		<0.0001	
Abbreviations: CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumour				

For the pNET cohort, cabozantinib resulted in a 77% reduction in risk of disease progression, with median PFS increasing by 9.4 months. Kaplan-Meier (KM) curves highlighted the benefits of cabozantinib over placebo throughout the course of the trial, with the curves separating from the first follow-up assessment point of 12 weeks onwards (Figure 3), indicating the ongoing benefits of cabozantinib for PFS.

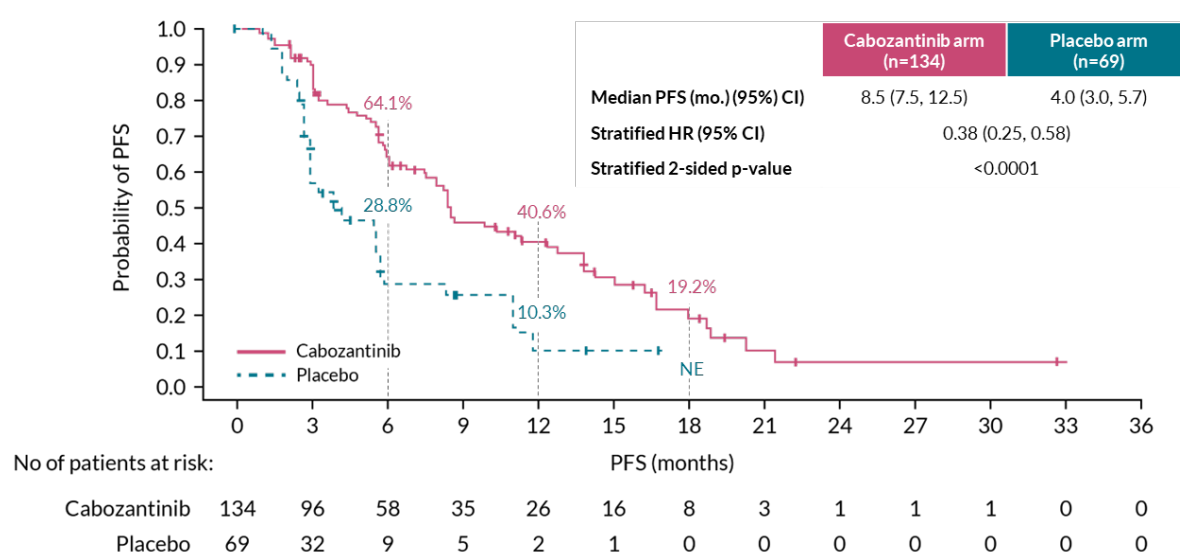
Figure 3. KM plot for PFS in the pNET cohort. Reproduced from Figure 8 of CS



Abbreviations: HR, hazard ratio; KM, Kaplan-Meier; PFS, progression-free survival

For the epNET cohort, cabozantinib resulted in a 62% reduction in risk of disease progression, with median PFS increasing by 4.5 months. As with the pNET cohort, the KM curves highlighted the ongoing benefits of cabozantinib throughout the trial, with the curves again separating from the first assessment point onwards (Figure 4).

Figure 4. KM plot for PFS in the epNET cohort. Reproduced from Figure 9 of CS



Abbreviations: HR, hazard ratio; KM, Kaplan-Meier; PFS, progression-free survival

While the analyses for both cohorts indicate the benefits of cabozantinib over placebo for PFS, the interim analysis methods warrant some caution in the interpretation of results particularly for the pNETs population (**Key issue 6**) (see Section 3.2). The company reported that a sequential testing approach with alpha spending was incorporated into the methods, according to the FDA guidelines on survival analysis, which reduces concerns about the risks of a false positive result. However, the EAG considers that the low participant numbers in the pNET cohort, and the risks of over-estimation of the treatment effect that is associated with interim analysis methods, should still be considered when interpreting the results.

3.3.1.1 Additional analysis requested by the EAG

As discussed in Section 2.3.1, the EAG's clinical experts highlighted the importance of considering lung NETs separately to the other sites in the epNET cohort (**Key issue 2**). In response to clarification questions, the company provided the baseline characteristics and results for PFS and OS for the lung NET patients and for epNET patients (without lung NETs). The company highlighted limitations of the analysis, noting that the lung NETs subgroup was not prespecified in the trial. The company also noted the low number of patients included in the lung NET group (cabozantinib: n=33, placebo: n=16) and the differences in baseline characteristics between cabozantinib and placebo, particularly for race, mean disease duration, proportion of Grade 1 tumours and proportion of patients with functional disease (Table 20).

The EAG agrees that there is a marked difference in baseline characteristics of patients in the cabozantinib and the placebo arms for the lung NET group (Table 20). These differences could potentially bias the results in favour of cabozantinib, as they appear to be indicative of a worse prognosis in the placebo group: Disease duration in the placebo arm was [REDACTED] longer than in the cabozantinib arm, nearly [REDACTED] more patients in the placebo arm had functional tumours compared to the cabozantinib arm [REDACTED], and nearly [REDACTED] more patients in the cabozantinib arm had Grade 1 tumour compared to the placebo arm [REDACTED]

While the EAG acknowledges the uncertainty in the results of a post-hoc subgroup analysis it still considers this to be a crucial subgroup, given the expected difference in clinical outcomes for lung NETs when compared to the other epNETs.

Table 20. Key baseline differences identified by the company for the lung NET patients in the CABINET trial

	Lung NETs	
	Cabozantinib (n=33)	Placebo (n=16)
Race		
White, n (%)	[REDACTED]	[REDACTED]
Asian, n (%)	[REDACTED]	[REDACTED]
Black or African American, n (%)	[REDACTED]	[REDACTED]
Not reported, n (%)	[REDACTED]	[REDACTED]
Unknown, n (%)	[REDACTED]	[REDACTED]
Disease duration to randomisation, mean, months (SD)	[REDACTED]	[REDACTED]
Grade 1 tumours, n (%)	[REDACTED]	[REDACTED]
Functional disease, n (%)	[REDACTED]	[REDACTED]
Abbreviations: NETs, neuroendocrine tumours; SD, standard deviation		

Median PFS was longer with cabozantinib than placebo for both lung NETs and epNETs without lung NETs. Median PFS for placebo patients was shorter for patients with lung NETs than with epNETs without lung NETs, reflecting the worse prognosis of the lung NETs group (Table 21). Both lung NETs and epNETs (without lung) demonstrated statistically significant improvements in PFS with cabozantinib, although a much larger benefit was seen for the lung NET group. As such, although of a potentially different magnitude, cabozantinib appears to have PFS benefits for all epNET patients.

Table 21. PFS from the CABINET trial for lung NET patients and epNET patients (excluding lung NETs)

PFS	Lung NETs		epNETs (excluding lung)	
	Cabozantinib (n=33)	Placebo (n=16)	Cabozantinib (n=101)	Placebo (n=53)
Number of events, n (%)	████████	████████	████	████
Median PFS (months)	████████	████████	██	██
Unstratified HR (95% CI)	████████		████████	
Abbreviations: CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; NET, neuroendocrine tumour; PFS, progression-free survival				

3.3.2 Secondary outcomes

3.3.2.1 Overall survival

OS results – first DCO

The CABINET trial included the option for patients in the placebo arm to cross over to open-label cabozantinib once they experienced disease progression. As crossover was only permitted at the time of progression, this did not affect PFS data collected during the trial. However, the crossover design affected OS outcomes, as patients who crossed over from the placebo arm gained survival benefits from the cabozantinib treatment that they otherwise would not have experienced with placebo. With the additional benefits expected from crossover in the placebo arm, the ITT analysis overestimated OS with placebo, thereby underestimating the relative benefits of cabozantinib. To mitigate these effects, the company used crossover adjustment methods as part of the OS analysis. The company explored using the following methods for crossover adjustment: the rank-preserving structural failure time model (RPSFTM), inverse probability of censoring weights (IPCW) and the two-stage method.

The company's preferred method of adjustment was IPCW, based on its ability to correct the bias "resulting from imbalances in prognostic factors between treatment arms in the epNET subgroups" and being able to "adequately adjust a HR close to 1". The covariates included in the IPCW OS model for probability of crossover were as follows: number of prior therapies, prior SSA use; age; primary tumour site; tumour grade; and functional status. The coefficients for the IPCW probabilities of crossover are reported in Table 44 of Appendix L of the CS, for both the pNET and the epNET population.

The company concluded that use of the two-stage method model was not feasible due to the small number of patients eligible for crossover, and the extremely small number of OS events among patients that switched. The EAG agrees that the two-stage method is not appropriate in this context.

The EAG is concerned that the IPCW method has severe limitations to adequately adjust for crossover in the CABINET trial. The EAG considers that the company has presented insufficient evidence of the 'no unmeasured confounder' assumption, which is a necessary assumption for the IPCW methodology. Furthermore, the small number of patients crossing over means that it is likely that the IPCW weights will be unstable and highly uncertain. While there were no extreme weights reported in the company's analysis, the EAG notes that the small sample sizes in the trial still lead to considerable uncertainty in the weights. As discussed in NICE DSU TSD 24, "...when switching proportions are high IPCW results can be prone to substantial bias, especially when sample sizes are small, primarily because in these cases extreme weights are common".¹⁶ This uncertainty is demonstrated in some of the coefficients for the company's IPCW weightings, where the 95% CIs for unknown functional status ranged from 0.00 to infinity. The percentage of patient crossover in each cohort, for the first DCO was:

- pNET cohort: █ patients crossed over to cabozantinib, amounting to █ of the patients who were eligible for treatment switching (i.e., █ patients who survived to progression in the placebo arm);
- epNET cohort: █ patients crossed over, amounting to █ of the patients who were eligible for treatment switching (i.e., █ patients who survived to progression in the placebo arm).

Therefore, the number of patients included in the analyses is very small, particularly in comparison with the 12 covariates that were used to fit the probabilities of crossover in the IPCW approach (further details are given in Appendix L.5.2 of the CS).

The EAG also does not agree with the company's argument for considering the RPSFTM methodology less robust than an IPCW adjustment; while Latimer *et al.* 2024 does suggest that RPSFTM may perform poorly when the ITT OS HR is 'close to 1', this is on the basis of a case study of a single RCT; it is unclear to what extent this conclusion is generalisable to other trials (for example, how 'close to 1' the ITT HR must be for the RPSFTM-derived HR to be unreliable).¹⁷ The EAG also notes that previous studies validating both IPCW and RPSFTM crossover analysis methodology were

conducted in much larger patient cohorts than those in the CABINET trial (for example, Latimer *et al.* 2014 and Latimer *et al.* 2016).^{18, 19} As far as the EAG is aware, neither methodology has been validated in a cohort as small as those in the CABINET trial, particularly the size of the pNETs cohort, and therefore the robustness of these methodologies in the current context has not been definitively established.

For the first DCO, effect estimates numerically favoured cabozantinib for OS, but differences were non-statistically significant in the ITT, IPCW and the RPSFTM methods (Table 22) in both NET cohorts. The lack of statistical significance in the results may be related to the maturity of the OS data, with ■ of patients experiencing an OS event during the first DCO. Concerns about data immaturity are greatest for the pNET cohort, where median OS was ■ months for cabozantinib and ■ months for placebo, while median follow-up times were 23.2 months for cabozantinib and 25.2 months for placebo. The EAG notes that the trials included in TA449 and TA539 (RADIANT-3 and RADIANT-4 for everolimus vs. BSC and Raymond *et al.* (2011) for sunitinib vs BSC) also showed numerically advantageous but non-statistically significant HRs (both ITT and RPSFTM) for OS for the respective treatments vs. placebo. The follow-up period across all the NET trials (including CABINET) was not dissimilar, which may be an indication of follow-up being too short to capture an observable survival benefit. Furthermore, the EAG notes that compared to the RADIANT and the Raymond *et al.* trials, CABINET has a much smaller population, which added to the uncertainty around the OS estimates:

- CABINET: pNET cohort, n=95; epNET cohort, n=203
- RADIANT-3: n=410
- RADIANT-4: n=302
- Raymond *et al.* (2011): n=171.

Table 22. OS from the CABINET trial for pNET and epNET cohorts – first DCO (adapted from Table 3 of CQ response addendum)

Population	Measure	ITT Analysis (95% CI)	RPSFTM (95% CI)	IPCW - untruncated weights (95% CI)
First DCO (cabozantinib vs placebo)				
pNET	Stratified HR	0.95 (0.45 to 2.00)	■	0.74 (0.36 to 1.52)
epNET	Stratified HR	0.86 (0.56 to 1.31)	■	0.65 (0.39 to 1.07)
Abbreviations: CI, confidence interval; DCO, data cutoff; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; IPCW, Inverse probability of censoring weights; ITT, intention to treat; OS, overall survival; pNET, pancreatic neuroendocrine tumour; RPSFTM, rank-preserving structural failure time modelling				

Given the small number of patients crossing over, paired with a high percentage of crossover, the EAG considers that the RPSFTM may be preferable to the IPCW method. Furthermore, considering that each method of crossover adjustment is associated with limitations, results of the ITT analysis are also presented in the EAG's critique, as recommended by NICE DSU TSD 16.²⁰ The inclusion of the ITT results allows for comparisons with the most conservative estimates of the effects of cabozantinib.

Length of follow-up

Overall survival was provided until the first data cut-off (DCO) when the CABINET trial was terminated (August 2023) (**Key issue 3**). The EAG requested the analyses of any additional OS results that were collected beyond this point, and the company provided a further 12 months of follow-up data, until September 2024 (hereafter referred to as the updated DCO). The company reported that the additional data was the result of an unplanned OS sweep requested during the marketing authorisation assessment, and it noted that it did not come from a pre-specified analysis. Further information about the OS sweep was not provided, and so it is unclear whether there were any interruptions in the follow-up of patients during the additional year of data collection. The company highlighted a number of factors that they considered to be limitations of the OS data from the updated DCO, including:

- Imbalances in prognostic factors across treatment arms in the largest population stratum of CABINET (patients with concomitant SSA use and without prior sunitinib use) for the pNETs cohort. The company reported that the impact of these imbalances was more pronounced in the updated DCO than the first DCO.
- A high proportion of censoring in the updated DCO, as patients who had not died prior to the first DCO were censored at their last alive date, or at the DCO date if their last alive date was unknown. The tails of the OS curves were therefore informed by few patients at risk; and
- A high proportion of patients in the updated DCO who received subsequent treatments, including crossover cabozantinib for placebo patients. The company was concerned that the higher proportion of patients crossing over to cabozantinib could lead to poorer performance of crossover adjustment methods.

Given the concerns above, the company considered it more appropriate to use the OS data from the first DCO to inform their base case.

While the EAG acknowledges that the issues raised by the company can introduce uncertainty to the OS analysis, it is not clear why most (if not all) of these concerns are not also applicable to the first DCO:

1. The imbalance in prognostic factors in the largest stratum of pNET patients raised by the company were based on:
 - The number of patients receiving three or more prior treatments (■■■ cabozantinib; ■■■ placebo). The EAG notes that, while smaller, a similar imbalance was evident in the first DCO for patients with three or more prior treatments in the overall pNET cohort (■■■ cabozantinib; ■■■ placebo). Additionally, as discussed in Section 3.3.4.2, the company's subgroup analyses suggest that the number of prior treatments does not affect the relative treatment effect of cabozantinib on OS;
 - The number of patients with Grade 3 tumours (■■■% for cabozantinib vs ■■■% for placebo). While this could impact on treatment response, the EAG notes that similar concerns are apparent in the first DCO. For instance, in lung NET patients, nearly ■■■ more patients in the cabozantinib arm had Grade 1 tumours compared to the placebo arm(■■■ indicating more severe disease for the placebo patients.
 - ECOG status greater than 0 (■■■% for cabozantinib vs ■■■% for placebo). The EAG notes that, while smaller, imbalances in ECOG status are also apparent in the first DCO. Additionally, the EAG notes that the assessment of ECOG status can vary between clinicians, and it is unclear how much of an impact the difference between an ECOG score of 0 or 1 would have on treatment response. As such, the potential impact of this imbalance is unclear.
2. The company stated that *"with the small number of patients at risk for later timepoints, there is high uncertainty arising from fewer events being observed as time progresses, which diminishes the precision and reliability of survival estimates at later timepoints"*. In the pNET cohort, ■■■% of cabozantinib and ■■■% of placebo patients were censored alive at the first DCO, while in the epNET cohort, ■■■% of cabozantinib and ■■■% of placebo patients were censored. While the EAG agrees that a small number of patients can introduce uncertainties into the analysis, it does not consider these uncertainties to be considerably greater than

those for the first DCO, where 67% of cabozantinib patients and 65% of placebo patients were censored in the pNET cohort and 55% of cabozantinib patients and 46% of placebo patients were censored in the epNET cohort. The EAG does not consider data censoring in the updated DCO to invalidate the use of a more mature dataset.

3. The EAG also has few concerns about the higher proportion of patients who have subsequent treatments in the updated DCO. Although this should be acknowledged when interpreting the results, particularly as placebo patients had a higher percentage of subsequent treatments than those in the cabozantinib arm, this is likely to reflect clinical practice. As discussed in Section 3.3.2.1, the EAG has presented results of the ITT analysis in addition to the results of crossover adjustments to provide a comparison with the most conservative estimate of the effects of cabozantinib.

Based on the points outlined above, the EAG considers that the use of more mature OS data is the more appropriate approach, and therefore, prefers the use of the updated DCO in the analysis. Nonetheless, for completeness, results from both DCOs are included in the EAG's critique.

OS results – updated DCO

For the updated DCO, effect estimates numerically favoured placebo, but differences were not statistically significant (Table 23). Effect estimates for the ITT analysis and the RPSFTM adjustment were similar for the pNET population, which the company attributed to the HRs being close to 1; in particular, ITT and RPSFTM OS HRs were equal up to two decimal places in the pNET population (both point estimate and 95% CI). Differences were more apparent for the epNET cohort, with the effect estimate numerically favouring cabozantinib with IPCW, although results were not statistically significant for either method of adjustment.

The updated DCO data may have similar limitations relating to data immaturity as the first DCO, although the OS data sweep had an additional 12-month follow-up. The percentage of patients crossing over in the updated DCO was:

- pNET cohort: ■ patients crossed over to cabozantinib, amounting to ■ of the patients in the placebo arm of the updated DCO;
- epNET cohort: ■ patients crossed over, amounting to ■ of the patients in the placebo arm of the updated DCO.

As for the original DCO, the EAG considers that the RPSFTM approach provides a step in the right direction for adjusting the OS data for crossover, when compared to the IPCW and the unadjusted ITT analysis. Nonetheless, the EAG notes that the RPSFTM method is still likely to produce uncertain estimates of survival given the small number of patients who crossed over. As a result, ITT OS HRs unadjusted for crossover are also explored in subsequent analyses.

Table 23. OS from the CABINET trial for pNET and epNET cohorts - updated DCO (adapted from Table 3 of CQ response addendum)

Population	Measure	ITT Analysis (95% CI)	RPSFTM (95% CI)	IPCW - untruncated weights (95% CI)
pNET	Stratified HR	■	■	■
epNET	Stratified HR	■	■	■
Abbreviations: CI, confidence interval; DCO, data cutoff; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; IPCW, Inverse probability of censoring weights; ITT, intention to treat; NET, neuroendocrine tumour; PFS, progression-free survival; RPSFTM, rank-preserving structural failure time modelling				

3.3.2.1.1 Additional analysis requested by the EAG

Following a clarification request by the EAG, the company provided the OS analysis for the lung NET and epNETs (without lung NETs) subgroups. Results were provided for both the first DCO and the updated DCO, both of which are considered below. Median OS was considerably longer with cabozantinib than placebo for lung NETs. In contrast, median OS was longer for the placebo group than with cabozantinib for patients with epNETs without lung:

- Median OS lung NETs (ITT):
 - First DCO: cabozantinib ■ placebo ■
 - Updated DCO: cabozantinib ■ ■ placebo ■
- Median OS epNETs (without lung):
 - First DCO: cabozantinib ■ placebo ■
 - Updated DCO: cabozantinib ■ placebo ■.

The HRs reported in Table 24 highlight the considerable difference in the effect of cabozantinib on OS between the lung NET patients and those with other types of epNETs. The results consistently show a statistically significant effect of cabozantinib on OS in the lung NET population (even for the

ITT population). In the epNET (without lung) group, HRs numerically favour placebo but are not statistically significant.

The EAG draws attention to the pooled epNET OS HRs presented in the previous section for the updated DCO of [REDACTED] for the ITT population and RPSFTM HR of [REDACTED] for the epNET population.

Comparing these results with those reported in Table 24, suggests that while cabozantinib might not demonstrate a survival benefit in the pooled epNET population, it does show a benefit for those with lung NETs, when compared to placebo. The EAG acknowledges the uncertainty in these conclusions, given that the lung NET comparisons are based on a *post-hoc* analysis and the fact that these results are subject to the same considerations as the PFS analysis about the imbalances in baseline characteristics in the lung NET population, which are likely to favour the cabozantinib group (Section 3.3.1.1).

Table 24. OS from the CABINET trial for lung NET patients and epNET patients (without lung NETs). ITT analysis.

OS	Lung NETs (n=49)			epNETs (without lung) (n=154)		
	ITT Analysis	RPSFTM	IPCW	ITT Analysis	RPSFTM	IPCW
Primary DCO						
Unstratified HR (95% CI)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Updated DCO						
Unstratified HR (95% CI)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Abbreviations: CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; IPCW, Inverse probability of censoring weights; ITT, intention to treat; NET, neuroendocrine tumour; OS, overall survival; RPSFTM, rank preserving structural failure time model						

3.3.2.2 Summary of results from CABINET

The EAG considered the apparent discrepancy in the direction of the PFS and OS results in the CABINET trial, particularly when the updated DCO OS data are used. The EAG's preference remains to use the more mature OS data (**Key issue 3**), and notes that 12 months of additional OS trial data should not be ignored (as is the company's preference in their base case). The EAG acknowledges that the number of patients in CABINET is considerably small, leading to a small number of patients

crossing over and a reduced number of OS events in patients who crossed over. Consequently, OS results with different adjustment methods are uncertain.

After consideration of the evidence, the EAG concluded that assuming equal survival for cabozantinib and BSC in the economic model was a more plausible approach than using the ITT or the RPSFTM HRs for the updated DCO. The latter imply a survival advantage for placebo against cabozantinib, which lacks clinical validity. Results of the EAG's exploratory analysis are reported in Section 6.

3.3.2.3 Objective response rate

Objective response rate (ORR) was based on patient's best overall response to treatment of either:

1. Complete response, defined as an absence of detectable cancer; or
2. Partial response, reflecting a reduction in the size of the tumour of more than 30%.

No patients in either cohort experienced a complete response with cabozantinib or placebo (Table 25). In contrast, cabozantinib resulted in 19% of patients in the pNET cohort and 5.2% of patients in the epNET cohort achieving a partial response, while no patients achieved a partial response with placebo in either cohort. The benefits of cabozantinib over placebo are therefore demonstrated in the ORR treatment difference for both cohorts (Table 25), indicating better partial response to treatment.

Although both cohorts demonstrated benefits of cabozantinib for ORR, the greatest benefits were seen for the pNET cohort (Table 25), where differences between cabozantinib and placebo were statistically significant. The difference in ORR was less pronounced for the epNET cohort, with a non-significant difference between trial arms. Although the proportion of patients benefiting from cabozantinib were larger for the pNET cohort, the time to experience any benefit was similar between cohorts (median time to confirmed objective response: 5.78 months for pNET, 5.5 months for epNET).

Table 25. ORR from the CABINET trial for pNET and epNET cohorts (reproduced from Table 15 of CS).

ORR	pNET		epNET	
	Cabozantinib (n=64)	Placebo (n=31)	Cabozantinib (n=134)	Placebo (n=69)
Complete response, n (%)	0	0	0	0
Partial response, n (%)	12 (19%)	0	7 (5.2%)	0

ORR (95% CIs)	19% (10.1% to 30.5%)	0 (0.0% to 11.2%)	5.2% (2.1% to 10.5%)	0 (0.0% to 5.2%)
ORR treatment difference (95% CIs)	18.8% (9.2% to 28.3%)		5.2% (1.5% to 9.0%)	
p value	0.0115		0.0524	
Abbreviations: CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumour; ORR, objective response rate; pNET, pancreatic neuroendocrine tumour				

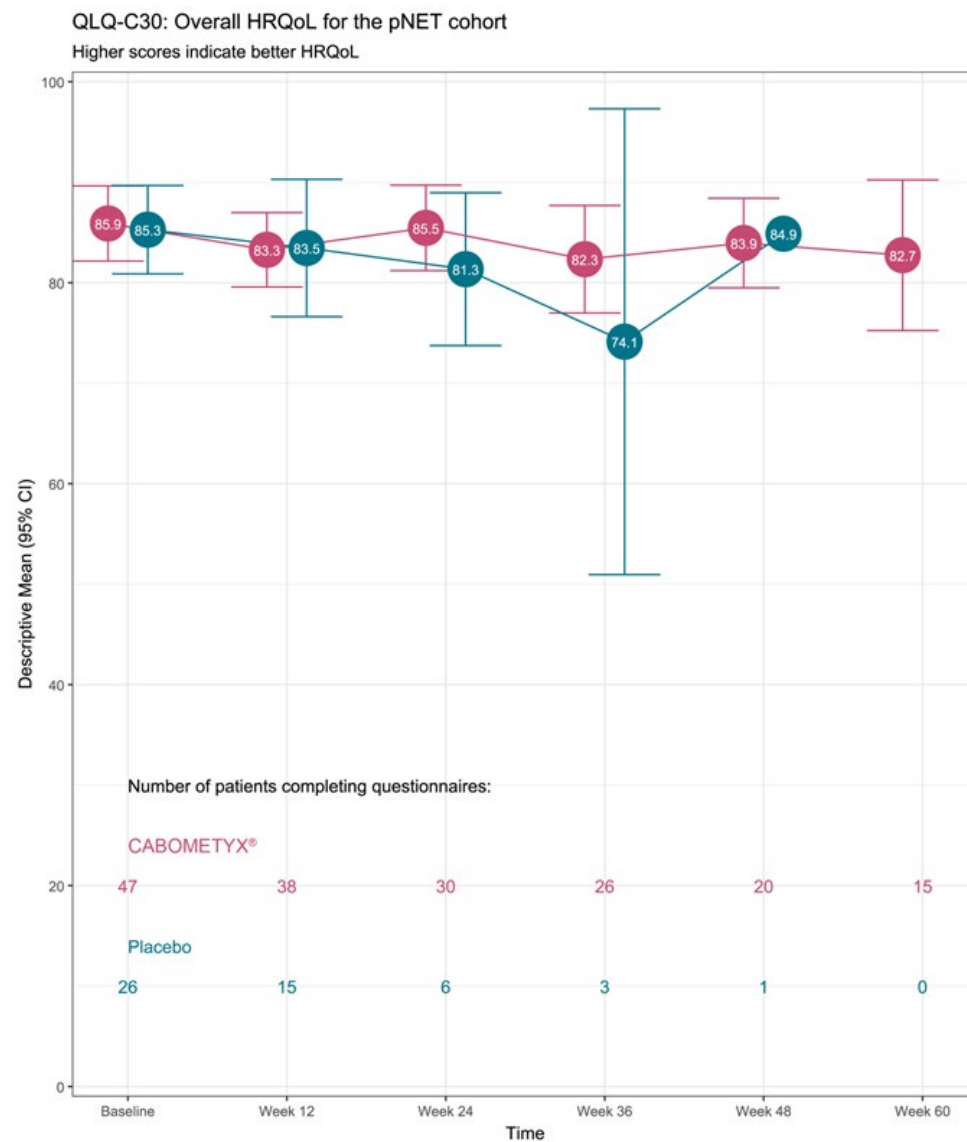
3.3.3 Quality of life

Health-related quality of life (HRQoL) was measured as part of a sub-study to the CABINET trial, as discussed in Sections 2.3.4 and 3.2. While the sub-study used three measures to assess HRQoL (EORTC-QLQ-C30, QLQ-GINET21 and PGIC), the CS focused on the summary scores and global health domain scores of the EORTC-QLQ-C30, stating that the results of the QLQ-GINET21 and PGIC questionnaires are consistent with those of the EORTC-QLQ-C30. The EAG is satisfied that this approach did not overlook any different trends from the QLQ-GINET21 and PGIC questionnaires and so the critique below will focus on the EORTC-QLQ-C30. Although the CS did not report any values to determine whether a difference between arms is considered clinically meaningful, the EAG notes that research suggests a difference in EORTC-QLQ-C30 score of 10.0 points is considered clinically meaningful for a range of cancer types.²¹

For the pNET cohort, overall HRQoL was similar between cabozantinib and placebo throughout the trial and did not exceed the threshold for a clinically meaningful difference between treatments at any point (Figure 5). Differences between trial arms were more apparent for the global health status scores, with cabozantinib patients reporting higher scores, and therefore greater HRQoL, than those in the placebo arm from week 36 onwards. This was driven by a fall in scores in the placebo arm, while scores in the cabozantinib arm remained relatively stable.

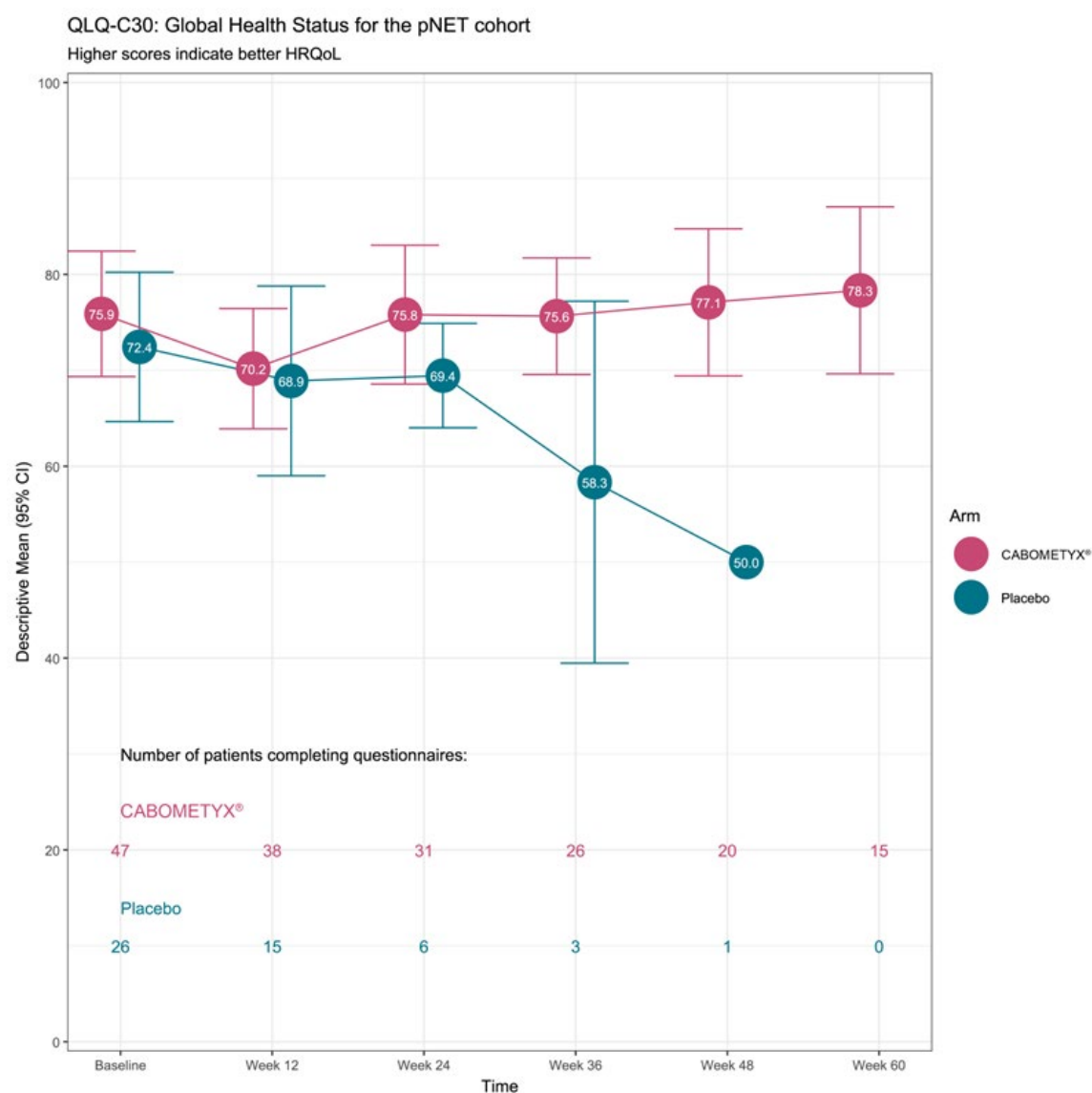
For epNET patients, the first 36 weeks of the trial show a similar trend to the pNET cohort, with similar scores reported by the patients in both trial arms. However, with a rise in scores in the placebo group over time, overall HRQoL and global health status both favoured placebo towards the end of the trial. This exceeds the threshold for a minimal clinically important difference from week 36 onwards for global health status.

Figure 5. EORTC-QLQ-C30 overall scores in the pNET cohort (higher scores represent better HRQoL).
Reproduced from Figure 14 of CS



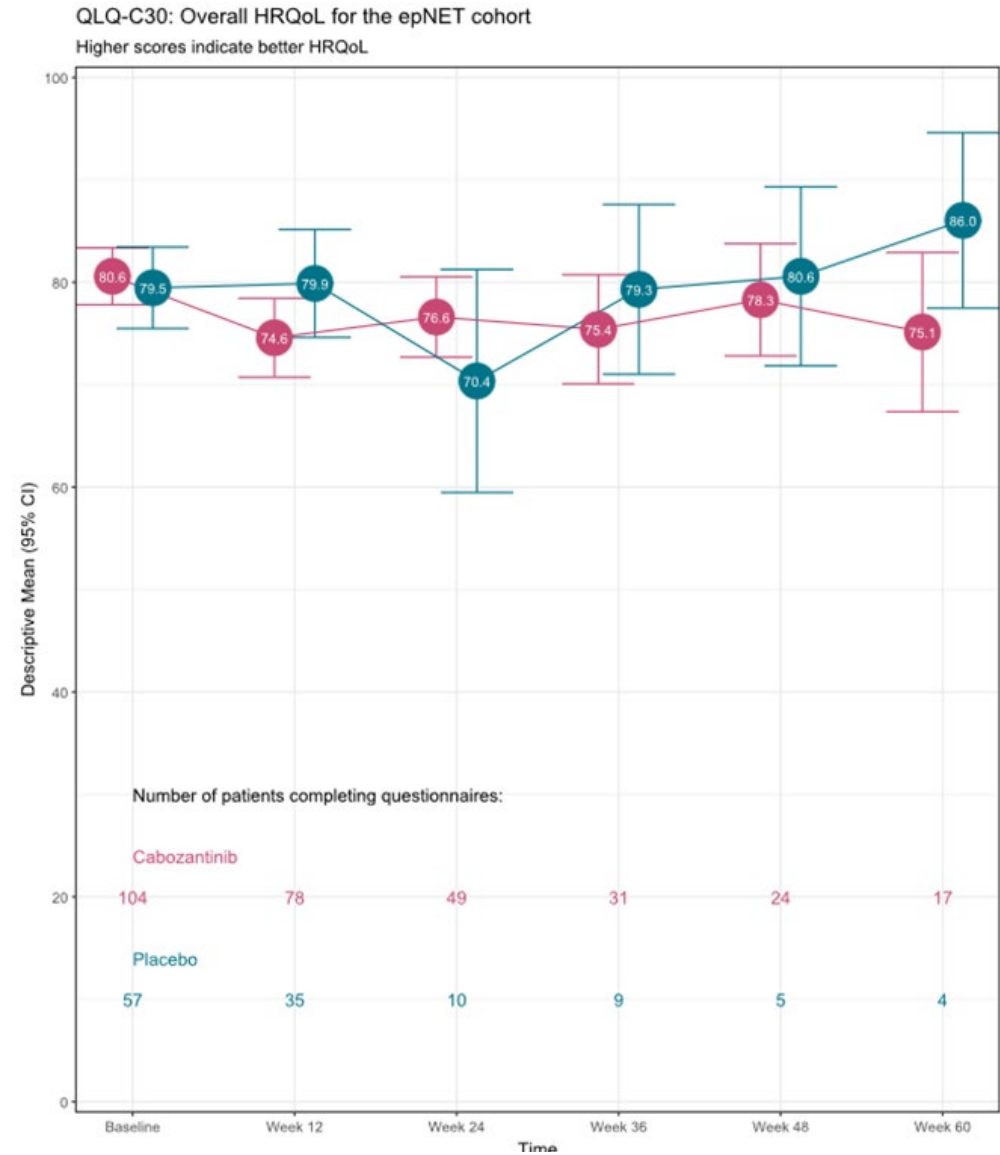
Abbreviations: CI, confidence interval; CS, company submission; HRQoL, health-related quality of life; pNET, pancreatic neuroendocrine tumour; QLQ-C30, Quality of Life Questionnaire

Figure 6. EORTC-QLQ-C30 global health status scores in the pNET cohort (higher scores represent better HRQoL). Reproduced from Figure 14 of CS



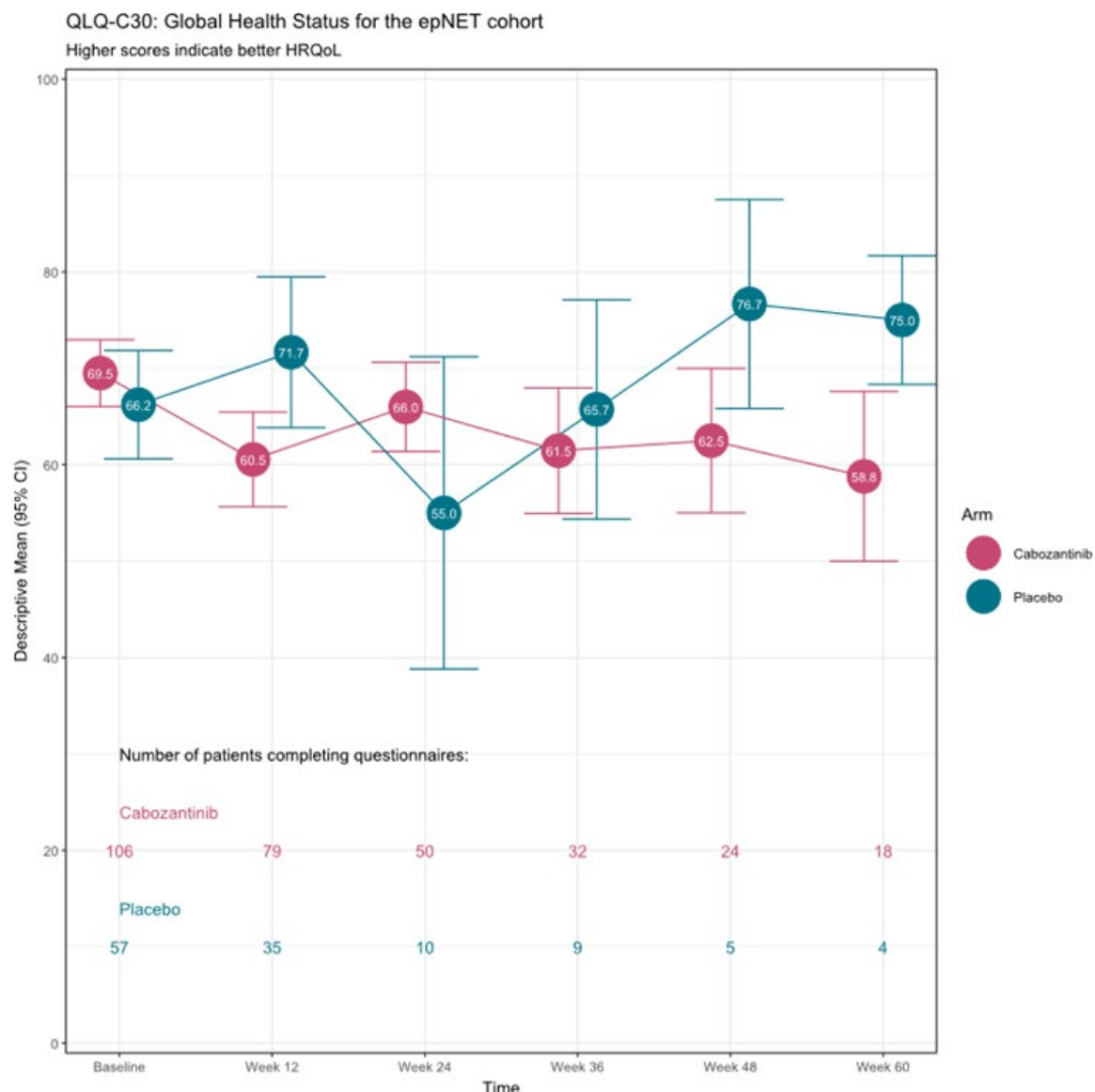
Abbreviations: CI, confidence interval; CS, company submission; HRQoL, health-related quality of life; pNET, pancreatic neuroendocrine tumour; QLQ-C30, Quality of Life Questionnaire

Figure 7. EORTC-QLQ-C30 overall scores in the epNET cohort (higher scores represent better HRQoL). Reproduced from Figure 15 of CS



Abbreviations: CI, confidence interval; CS, company submission; HRQoL, health-related quality of life; pNET, pancreatic neuroendocrine tumour; QLQ-C30, Quality of Life Questionnaire

Figure 8. EORTC-QLQ-C30 global health status scores in the epNET cohort (higher scores represent better HRQoL). Reproduced from Figure 15 of CS



Abbreviations: CI, confidence interval; CS, company submission; HRQoL, health-related quality of life; pNET, pancreatic neuroendocrine tumour; QLQ-C30, Quality of Life Questionnaire

While results for the pNET cohort indicate greater global health status scores with cabozantinib, the EAG has concerns about the robustness of the comparisons for both the pNET and epNET cohorts (**Key issue 7**). As discussed in Sections 2.3.4 and 3.2, participation in the HRQoL sub-study was optional and the results therefore break randomisation. To address these concerns, the EAG requested the baseline characteristics for the HRQoL sub-study. While many of the baseline characteristics were similar between trial arms, there were some notable differences (Table 26). Although some of these characteristics were not raised as treatment effect modifiers by the

company or the EAG's clinical experts, others may have more of an impact. For instance, a higher percentage of patients had Grade 3 tumours in the cabozantinib arm of the pNET cohort, and a higher percentage had three or more prior systemic treatments in the cabozantinib arm for both pNETs and epNETs. No information was provided about primary tumour location, which could also be crucial given the EAG's concerns about the difference between treatment effectiveness for lung NETs and other epNETs. Concerns about the robustness of the HRQoL data also impacted the economic modelling, which is discussed in Section 4.2.6.1.1.

Table 26. Key differences in baseline characteristics from the CABINET HRQoL sub-study (adapted from Table 12 of the clarification response).

	pNET		epNET	
	Cabozantinib (n=55)	Placebo (n=28)	Cabozantinib (n=113)	Placebo (n=58)
Sex – male, n (%)	■	■	■	■
Race, n (%)				
White	■	■	■	■
Black or African American	■	■	■	■
Asian	■	■	■	■
American Indian or Alaska Native	■	■	■	■
Native Hawaiian or Other Pacific Islander	■	■	■	■
Not reported	■	■	■	■
Unknown	■	■	■	■
Ethnicity, n (%)				
Hispanic or Latino	■	■	■	■
Not Hispanic or Latino	■	■	■	■
Not reported	■	■	■	■
Unknown	■	■	■	■
ECOG performance status, n (%)				
0	■	■	■	■
1	■	■	■	■
2	■	■	■	■
Tumour grade				
Grade 1	■	■	■	■
Grade 2	■	■	■	■
Grade 3	■	■	■	■
Unknown	■	■	■	■

Number of prior systemic treatments (excluding SSAs), n (%)				
1	■	■	■	■
2	■	■	■	■
≥3	■	■	■	■
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; epNET, extra-pancreatic neuroendocrine tumour; ORR, objective response rate; pNET, pancreatic neuroendocrine tumour; SSA, somatostatin analogue				

In addition to concerns about randomisation, the low number of patients in the sub-study may affect interpretation of the results (**Key issue 7**). By week 48, where the greatest difference was seen between trial arms for global health status (27.1 points) in the pNET cohort, there was only one patient remaining in the placebo arm, compared to 20 patients for cabozantinib (Figure 5 and Figure 6). It is therefore unclear whether the reduced scores in the placebo arm reflect a reduction in HRQoL over time or are instead a result of the placebo patients who reported higher HRQoL no longer being included in the analysis. With limited information in the CS about reasons for dropout from the sub-study, concerns about differences in baseline characteristics, and no separation of epNET results based on primary tumour location, the EAG considers there to be substantial uncertainties surrounding the benefits of cabozantinib over placebo for HRQoL.

3.3.4 Subgroup analysis

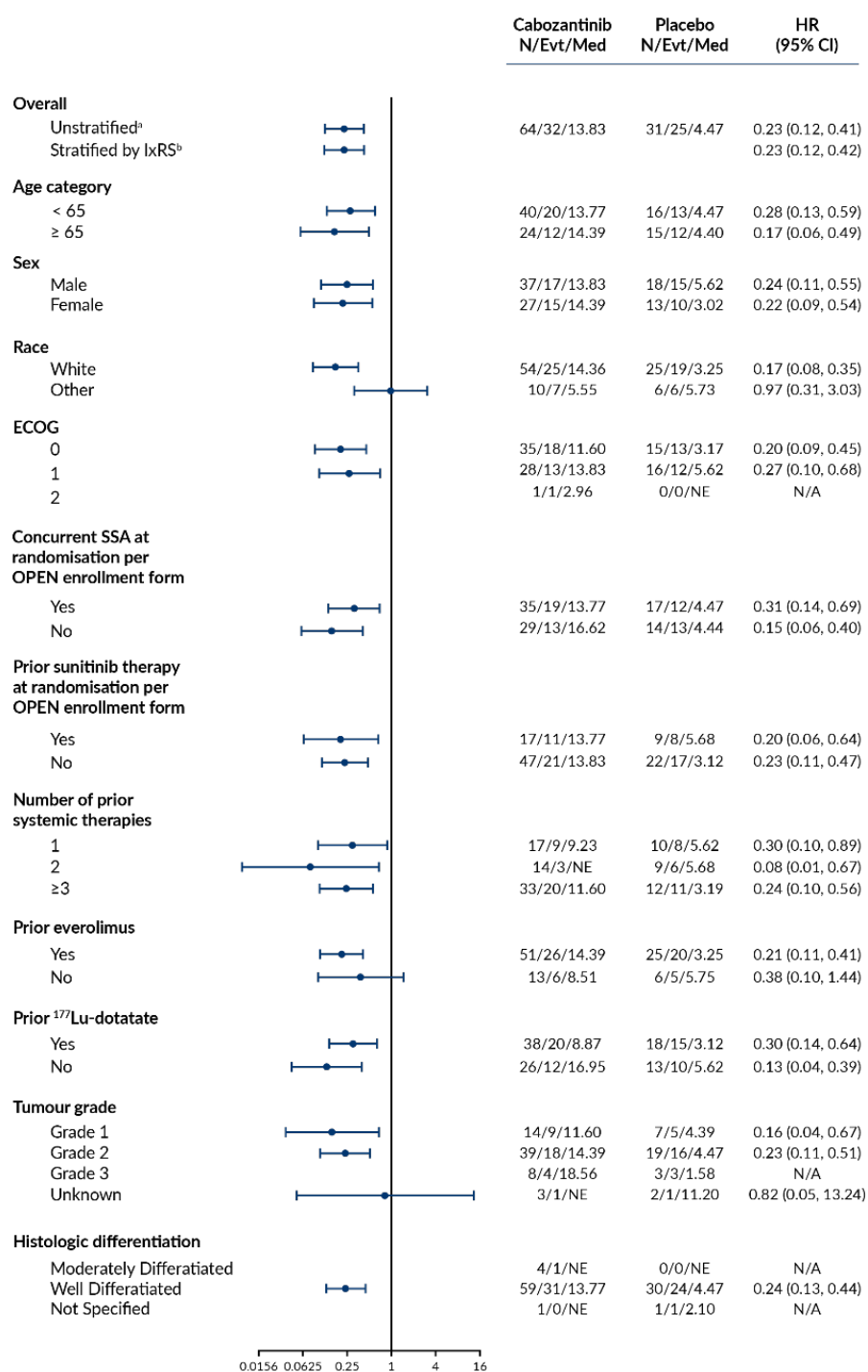
3.3.4.1 Progression free survival

The CS reported a wider range of subgroups for PFS than was outlined in the NICE scope (Figure 9 and Figure 10). Results were similar within subgroups with effect estimates numerically favouring cabozantinib throughout. Some subgroups were associated with wider uncertainty, such as race, where the 'Other' subgroup had substantially wider 95% CIs than the 'White' subgroup in both cohorts. However, much of the additional uncertainty in these instances appears to be from low patient numbers in one of the subgroups.

The two subgroups which matched the NICE final scope were histologic differentiation (for pNETs and epNETs) and primary tumour site (for epNETs, separated by midgut GI and non-midgut GI). It is not possible to determine the effects of histologic differentiation on treatment effectiveness in either cohort, as low patient and event numbers meant that results were only available for the well differentiated subgroup (Figure 10). Results for the well differentiated group (pNET: HR 0.24, 95% CIs 0.13 to 0.44; epNET: HR 0.51, 0.33 to 0.78) indicated similar PFS benefits of cabozantinib to the ITT analysis.

Analysis of primary tumour site in the epNET cohort indicated greater benefits of cabozantinib on PFS for the midgut than the non-midgut GI greater uncertainty for the non-midgut GI group, with the upper 95% CI crossing the line of no effect. The company attributed this to low patient numbers but noted that both effect estimates numerically favoured cabozantinib.

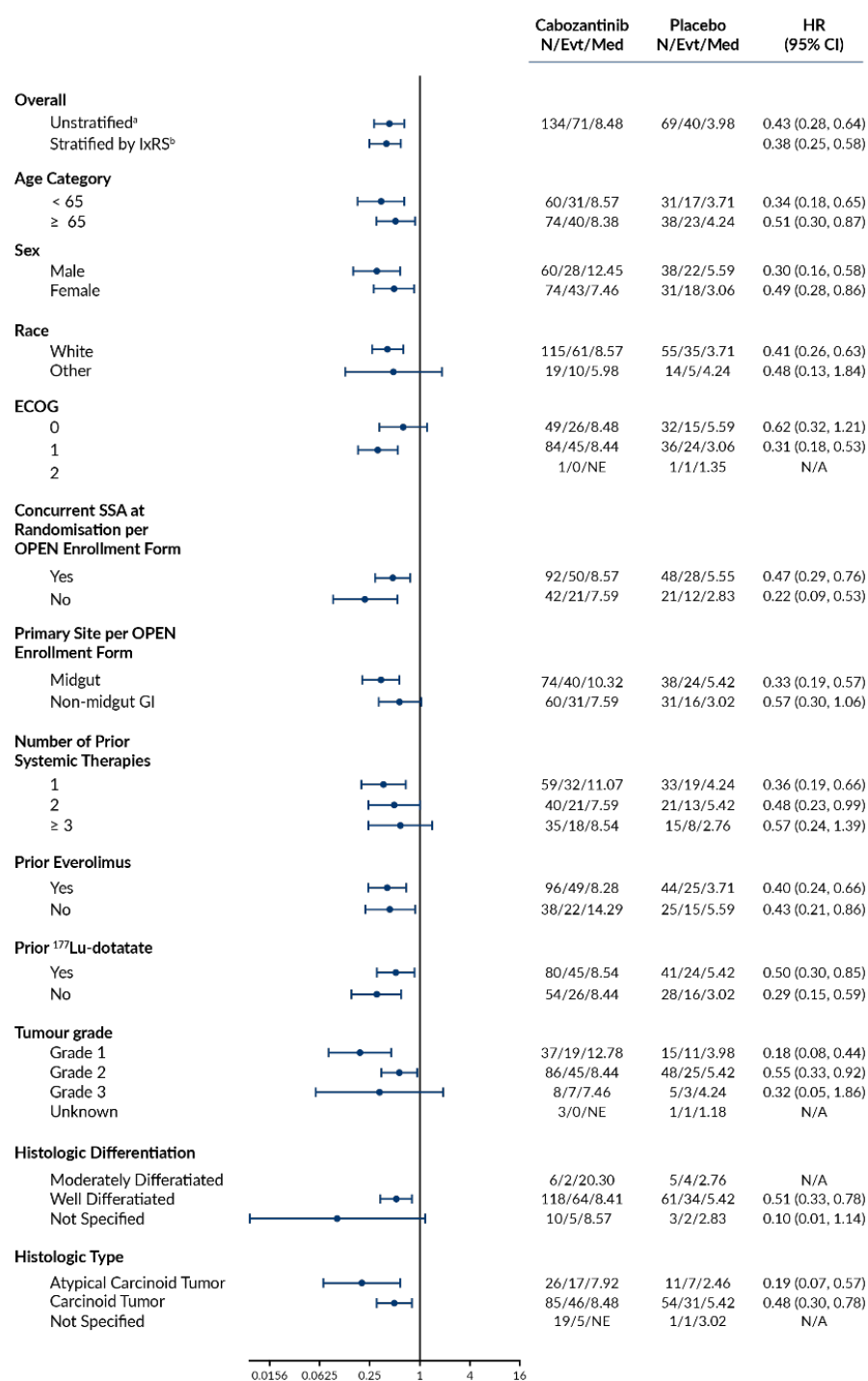
Figure 9. PFS subgroup analyses for the pNET cohort. Reproduced from Figure 16 of CS



^a HR and 95% CI estimates from the unstratified Cox proportional hazards model are presented for both subgroups. ^b Stratification factors are as follows: (1) concurrent SSA use (yes, no) and (2) prior sunitinib therapy (yes, no).

Abbreviations: BIRC: blinded independent review committee; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; Evt: number of patients with events; HR: hazard ratio; ITT: intent-to-treat; IxRS: interactive voice/web response system (ie, the OPEN registration system); Med: median; N: number of patients; NA: not applicable; NE: not estimable; OPEN: Oncology Patient Enrolment Network; pNET: pancreatic neuroendocrine tumour

Figure 10. PFS subgroup analyses for the epNET cohort. Reproduced from Figure 17 of CS



^a HR and 95% CI estimates from the unstratified Cox proportional hazards model are presented for both subgroups. ^b Stratification factors are as follows: (1) concurrent SSA use (yes, no) and (2) primary site (midgut/unknown versus non-midgut GI/lung/other).

Abbreviations: BIRC: blinded independent review committee; CI: confidence interval; DCO: data cut-off; ECOG: Eastern Cooperative Oncology Group; Evt: number of patients with events; GI: gastrointestinal; HR: hazard ratio; ITT: intent-to-treat; IxRS: interactive voice/web response system (i.e. the OPEN registration system); Med: median; N: number of patients; NA: not applicable; OPEN: Oncology Patient Enrolment Network; SSA: somatostatin analogue.

In addition to the pre-planned subgroup analyses, the company performed an additional *post-hoc* analysis for primary tumour site in the epNET cohort, separating patients with lung NETs; GI NETs; and “Other” (Table 27). As discussed in Section 3.3.1.1, cabozantinib resulted in greater PFS benefits for the lung NET subgroup than the other epNET sites pooled together. The EAG also notes that the GI subgroup shows a numerical advantage to cabozantinib, albeit not statistically significant, and that the “Other” subgroup, which the company stated included small bowel, mesenteric, ampullary, midgut (jejunum, ileum and cecum), hindgut, biliary tract, larynx, pre-sacral, kidney and ethmoid sinus, presented a statistically significant benefit for cabozantinib, albeit numerically smaller than the one observed in the lung subgroup. The EAG therefore considers that the results for both the lung and the “Other” subgroup are driving the results for the epNET subgroup, and that cabozantinib appears to have fewer benefits over placebo for patients with GI NETs. However, as discussed in Section 3.3.1.1, epNET primary tumour site was not a stratification factor at randomisation. This was highlighted in the CS for the GI subgroup, where patients in the cabozantinib arm had more prior therapies, a longer disease duration, and a higher proportion of patients with an ECOG status of 1 than placebo. It is therefore likely that the differences between epNET primary tumour locations reflect both a difference in treatment response and differences in disease severity between trial arms.

Table 27: PFS post-hoc analysis by primary tumour site in the epNET cohort. Reproduced from Table 11 of CS, Appendix C.

Primary site (per OPEN enrolment form)	Cabozantinib n/Events/Median	Placebo n/Events/Median	HR (95% CI)
epNET	■	■	■
GI	■	■	■
Lung/thymus	■	■	■
Unknown/other	■	■	■
Abbreviations: CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumour; GI, gastrointestinal; HR, hazard ratio			

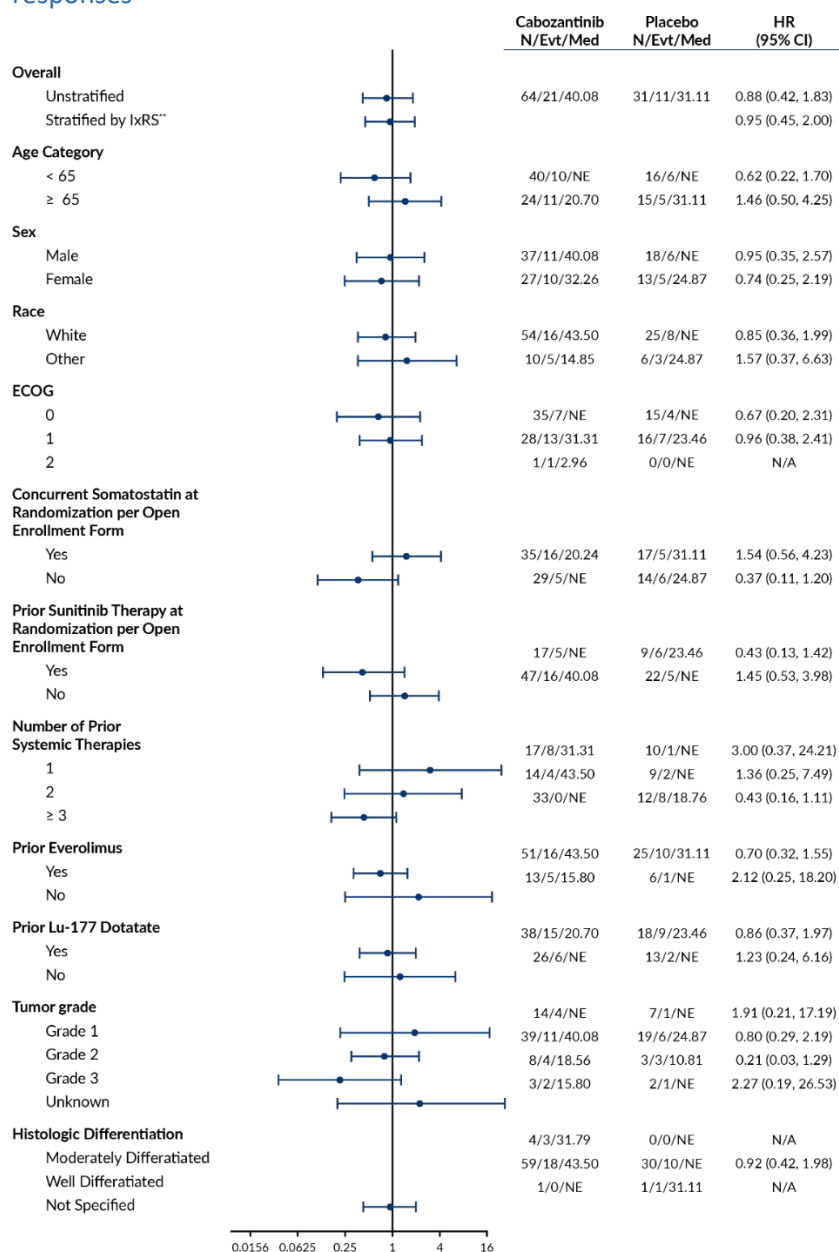
3.3.4.2 Overall survival

Similar to the ITT analysis, the subgroup analyses for OS are subject to more uncertainties than those observed for PFS. Effect estimates were close to the line of no effect for most subgroups, with wide 95% CIs (Figure 11 and Figure 12). As with PFS, some of the uncertainty associated with the effect estimates are likely to be a result of low patient numbers in the subgroups.

As for PFS, low patient and event numbers for histologic differentiation meant that comparisons for the pNET cohort were not possible, with results only available for the well-differentiated subgroup. For the epNET cohort, the moderately differentiated subgroup appeared to benefit more from cabozantinib than the well differentiated subgroup (Figure 12). However, with very low patient numbers in the moderately differentiated subgroup (cabozantinib n=6; placebo n=5), it is not possible to draw any strong conclusions on the effects of histological differentiation on treatment response.

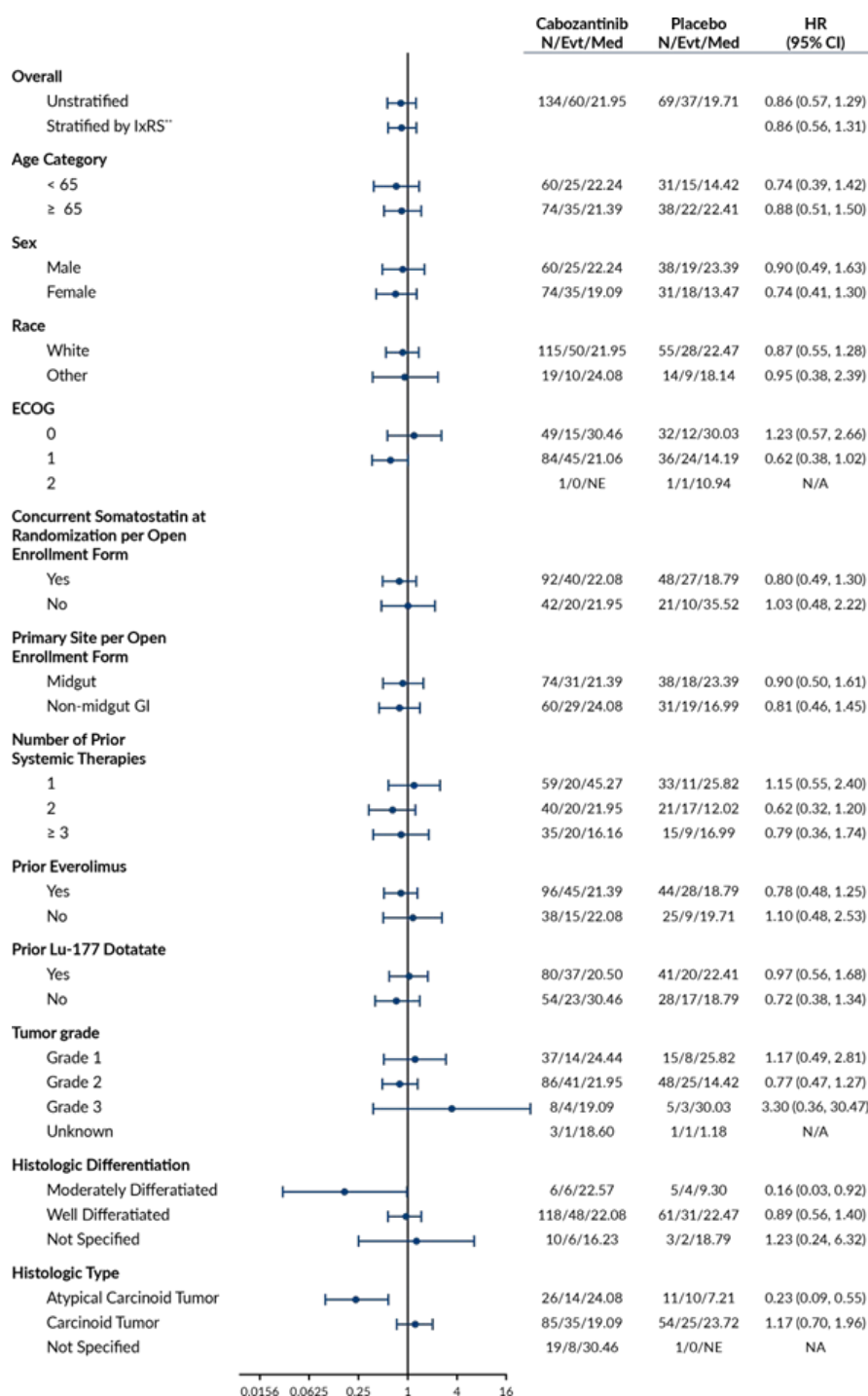
The only subgroup which appeared to affect treatment response was histologic tumour type in the epNET cohort (Figure 12), where statistically significant benefits were seen with cabozantinib for patients with atypical carcinoid tumours, compared to a non-significant difference for typical carcinoid tumours. These differences may not be surprising, as the EAG's clinical experts noted that patients with atypical carcinoid tumours typically have a worse prognosis and more aggressive disease than those with typical carcinoid tumours, and therefore potentially stand to benefit more from treatment. Additionally, the EAG notes that there was a small imbalance in this characteristic at baseline, with more patients with atypical carcinoid tumours in the cabozantinib (19%) than placebo arm (16%).

Figure 11. OS subgroup analyses for the pNET cohort. Reproduced from Figure 6 of clarification responses



Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; Evt, number of patients with events; ITT, intent-to-treat; IxRS, interactive voice/web response system; Med, median; N, number of patients; NA, not applicable; NE, not estimable; OPEN, Oncology Patient Enrollment Network; pNET, pancreatic neuroendocrine tumour

Figure 12. OS subgroup analyses for the epNET cohort. Reproduced from Figure 7 of clarification responses



Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; epNET, extra-pancreatic neuroendocrine tumour; Evt, number of patients with events; GI, gastrointestinal; HR, hazard ratio; ITT, intent-to-treat; IxRS, interactive voice/web response system; Med, median; N, number of patients; NA, not applicable; OPEN, Oncology Patient Enrollment Network

3.3.5 Safety

The CS presented information on adverse events (AEs), serious AEs (SAEs), Grade 3/4 AEs, Grade 5 AEs and AEs leading to dose modification or reduction. In both cohorts, all patients had at least one AE (Table 28). A higher percentage of patients experienced each type of AE with cabozantinib than placebo. No Grade 5 AEs were reported in either trial arm for pNETs. For epNETs, the percentage of Grade 5 AEs was small, and similar for the two trial arms.

When comparing patients in the cabozantinib arm, the percentage of AEs, SAEs and AEs leading to dose modifications were similar between the pNET and epNET cohorts (Table 28).

Table 28. Safety outcomes in the pNET and epNET cohorts. Reproduced from Table 17 of CS

	pNET		epNET	
	Cabozantinib (n=63)	Placebo (n=31)	Cabozantinib (n=132)	Placebo (n=67)
AE, n (%)	63 (100%)	31 (100%)	132 (100%)	67 (100%)
SAE, n (%)	29 (46%)	7 (23%)	58 (44%)	27 (40%)
Worst Grade 3 or 4 AE, n (%)	46 (73%)	14 (45%)	89 (67%)	26 (39%)
Worst Grade 5 AE, n (%)	0 ^a	0	9 (6.8%)	5 (7.5%)
AE leading to dose modification (reduction or hold), n (%)	56 (89%)	16 (52%)	113 (86%)	28 (42%)
AE leading to treatment discontinuation, n (%)	12 (19%)	3 (9.7%)	36 (27%)	13 (19%)
Abbreviations: AE, adverse event; epNET, extra-pancreatic neuroendocrine tumour; pNET, pancreatic neuroendocrine tumour; SAE, serious adverse event				
^a A single death occurred due to tumour (per the patient status CRF) during the safety reporting window but was not entered as a Grade 5 AE				

The most frequently reported AEs from the CABINET trial are reported in Table 29, with solicited events, which patients were requested to report, highlighted in bold. In the pNET cohort, fatigue, elevated aspartate aminotransferase, elevated alanine aminotransferase, diarrhoea and hypertension were most common with cabozantinib (reported by >50% of patients). The same AEs were also most reported for the epNET cohort, in addition to platelet count reduction.

Table 29. Most frequently reported all-cause AEs in the pNET and epNET cohorts. Reproduced from Table 18 of CS

	pNET		epNET	
	Cabozantinib (n=63)	Placebo (n=31)	Cabozantinib (n=132)	Placebo (n=67)
Fatigue	50 (79%)	19 (61%)	95 (72%)	39 (58%)
AST increased	48 (76%)	15 (48%)	93 (70%)	15 (22%)
Diarrhoea	40 (63%)	7 (23%)	86 (65%)	28 (42%)
Hypertension	40 (63%)	15 (48%)	84 (64%)	27 (40%)
ALT increased	46 (73%)	12 (39%)	83 (63%)	15 (22%)
Platelet count decreased	21 (33%)	6 (19%)	68 (52%)	8 (12%)
Nausea	24 (38%)	10 (32%)	52 (39%)	14 (21%)
Stomatitis^a	30 (48%)	3 (9.7%)	51 (39%)	8 (12%)
WBC count decreased	-	-	49 (37%)	3 (4.5%)
Neutrophil count decreased	14 (22%)	2 (6.5%)	45 (34%)	4 (6.0%)
PPE syndrome	27 (43%)	4 (13%)	45 (34%)	4 (6.0%)
Decreased Appetite	15 (24%)	6 (19%)	44 (33%)	10 (15%)
Dysgeusia	18 (29%)	2 (6.5%)	43 (33%)	2 (3.0%)
Hypothyroidism	-	-	41 (31%)	2 (3.0%)
Anaemia	16 (25%)	10 (32%)	39 (30%)	13 (19%)
Blood alkaline phosphatase increased	13 (21%)	7 (23%)	38 (29%)	21 (31%)
Hyperglycaemia	21 (33%)	13 (42%)	36 (27%)	23 (34%)
Lymphocyte count decreased	14 (22%)	5 (16%)	36 (27%)	11 (16%)
Weight decreased	-	-	36 (27%)	5 (7.5%)
Abdominal pain	14 (22%)	5 (16%)	34 (26%)	27 (40%)
Blood creatinine increased	-	-	31 (23%)	8 (12%)
Hypophosphatemia	16 (25%)	2 (6.5%)	-	-
Vomiting	16 (25%)	5 (16%)	-	-
Dizziness	15 (24%)	1 (3.2%)	-	-
Blood thyroid stimulating hormone increased	13 (21%)	0	-	-
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; epNET, extra-pancreatic neuroendocrine tumour; pNET, pancreatic neuroendocrine tumour; PPE, palmar-plantar erythrodysesthesia; WBC, white blood count.				

The CS reported the number of deaths in each trial arm, alongside the reason for death (Table 30). No deaths were drug-related but, notably, a higher percentage of deaths in the cabozantinib arm were tumour-related. The company stated that most of these deaths occurred more than 30 days after the last dose of the study drug, but the percentage was not reported. Comparisons of mortality between cabozantinib and placebo are therefore associated with some uncertainty.

Table 30. Deaths and primary reason for death in the pNET and epNET cohorts. Reproduced from Table 20 of CS

	pNET		epNET	
	Cabozantinib (n=63)	Placebo (n=31)	Cabozantinib (n=132)	Placebo (n=67)
Total number of deaths, n (%)	21 (33%)	8 (26%)	58 (44%)	27 (40%)
Primary reason for death				
Tumour (progressive disease), n (%)	15 (24%)	5 (16%)	35 (27%)	14 (21%)
Drug-related, n (%)	0	0	0	0
Unknown, n (%)	5 (7.9%)	2 (6.5%)	14 (11%)	8 (12%)
Other, n (%)	1 (1.6%)	1 (3.2%)	9 (6.8%)	5 (7.5%)
Abbreviations: epNET, extra-pancreatic neuroendocrine tumour; pNET, pancreatic neuroendocrine tumour				

3.4 Indirect treatment comparison conducted by the EAG

As discussed in Sections 2.3 and 3.2, the company considered BSC to be the most appropriate comparator for cabozantinib. With the direct evidence from the CABINET trial comparing cabozantinib with placebo, the company did not consider it possible to perform any indirect treatment comparisons (ITCs) for the other comparators in the NICE final scope (**Key issue 1**). This conclusion was based on the company's ITC feasibility assessment, which concluded that the small sample sizes in the CABINET trial, and differences in populations and treatment effect modifiers between trials meant that robust ITCs could not be provided (Appendix A of clarification responses). Nonetheless, the EAG considers that conducting an ITC would be of paramount importance to account for all relevant comparators to cabozantinib, with any limitations of the analysis acknowledged alongside the results.

As stated in Sections 2.3 and 3.2, the EAG considers that other comparators need to be included in the analysis for the population, which reflects the company's marketing authorisation and the company's intended positioning for cabozantinib in the treatment pathway as a second (or later) systemic treatment (excluding SSAs as a prior treatment). As a result, the EAG requested that the company performed ITCs between the CABINET trial and the other comparators in the NICE final scope. The relevant comparators suggested by the EAG, based on discussion with the EAG's clinical experts, for each population were:

- For the pNET cohort: everolimus, sunitinib and PRRT;
- For the epNET population (without lung NETs): Everolimus and PRRT.

- The epNET population (lung): everolimus for patients who have received first line systemic chemotherapy.

The EAG acknowledges that the comparators outlined above are a simplification of the treatment pathway, and that in each cohort there will be patients who are not eligible for certain treatments, such as those with functional GI NETs in the epNET cohort. However, it considers these to be the comparators available to many patients in each group, particularly for the pNET and epNET cohorts.

The company did not perform the requested analyses due to their concerns discussed in Section 2.3.3, including the broad marketing authorisation of cabozantinib and the individualised treatment pathways which vary depending on individual patient characteristics.

Although the company highlighted that everolimus is the only systemic therapy available for the treatment of lung NETs (therefore not making it a comparator), the EAG notes that any patients who have a non-functional lung NET and have chemotherapy (after SSAs) will meet the criteria for being eligible to receive either everolimus or cabozantinib. This is a relatively small number of patients, but with their poor prognosis and few alternative treatment options, the EAG considers them an important group to assess. The EAG notes that wherever everolimus is discussed as a comparator for lung NET patients in the section below, this refers to patients with non-functional lung NETs who have had prior chemotherapy. However, the exploratory ITCs include all patients due to a lack of data solely for the non-functional lung NET group.

In the absence of additional analyses from the company, the EAG performed exploratory ITCs between cabozantinib and other systemic treatments for PFS and OS. Given data availability and time restraints, the EAG conducted simple Bucher comparisons, and notes that the results should be interpreted in the context of exploratory analyses.

While there are limitations to the EAG's analysis (discussed in Section 3.4.1), the EAG considers this exploratory analysis to be crucial to facilitate the decision-making process for the full population included in the company's marketing authorisation for cabozantinib.

3.4.1 Statistical methods

Given time restraints, it was not possible for the EAG to conduct a systematic literature review to inform the ITC. The EAG was aware of trials that had been used in previous NICE technology appraisals (TAs) to assess the effectiveness of sunitinib or everolimus for pNET and epNET patients.

TA449 and TA539 included four studies (RADIANT-3, RADIANT-4, NETTER-1 and A6181111 (since then published as Raymond *et al.* 2011) for the assessment of everolimus, lutetium-177 DOTATATE (PRRT) and sunitinib for treating unresectable or metastatic NETs with disease progression.^{12, 22-24}

NETTER-1, comparing PRRT and octreotide 30 mg to octreotide 60 mg, was not included in the EAG's exploratory analyses because it only included patients with midgut NETs of the small bowel and did not include BSC, to act as a common comparator. Therefore, the EAG could not include PRRT in either the pNET or epNET analysis. This limitation of the EAG's analysis may be partly mitigated by the fact that some of the EAG's clinical experts stated that there is a move towards prescribing PRRT prior to the other oral systemic therapy options in clinical practice. As such, PRRT may not be considered a comparator to cabozantinib for some patients.

The other studies included in TA449 and TA539 provided evidence for the following comparisons between cabozantinib and either sunitinib or everolimus:

- For the pNET cohort:
 - RADIANT-3: everolimus vs BSC;
 - Raymond et al. (2011): sunitinib vs BSC.
- For the epNET cohort (GI and lung):
 - RADIANT-4: everolimus vs BSC.
- For the epNET (lung) cohort:
 - RADIANT-4: everolimus vs BSC.

Median treatment duration and follow-up times were relatively similar for most of the trials, particularly those for CABINET and the everolimus trials (RADIANT-3 and RADIANT-4) (Table 31).

Table 31. Median follow-up time and treatment duration for trials included in the EAG's exploratory ITCs

Trial	Intervention		Placebo (BSC)	
	Median treatment duration (months)	Median follow-up time (months)	Median treatment duration (months)	Median follow-up time (months)
CABINET (pNET cohort)	8.28	23.3	2.86	23.0
CABINET (epNET cohort)	5.37	23.3	2.79	23.0
RADIANT-3	8.79	17*	3.74	17*
RADIANT-4	9.3	21*	4.5	21*

Raymond et al., 2011	4.6	34.1*	NR†	34.1*

* Median follow-up time not reported separately for each trial arm
† Median treatment duration redacted for the BSC arm
Abbreviations: BSC, best supportive care; epNET, extra-pancreatic neuroendocrine tumour; pNET, pancreatic neuroendocrine tumour

In the absence of individual patient data (IPD), analyses using Bucher ITCs were performed using the HRs from CABINET and each of the above trials for the primary and secondary outcomes of PFS and OS. The EAG considers these analyses to be exploratory, as these are associated with a number of limitations, including differences in the populations included in each study and the number of prior treatments received by patients.

The EAG could not conduct any ITCs for time to treatment discontinuation (TTD), as these were not available in the published TAs.

As discussed in Section 3.1, the company excluded a number of studies from a potential ITC because <70% of the population did not receive a relevant prior line of therapy. The EAG considers that these studies may still provide reasonable data for comparison, and it is therefore likely that more evidence is available to inform the ITCs.

3.4.2 Clinical effectiveness results of EAG's exploratory analysis

3.4.2.1 Progression-free survival

The primary outcome from the CABINET trial was PFS assessed by blinded independent review committee (BIRC). The primary outcome from the RADIANT-3 and Raymond *et al.* 2011 studies was PFS, assessed by local or investigator assessment, but each trial also reported PFS as assessed by independent/central review. The independent review results were therefore used for the ITCs for consistency with the CABINET trial.

The following effect estimates were used for comparisons between cabozantinib, everolimus and sunitinib (all HRs presented below are the named treatment vs placebo):

- pNETs:
 - Cabozantinib (CABINET trial): HR 0.23 (95% CI: 0.12 to 0.42);
 - Everolimus (RADIANT-3): HR 0.34 (95% CI: 0.26 to 0.44);
 - Sunitinib (Raymond *et al.* 2011): HR 0.32 (95% CI: 0.18 to 0.55).
- epNETS:

- Cabozantinib (CABINET trial): HR 0.38 (95% CI: 0.25 to 0.58);
- Everolimus (RADIANT-4): HR 0.48 (95% CI: 0.35 to 0.67).
- Lung NETs:
 - Cabozantinib (CABINET trial): HR 0.36 (95% CI: 0.23 to 0.54);
 - Everolimus (RADIANT-4): HR 0.50 (95% CI: 0.28 to 0.88).
- epNETs (without lung):
 - Cabozantinib (CABINET trial): HR 0.36 (95% CI: 0.23 to 0.54);
 - Everolimus (RADIANT-4): HR 0.56 (95% CI: 0.37 to 0.84).

For PFS in all cohorts, the effect estimates numerically favoured cabozantinib over both comparators, but were not statistically significant. (Table 32). Lack of statistical significance is not unexpected in a Bucher ITC consisting of only two trials due to the inherent uncertainty introduced in the estimation. While the numerical benefit with cabozantinib appears to be similar for the pNET and overall epNET cohorts, the HRs indicate that patients with lung NETs experience the greatest numerical benefit of cabozantinib on PFS.

Table 32. Results of Bucher ITCs for PFS

Comparator	HR (95% CI)
pNETs	
Cabozantinib vs everolimus	0.68 (0.34 to 1.33)
Cabozantinib vs sunitinib	0.73 (0.32 to 1.68)
epNETs (all)	
Cabozantinib vs everolimus	0.79 (0.47 to 1.35)
epNETs (lung)	
Cabozantinib vs everolimus	0.36 (0.11 to 1.21)
epNETs (without lung)	
Cabozantinib vs everolimus	0.86 (0.46 to 1.59)
Abbreviations: CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; pNET, pancreatic neuroendocrine tumour	

The main limitation for the EAG's exploratory ITCs is the difference between trial populations. While patients in the CABINET trial were heavily pretreated, patients in RADIANT-3, RADIANT-4 and the Raymond *et al.* 2011 trial had only received prior chemotherapy. Patients in the comparator trials were therefore earlier in the treatment pathway than most patients in the CABINET trial.

Nonetheless, the EAG notes that the company has conducted subgroup analysis by number of prior systemic treatments, which reports similar results for the relative benefit observed with

cabozantinib for PFS and OS whether patients had 1, 2 or ≥ 3 prior systemic treatments (Figures 16 and 17 of CS). The EAG notes that while the company's subgroup analysis only considers the impact of prior treatment on the relative treatment effect of cabozantinib, a post-hoc analysis of the RADIANT-4 trial indicates that prior systemic treatments (SSA therapy, chemotherapy or radiotherapy including PRRT) also have a limited impact on the effects of everolimus in comparison to placebo for patients with nonfunctional lung NETs and GI NETs.²⁵ However, it is not aware of any evidence to inform how the relative treatment effect of sunitinib could be affected by the number of prior treatments received. Therefore, while the difference in the number of prior systemic treatments between studies must be acknowledged, the EAG does not consider it a sufficient limitation to prevent consideration of the exploratory analysis.

An additional limitation of the lung NET analysis is the lack of separation of results between patients who had, or did not have, prior chemotherapy and those who had functional, or non-functional, tumours. As noted in Section 3.4, everolimus is only a relevant comparator for lung NET patients who have non-functional tumours and have had prior chemotherapy. Neither the results from the CABINET trial nor those from RADIANT-4 were stratified by functional status or prior chemotherapy, although the *post-hoc* analysis of patients in RADIANT-4 with lung NETs reported that 39.7% of patients in the everolimus group and 48.1% of patients in the placebo group had prior chemotherapy.²⁶ As such, the lung NETs analysis includes everolimus patients who would not be eligible for cabozantinib in the NHS. However, the EAG considers that the inclusion of these exploratory results are still a useful indication of the differences in treatment response between lung NET patients and those with other types of epNET.

It should also be noted that the results which inform the exploratory ITCs for the lung NETs and epNETs (without lung) analyses were based on *post-hoc* analyses. Neither CABINET, nor comparator trials were stratified for lung NETs at randomisation, and so the results for these groups break randomisation, adding further uncertainties to the exploratory results.

3.4.2.2 Overall survival

First DCO

Bucher ITCs for OS were performed for the pNET and epNET cohorts, but ITCs could not be performed for the RPSFTM adjustment for epNETs, as no adjusted results were available from the previous TAs for this population. Instead, ITT results were used for the ITCs for the epNET cohort. No

ITCs could be performed for the lung NET, or epNET (without lung), subgroups as OS results were not available from RADIANT-4 for these groups.

The following effect estimates were used for comparisons between cabozantinib, everolimus and sunitinib in the first DCO (all HRs presented below are the named treatment vs placebo):

- pNETs (ITT, as a scenario analysis):
 - Cabozantinib (CABINET trial): HR 0.95 (95% CI: 0.45 to 2.00);
 - Everolimus (RADIANT-3): HR 0.94 (95% CI: 0.73 to 1.20);
 - Sunitinib (Raymond *et al.* 2011): HR 0.73 (95% CI: 0.50 to 1.06).
- pNETs (RPSFTM-adjusted, EAG preferred method):
 - Cabozantinib (CABINET trial): HR [REDACTED]
 - Everolimus (RADIANT-3): HR 0.60 (95% CI: 0.09 to 3.95);
 - Sunitinib (Raymond *et al.* 2011): HR 0.34 (95% CI: 0.14 to 1.28).
- epNETs (ITT):
 - Cabozantinib (CABINET trial): HR [REDACTED]
 - Everolimus (RADIANT-4): HR 0.73 (95% CI: 0.48 to 1.11).

Results for both the pNET and epNET cohorts numerically favoured the comparators (everolimus and sunitinib) but were not statistically significant (Table 33). This is driven by the direct evidence from CABINET, which shows a HR close to 1 for cabozantinib vs placebo (HR 0.95).

The EAG notes the uncertainty in the results of the exploratory ITC analysis, as discussed in the previous section for PFS. As discussed in Section 3.3.2.1, the EAG's concerns about OS data immaturity in the CABINET trial and small numbers of patients introduce further uncertainties to the results of the OS exploratory ITCs.

As discussed by the EAG, the assessment of the direct evidence (Section 3.3.2.1.1) suggests that the only group where a statistically significant (and numerical) OS advantage over placebo is observed is the population with lung NETs (based on a *post-hoc* analysis). However, the lack of reporting of OS results from the RADIANT-4 trial means it was not possible to determine the relative treatment effect of cabozantinib compared to everolimus in this group (note that sunitinib is not recommended for epNETs).

Table 33. Results of Bucher ITCs for OS (first DCO)

Comparator		HR (95% CI)
pNETs		
Cabozantinib vs everolimus	ITT	1.01 (0.46 to 2.22)
	RPSFTM	1.48 (0.13 to 17.04)
Cabozantinib vs sunitinib	ITT	1.30 (0.56 to 3.00)
	RPSFTM	2.62 (0.39 to 17.50)
epNETs (all)		
Cabozantinib vs everolimus	ITT	1.18 (0.65 to 2.14)
	RPSFTM	N/A*
* RPSFTM data for the comparator trial not available from previous TAs in this population Abbreviations: CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; ITT, intention to treat; N/A, not available; pNET, pancreatic neuroendocrine tumour; RPSFTM, rank-preserving structural failure time modelling		

Updated DCO

The following effect estimates were used for comparisons between cabozantinib, everolimus and sunitinib in the updated DCO. Effect estimates used from RADIANT-3 and Raymond *et al.* (2011) were the same as those used in the ITC for the first DCO, as the previous NICE TAs only reported the results from a single timepoint (all HRs presented below are the named treatment vs placebo):

- pNETs (ITT, EAG's exploratory analysis):
 - Cabozantinib (CABINET trial): [REDACTED]
 - Everolimus (RADIANT-3): HR 0.94 (95% CI: 0.73 to 1.20);
 - Sunitinib (Raymond *et al.* 2011): HR 0.73 (95% CI: 0.50 to 1.06).
- pNETs (RPSFTM-adjusted, EAG's preferred method):
 - Cabozantinib (CABINET trial): [REDACTED]
 - Everolimus (RADIANT-3): HR 0.60 (95% CI: 0.09 to 3.95);
 - Sunitinib (Raymond *et al.* 2011): HR 0.34 (95% CI: 0.14 to 1.28).
- epNETS (ITT):
 - Cabozantinib (CABINET trial): [REDACTED]
 - Everolimus (RADIANT-3): HR 0.73 (95% CI: 0.48 to 1.11).

Results using the updated OS DCO numerically favoured everolimus and sunitinib over cabozantinib, and differences were larger than those seen for the first DCO (Table 34). Results remained non-significant and subject to considerable uncertainties, particularly for comparisons of the RPSFTM-adjusted data.

Table 34. Results of Bucher ITCs for OS (updated DCO)

Comparator		HR (95% CI)
pNETs		
Cabozantinib vs everolimus	ITT	1.18 (0.60 to 2.33)
	RPSFTM	1.85 (0.25 to 13.59)
Cabozantinib vs sunitinib	ITT	1.52 (0.73 to 3.17)
	RPSFTM	3.26 (0.91 to 11.68)
epNETs (all)		
Cabozantinib vs everolimus	ITT	1.42 (0.81 to 2.51)
	RPSFTM	N/A*
* RPSFTM data for the comparator trial not available from previous TAs in this population Abbreviations: CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; ITT, intention to treat; N/A, not available; pNET, pancreatic neuroendocrine tumour; RPSFTM, rank-preserving structural failure time modelling		

3.4.2.3 Summary of results for the EAG's exploratory analysis

Results of the EAG's exploratory ITC indicate that cabozantinib has a numerical benefit for PFS compared to everolimus and sunitinib. Nonetheless, none of the PFS HRs in the EAG's exploratory analyses were statistically significant, which is not unexpected, given the Bucher method used for the exploratory analysis. For OS, the exploratory ITC HRs numerically favoured the comparators for both pNETs and epNETs. The EAG notes that these results are driven by the direct evidence from CABINET, particularly with the updated OS DCO, where placebo shows a numerical survival advantage to cabozantinib.

The EAG considered the apparent discrepancy in the direction of the PFS and OS results in its exploratory analyses. The EAG's clinical experts considered that, with no evidence of a significant deterioration in quality of life, or a greater number of treatment-related deaths with cabozantinib, it would be unlikely that PFS would be better, while OS would be worse, with cabozantinib than BSC or other systemic treatments. Furthermore, the EAG considered external evidence showing that cabozantinib has a statistically significant survival advantage over everolimus in previously treated advanced renal cell carcinoma (METEOR trial) and a numerical but not statistically significant OS benefit against sunitinib (CABOSUN trial).^{27, 28} The EAG appreciates that assumptions across different disease areas should be interpreted with caution. However, it considered that assuming equal survival for cabozantinib, everolimus and sunitinib in the economic model was a more plausible approach than using the exploratory ITC results showing a PFS advantage for cabozantinib and an OS

disadvantage for the treatment against everolimus and sunitinib. Results of the EAG's exploratory analysis are reported in Section 6.

As discussed in Section 3.4.1, due to time constraints, the exploratory ITCs performed by the EAG were based only on trials used in previous NICE TAs. It is, therefore, possible that other evidence for lung NET patients is available which would allow additional comparisons to be made. Although there would be limitations to this analysis, such as the small patient numbers in the lung NET group from CABINET, this would provide a valuable insight into whether cabozantinib has OS benefits against everolimus for lung NETs.

The sources of uncertainty associated with the current analyses around difference in trial populations and number of previous treatments received are impossible to address with exploratory Bucher ITCs. Instead, the EAG considers that more advanced methods (such as matching-adjusted indirect comparisons - MAICs) could provide a more robust method of analysis for comparisons between cabozantinib and everolimus or sunitinib, taking into account difference in trial populations. MAICs would enable the CABINET population to be adjusted to more closely align with the populations from other trials, focusing on those patients who had fewer prior systemic treatments and are eligible for further systemic treatments prior to BSC.

Crucially, the EAG notes that 27% of cabozantinib patients and 32% of placebo patients in the pNET population in CABINET had received only one prior systemic therapy (other than SSAs), while in the epNET population, 44% of cabozantinib patients and 48% of placebo patients had received one prior systemic treatment. The EAG considers this subgroup of patients to be the key population of interest from CABINET to conduct the ITC.

Further analyses may also provide the opportunity to compare cabozantinib against PRRT, for which no relevant evidence was identified in the NICE TAs used for the EAG's exploratory analyses.

In summary, the EAG considers that additional evidence from MAICs (or an alternative method deemed more appropriate based on the available data) would aid decision-making for the population who are earlier in the treatment pathway, and where BSC may not be the only available treatment option. As such, the EAG recommends that the company provides (using the CABINET subgroup who only received one prior systemic treatment):

- MAICs for PFS and OS (and TTD whenever possible) for:

- pNET patients, with comparisons against PRRT, sunitinib and everolimus;
- epNET patients (without lung NETs), with comparisons against PRRT (for functional epNETs) and everolimus;
- lung NET patients, with comparisons against everolimus.

The EAG considers that the recommended analyses would reduce most of the uncertainties associated with the EAG's exploratory ITCs, thereby providing a more robust assessment with which to compare the effects of cabozantinib and other systemic treatments for patients who have had at least one prior systemic treatment (other than an SSA).

3.5 Conclusions of the clinical effectiveness section

The summary of the EAG's key concerns in relation to the CS are that:

- The clinical evidence presented by the company (based on the CABINET population) does not reflect all relevant comparators in the company's marketing authorisation and the company's intended positioning for cabozantinib in the treatment pathway. Therefore, the EAG separated its assessment into two populations. The first population is the CABINET population, where the EAG agrees that the main comparator of interest is BSC. These patients are heavily pretreated and at a late stage in the treatment pathway, which is as a second line systemic treatment option. The second population are patients who are at an earlier stage in the treatment pathway, having had only one (or more) prior systemic treatments (excluding SSAs). They are not all at the stage where the only available option would be BSC as they are eligible for other systemic treatments in the UK NHS, such as PRRT, everolimus or sunitinib.
- The EAG considers the CABINET trial to be a well-conducted trial, although it has concerns about some of the methods used, including:
 - The use of interim analysis methods, which could have resulted in an overestimation of treatment effects and also resulted in the recruitment of fewer patients than originally planned. This is a particular concern for the pNET cohort, where only half of the planned number of patients were recruited. The small number of pNET patients in the trial also had implications for the ability of the trial data to demonstrate a survival gain against placebo.

- The quality of the results from the HRQoL sub-study. Participation in the sub-study was optional and therefore subject to the breaking of randomisation. Patient numbers were very low for much of the trial.
 - Results of the CABINET trial showed a PFS advantage for cabozantinib over placebo for both the pNET and epNET cohorts. In contrast, results for OS were not statistically significant, and numerically favoured placebo in the updated DCO OS data. However, results of the OS analysis are subject to a number of limitations, including potential data immaturity and a small number of patients in the placebo groups, which rendered the results of cross-over adjustment survival highly uncertain.
 - The company did not provide an ITC including PRRT, everolimus or sunitinib as relevant comparators to cabozantinib. As no evidence was provided, the EAG performed exploratory Bucher ITCs to compare results from the CABINET trial with those from other trials which had been included in previously published NICE TAs. Comparisons were made against everolimus and sunitinib for patients with pNETs, epNETs, lung NETs or epNETs (without lung). Comparisons with PRRT were not possible.
- For PFS and OS, there were no statistically significant differences between cabozantinib and either everolimus or sunitinib for any group, with everolimus showing a numerical PFS advantage against the treatments and a numerical disadvantage for OS. The EAG considers its analyses exploratory due to the fact that there were marked differences in trial populations and number of previous treatments received across the different trials included in the ITCs, which are impossible to address with simple Bucher ITCs. Instead, the EAG considers that more advanced methods (such as matching-adjusted indirect comparisons [MAICs]) could provide a more robust method of analysis for comparisons between cabozantinib (using the CABINET subgroup of patients who had received one prior systemic treatment, other than SSAs) and everolimus or sunitinib, taking into account differences in trial populations. MAICs would enable the CABINET population to be adjusted to more closely align with the populations from other trials, focusing on those patients who had fewer prior systemic treatments. Further analyses may also provide the opportunity to compare cabozantinib against PRRT, for which no relevant evidence was identified in the NICE TAs used for the EAG's exploratory analyses.
- The CS uses a site-agnostic approach for epNETs. The EAG's clinical experts indicated that lung NETs have a worse prognosis and fewer treatment options than other epNETs, suggesting that it is not appropriate to group lung NETs with other types of epNETs. The

post-hoc analysis of the lung NET PFS and OS data from CABINET shows that cabozantinib is likely to have PFS benefits for all epNET patients (although of a much higher magnitude for lung NETs) and that while cabozantinib might not demonstrate a survival benefit in the pooled epNET population, it does show a benefit for patients with lung NETs, when compared to placebo. The EAG acknowledges the uncertainty in these conclusions, given that the lung NET comparisons are based on a *post-hoc* analysis and the fact that there is a marked difference in baseline characteristics of patients in the cabozantinib and the placebo arms for the lung NET group, which could potentially bias the results in favour of cabozantinib, as they appear to be indicative of a worse prognosis in the placebo group.

4 Cost effectiveness

This section presents a summary and critique of the cost effectiveness evidence included in the company's submission. Section 4.1 focuses on the company's review of cost-effectiveness evidence and Section 4.2 covers the company's economic evaluation.

Table 35 for pNET and Table 36 for epNET below presents the incremental cost-effectiveness results of the company's base case results. Results presented in this document are inclusive of a patient access scheme (PAS) discount for cabozantinib.

Table 35. Company's base case results pNET

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Cabozantinib	■	4.38	■	-	-	-	-
BSC	■	3.36	■	■	1.02	■	■
Probabilistic results							
Cabozantinib	■	4.46	■	-	-	-	-
BSC	■	3.35	■	■	1.11	■	■
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year							

Table 36. Company's base case results epNET

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Cabozantinib	■	2.95	■	-	-	-	-
BSC	■	1.84	■	■	1.11	■	■
Probabilistic results							
Cabozantinib	■	2.96	■	-	-	-	-
BSC	■	1.86	■	■	1.09	■	■
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year							

4.1 EAG comment on the company's review of cost effectiveness evidence

To inform the cost-effectiveness analysis, the company undertook three systematic literature reviews (SLRs) to identify previous economic evaluations, health-related quality of life (HRQoL) studies, and cost or resource studies, relevant to patients with advanced NETs, who had received

treatment with a prior systemic therapy. In the context of the SLRs, prior systemic therapies were considered to include everolimus, sunitinib, 177Lu-dotatate, capecitabine and temozolomide (CAPTEM), streptozotocin/5-fluorouracil (STZ/5-FU), folinic acid and fluorouracil and oxaliplatin (FOLFOX), and interferon alpha (IFN- α). All three SLRs were initially conducted in May 2024, and updated in January 2025.

Due to the limited evidence identified in all SLRs, the scope was expanded to include studies in which at least one patient had received at least one prior systemic therapy. The scope of the economic SLR was also subsequently expanded to capture any economic evaluations of patients with NETs at any stage published after 2014, in UK and European markets. The EAG considers that these expansions to the original scope of the SLRs were reasonable.

A summary of the methodology used to identify relevant evidence, and the EAG’s critique of this methodology, is presented in Table 37.

Table 37. EAG’s critique of company’s SLRs for existing cost-effectiveness, HRQoL, resource use and cost evidence

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix E.1.1	Appendix E.1.1	Appendix E.1.1	Appropriate Electronic database searches included: MEDLINE, Embase, NHS EED, and the international HTA database. Key conference proceedings were searched from 2002 onwards. HTA body websites, the CEA Registry and EQ-5D Publications Database were searched from 2010 onwards. The bibliographies of all identified systematic reviews, NMAs, HTAs and economic assessments were also searched. Search terms combined terms related to disease area, stage and prior treatments with relevant study design terms informed by the SIGN economic studies validated filter set.²⁹

Inclusion/ exclusion criteria	Appendix E.1.2 (original and expanded scope)	Appendix E.1.2 (original scope); Appendix F.1.2 (expanded scope)	Appendix E.1.2 (original scope); Appendix G.1.2 (expanded scope)	Appropriate Electronic dates were searched from inception; conference proceedings were searched from 2002 onwards, and other grey literature sources were searched from 2010 onwards. Inclusion and exclusion criteria captured appropriate study designs and patient populations.
Screening	Appendix E.1.2	Appendix E.1.2	Appendix E.1.2	Appropriate Titles and abstracts were reviewed by two independent reviewers and compared. Subsequently, all full-text articles were reviewed by two independent reviewers. Any disagreements were resolved by a third reviewer.
Data extraction	Appendix E.1.3	Appendix E.1.3	Appendix E.1.3	Appropriate Key information was extracted into a pre-specified data extraction grid by one reviewer and validated by a second independent reviewer, with any disagreements resolved by a third reviewer.
Quality assessment of included studies	Appendix E.1.5	N/A	N/A	Appropriate Economic evaluations were assessed using the Drummond checklist.³⁰ Quality assessment was performed by one reviewer and validated by a second independent reviewer. HRQoL and cost/resource use studies were not assessed for quality; the EAG considers that this is reasonable.

Abbreviations: CEA, cost-effectiveness analysis; CS, company submission; EAG, External Assessment Group; EQ-5D, EuroQol-5 Dimensions; HRQoL, health related quality of life; HTA, health technology assessment; NHS EED, National Health Service Economic Evaluation Database; NMA, network meta-analysis; SIGN, Scottish Intercollegiate Guidelines Network; SLR, systematic literature review.

The company's SLR of economic evaluations identified two relevant full text publications, both of which analysed the cost-effectiveness of 177Lu dotatate for the treatment of NETs.^{31, 32} The SLR also identified several relevant health technology appraisals, including the Scottish Medicine Consortium (SMC) appraisals for everolimus, 177Lu dotatate, and belzutifan, as well as the National Institute for Health and Care Excellence (NICE) appraisals of everolimus and sunitinib (TA449), and 177Lu dotatate (TA539).^{1, 33-36} The two NICE appraisals were also published as a free-standing publication

(Mujica-Mota *et al.* 2018).³⁷ A full list of identified studies is given in Appendix E.1.4.1, Table 21, and details of the economic outcomes and model features in each study are given in Table 21, Section 3.1 of the CS.

The HRQoL SLR identified 10 relevant studies, including the following:

- Two studies which considered a pNETs population;
- One study which considered an epNETs population;
- Six studies which considered a combined NETs population;
- One study which considered both an epNETs population and a combined NETs population.

Eight studies were specific to advanced NETs, while the other studies included a population of NETs at any stage. The results reported in the studies were based on the EORTC QLQ-C30 or EORT QLQ-GI.NET 21 tools for all studies, with the exception of Mujica-Mota *et al.* 2018, which reported EQ-5D results.³⁷ The studies covered multiple country contexts, with two studies specific to the UK (Alsadik *et al.* 2022 and Alsadik *et al.* 2023).^{38,39} The EAG notes that the majority of the reported studies were conducted in small populations (only three studies reported a sample size greater than 100). A full list of identified studies is given in Appendix F.1.4, Table 25, in the CS.

The cost and resource use SLR identified 11 studies for inclusion. All identified studies were resource use studies, with the exception of Mujica-Mota *et al.* 2018, which also included consideration of costs.³⁷ The studies included the following:

- Two studies which considered a pNETs population;
- Three studies which considered an epNETs population;
- Four studies which considered a combined NETs population;
- Two studies which considered a pNETs population, an epNETs population, and a combined NETs population.

Four studies were specific to advanced NETs, while the other studies included a population of NETs at any stage. None of the identified studies were relevant to a UK context, with the exception of Casciano *et al.* 2013, which was an international study including some UK patients, and Mujica-Mota *et al.* 2018, which was UK-specific.^{37,40} A full list of identified studies is given in Appendix G.1.4, Table 29, in the CS.

Overall, the EAG considers that the company's SLRs of existing cost-effectiveness evidence were broadly appropriate.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 38 summarises the EAG's assessment of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.

Table 38. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Adheres to the reference case
Perspective on costs	NHS and PSS	Adheres to the reference case
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Adheres to the reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Lifetime. Adheres to the reference case
Synthesis of evidence on health effects	Based on systematic review	Adheres to the reference case. The company performed an appropriate systematic review.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Adheres to reference case. Base case QALYs estimated using EORTC QLQ-C30 data from CABINET, mapped to the EQ-5D-3L.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EORTC QLQ-C30 reported directly by patients in CABINET.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Patients in CABINET were heavily pretreated, which is not entirely reflective of the population anticipated to be treated with cabozantinib according to the company's proposed indication of cabozantinib as a second-line (or further) systemic treatment (after

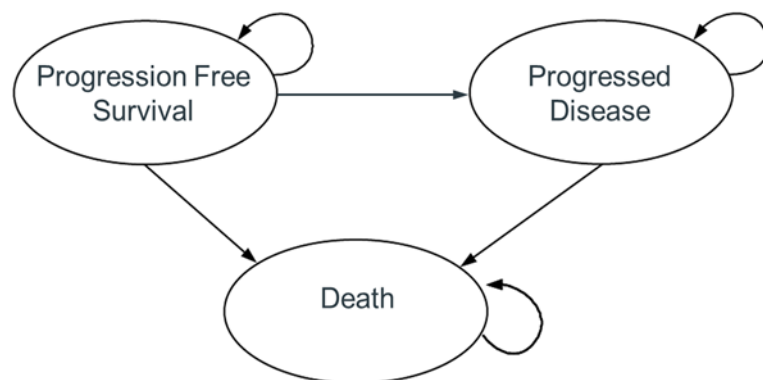
		previous SSAs). In addition, filling in the EORTC form was part of an optional sub-study in CABINET, and therefore did not cover the full trial population.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Adheres to the reference case.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Adheres to the reference case.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Adheres to the reference case.

Abbreviations: EAG, External Assessment Group; EORTC, European Organisation for Research and Treatment of Cancer; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year

4.2.2 Modelling approach and model structure

A single cost effectiveness model (CEM) was developed based on similar models submitted for TA539³⁶ and TA449¹. The CEM used a partitioned survival model (PSM) structure and was developed in Microsoft Excel[®]. The model used a 28-day cycle length with a half-cycle correction applied and three health states: progression-free (PF), progressed disease (PD) and death (Figure 13). The user could select whether to conduct the analysis on the pNET or the epNET population. Following clarification, the company also allowed the user to separately select the lung NET and w/o lung epNET subgroups.

Figure 13. Model structure (reproduced from Figure 18 of the company submission)



All patients enter the model in the PF state and are assumed to be on best supportive care (BSC), or cabozantinib and concomitant SSAs. Patients' discontinuation from treatment in both arms is modelled using separate time to treatment discontinuation (TTD) data.

The proportion of patients occupying a health state during any given cycle is based on parametric survival curves for the clinical outcomes of PFS and overall survival (OS). The proportion of patients occupying the progressed health state for any given cycle is calculated as the difference between OS and PFS per cycle. Data for health state occupancy is sourced from the CABINET trial. Mortality is bounded by general population life tables so OS can never result in lower rates of death than the UK general population.

The baseline patient demographic characteristics used in the model are listed in Table 39. All data was sourced from the CABINET trial ITT population. Following clarification, the company explained that body surface area was calculated using the Mosteller formula and calculating height based on BMI:

$$H(cm) = 100 * \sqrt{\frac{W}{BMI}}$$

$$BSA(m^2) = \sqrt{\frac{W \times H}{3600}}$$

Table 39. Baseline characteristics for the model population (reproduced from Table 24 of the company submission)

Model parameter	pNETs	epNETs
Mean age, years (SE)	60.22 (1.13)	63.09 (0.80)
Percentage female	42.11%	51.72%
Body weight, kg (SE)	80.81 (2.07)	78.85 (1.45)
Body surface area, m ² (SE)	1.95 (0.03)	1.91 (0.03)
*Estimated based on table 5 company CQ response- Not used in the model		
Abbreviations: pNET: pancreatic neuroendocrine tumour; epNET: extra-pancreatic neuroendocrine tumour, SE: standard error		

The model time horizon is 40 years. The perspective of the analysis is based on the UK National Health Service (NHS), with costs and benefits discounted using a rate of 3.5% as per the NICE reference case.

4.2.2.1 EAG critique

The model structure and the modelling approach is appropriate.

The EAG notes that the population in CABINET was heavily pretreated. Patients in the pNET group had received a mean number of three previous systemic treatments, excluding SSAs, in the cabozantinib and placebo arms (2.7 and 2.6, respectively), while patients in the epNET cohort had received a mean number of two systemic treatments, excluding SSAs (1.9 and 1.8, respectively). Therefore, many patients were at a late stage in the treatment pathway, where the only remaining option for most patients in the NHS would be BSC. However, the EAG notes that some patients in the trial were at an earlier stage in the treatment pathway and had only had one prior systemic treatment other than an SSA. These patients are not at the stage where the only available option would be BSC as many may also be eligible for other systemic treatments in the UK NHS

Therefore, the EAG considers that there are two populations of interest for this appraisal, which forms **key issue 1**:

1. The population, and the evidence, included in the CABINET trial, which are most appropriate to inform a scenario where cabozantinib is given as a fourth (or later) line of systemic treatment for pNET patients (excluding previous SSAs); and as a third (or later) line of systemic treatment for epNET patients, excluding previous SSAs. In this context, the EAG agrees that the main comparator of interest is BSC. Equally, for functional lung NETs, BSC is the most relevant comparator, as chemotherapy is the only available systemic treatment (excluding SSAs) which would be given before cabozantinib.
- 2. The less heavily pretreated population, who are not at the stage where the only available option would be BSC, and may have cabozantinib as a second (or later) systemic treatment (excluding SSAs as a prior treatment). The evidence for this analysis is sourced from the EAG's exploratory indirect treatment comparison (ITC), and all the results presented are part of an exploratory analysis, as discussed in Section 6. The appropriate comparators in this scenario are everolimus, sunitinib and PRRT; depending on tumour location; functional status and SSTR status.

Furthermore, as discussed in Section 3.3.1.1 the EAG considers that the lung NET and the epNET without lung populations should have been considered separately in the clinical and economic analysis. This is discussed in Section 4.2.4 in more detail and form **key issue 2**.

4.2.3 Treatment effectiveness

For the purpose of helping the discussion of the key issues, the EAG has divided this section into two subsections, covering the treatment effectiveness in the two populations of interest: 1 -The CABINET population, where the EAG agrees that the main comparator of interest is BSC; 2 - The less heavily pretreated population, where the EAG has used the results of an exploratory ITC including everolimus and sunitinib as comparator to cabozantinib.

4.2.3.1 CABINET population – BSC as a comparator

4.2.3.1.1 Overview of the company's approach to survival analysis

Clinical data for the outcomes of PFS, OS and TTD that inform the economic model are derived from the CABINET trial, described in Section 3. To extrapolate the CABINET Kaplan-Meier (KM) data, the company followed the guidelines for survival model selection outlined in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14⁴¹.

In the company's base case, a hazard ratio (HR) from the CABINET trial was applied to the estimated cabozantinib OS; PFS; and TTD curves to model the respective BSC curves. The company justified the use of HRs by stating that there was not sufficient evidence to reject the null hypothesis of proportional hazards (PHs) based on assessing Schoenfeld residuals, log cumulative and smoothed hazard plots. Nonetheless, the company also has added the functionality to the model to apply independently fitted PFS curves to the cabozantinib and BSC arms, respectively.

At clarification, the EAG requested that the company included the lung NET and the epNET without lung subgroups in the model, respectively. The company provided this analysis whilst caveating that using a *post-hoc* subgroup analysis breaks randomisation; imbalances baseline characteristics and may be underpowered due to small patient numbers.

4.2.3.1.2 Progression Free Survival

The company fitted a lognormal model to both pNET and epNET cabozantinib PFS KM data and applied the trial stratified HR (derived with a Cox PH model) to derive PFS for the BSC arm. The estimated PFS curves were bounded by the estimated OS curves so progression could not exceed mortality. The company explored alternative parametric curves for cabozantinib and independently fitted curves for cabozantinib and BSC, respectively.

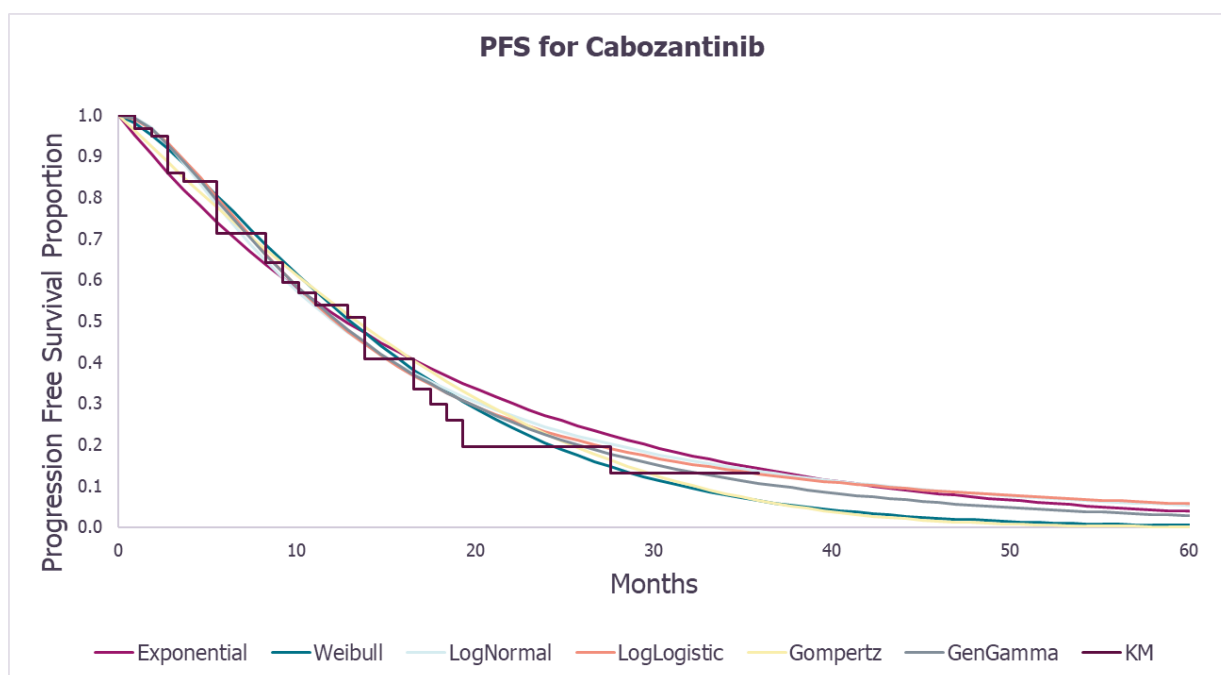
For the scenario analysis including lung NETS and epNETs without lung separately, the company fitted lognormal curves to both populations, to align with the pooled epNET population curve selection and due to these curves having the highest ranking AIC/BIC.

To note, is that the company evaluated AIC and BIC statistics by independently fitting survival curves to cabozantinib and BSC curves separately.

The trial HR, applied to the BSC arm, was stratified by concomitant SSA use and prior sunitinib use in the pNET population and concomitant SSA use and primary site (midgut/unknown vs non-midgut GI/lung/other) in the epNET population. At clarification, the company explained that the use of the stratified HR reflects the stratified randomisation into treatment arms from CABINET.

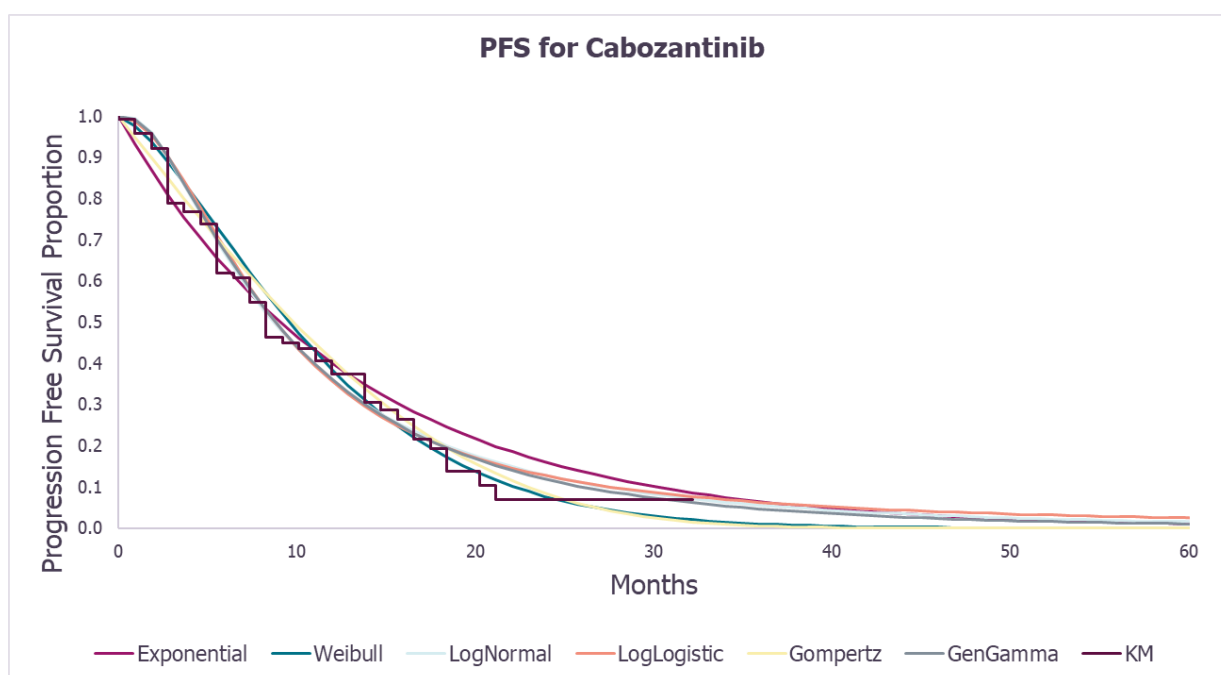
The company's base case lognormal curve for cabozantinib had the lowest AIC and BIC in both populations, though the company noted there were not substantial differences between scores. The cabozantinib fitted curves can be seen compared to the KM PFS data in Figure 14 for pNET and Figure 15 for epNET. The company's conclusion based on these figures was that all curves, with the exception of the exponential, provided a similar fit to the KM data. The BSCs derived from applying the stratified HR to the cabozantinib base case lognormal curves can be observed in Figure 16 and Figure 17.

Figure 14. Cabozantinib PFS extrapolations and KM curve (pNET)



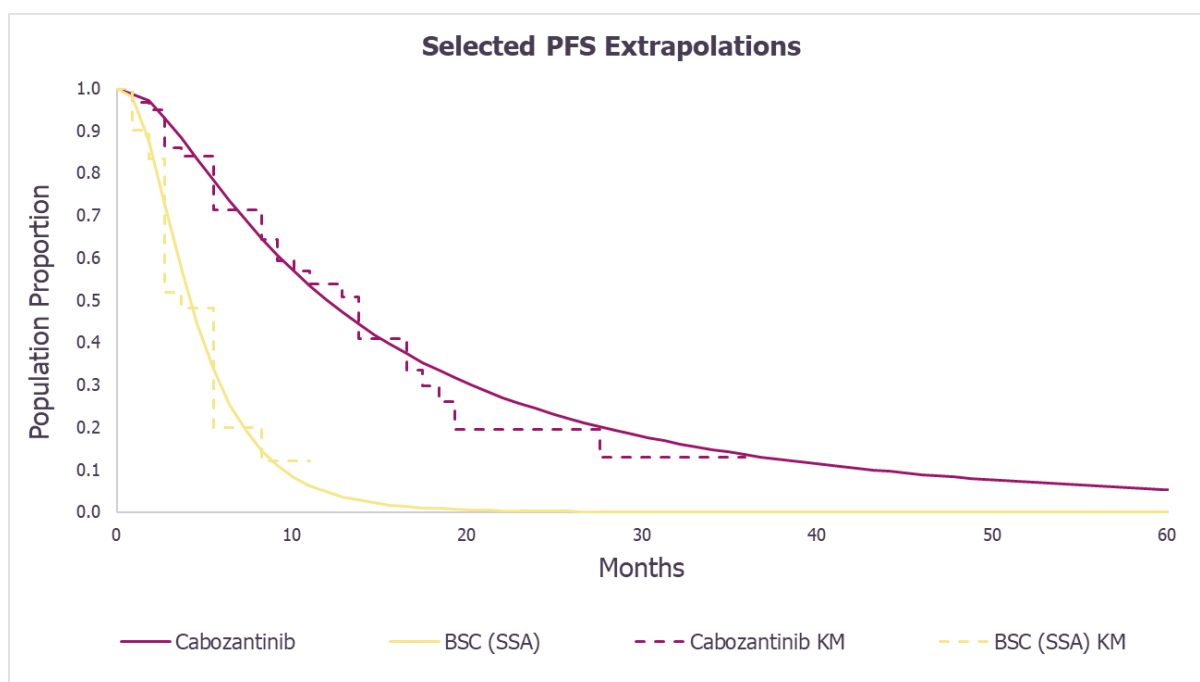
Abbreviations: BSC, best supportive care; pNET: pancreatic neuroendocrine tumour; KM, kaplan meier; PFS: progression free survival.

Figure 15. Cabozantinib PFS extrapolations and KM curve (epNET)



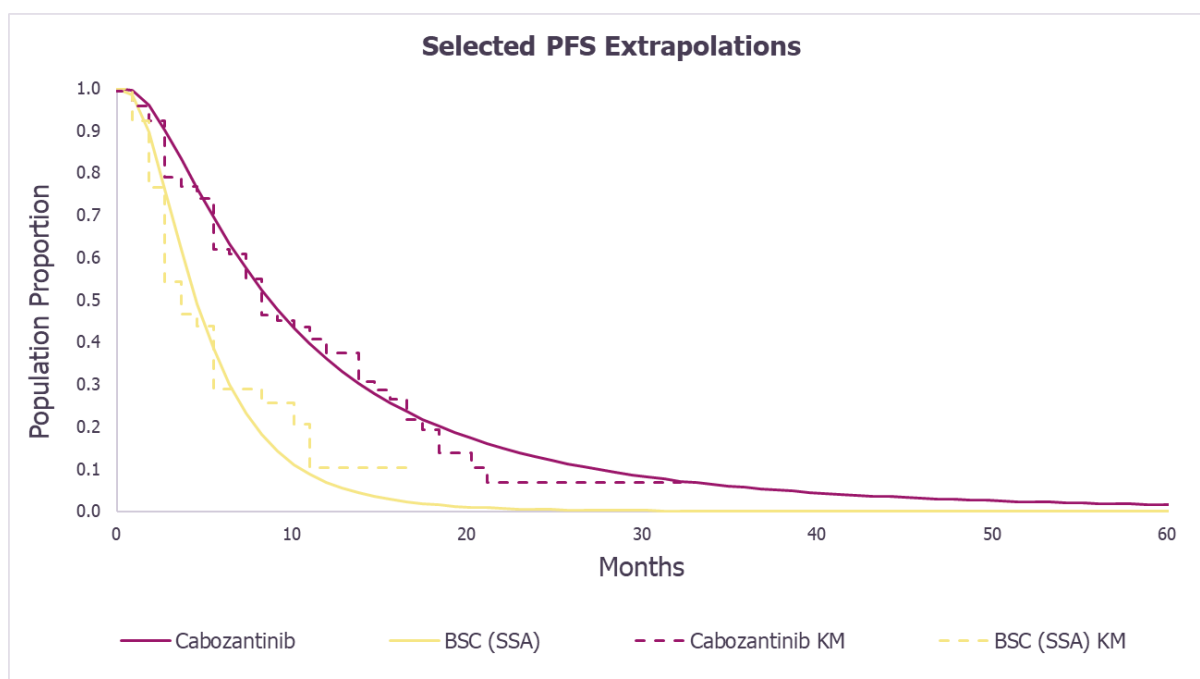
Abbreviations: BSC, best supportive care; epNET: extra-pancreatic neuroendocrine tumour; KM, kaplan meier; PFS: progression free survival.

Figure 16. Selected PFS curves pNET



Abbreviations: BSC, best supportive care; pNET: pancreatic neuroendocrine tumour; KM, kaplan meier; PFS: progression free survival.

Figure 17. Selected PFS curves epNET



Abbreviations: BSC, best supportive care; epNET: extra-pancreatic neuroendocrine tumour; KM, kaplan meier; PFS: progression free survival.

The company made a further point for choosing the lognormal extrapolation by pointing out it accounts for long term progression free survivors, previously identified in a 10-year PFS data from Fröss-Baron, *et al.* 2021⁴². The EAG considers that this data source is of limited relevance, as patients were being treated with PRRT.

The company noted there was limited PFS data available to validate the chosen survival curves. At clarification, the company provided landmark estimates comparing KM data to fitted survival curves for the pNET population, shown in Table 40, and the epNET population, shown in Table 41.

Table 40: KM and parametric survival landmark estimates for PFS for cabozantinib and BSC (pNETs)

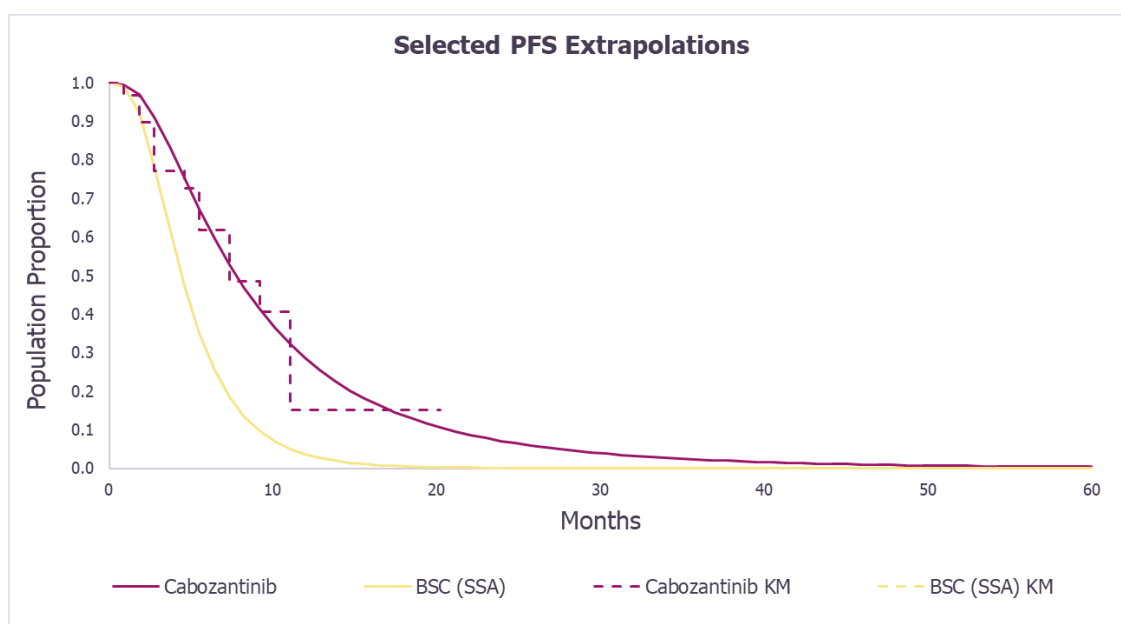
Category	Curve	PFS %		
		Year 1	Year 2	Year 5
Cabozantinib				
KM data (95% CI)	Cabozantinib	53.8% (38.1%, 67.1%)	19.5% (6.7%, 37.1%)	13.0%* (NR, NR)
Extrapolations	Exponential	52.1%	27.1%	3.8%
	Weibull	53.8%	20.5%	0.4%
	Log-logistic	50.7%	23.3%	5.7%
	Lognormal	50.1%	24.4%	5.3%
	Generalised gamma	51.0%	22.5%	2.8%
	Gompertz	54.5%	22.7%	0.1%
BSC				
KM data (95% CI)	Placebo	12.0%* (NE, NE)	NR (NE, NE)	NR (NR, NR)
Cabozantinib curve + HRs	Exponential	5.6%	0.3%	<0.1%
	Weibull	6.4%	0.1%	<0.1%
	Log-logistic	5.0%	0.2%	<0.1%
	Lognormal	4.7%	0.2%	<0.1%
	Generalised gamma	5.1%	0.1%	<0.1%
	Gompertz	6.8%	0.1%	<0.1%
*DCO 35.88 months cabo, 11.04 months BSC				
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; pNET: pancreatic neuroendocrine tumour; ITT: intent-to-treat; PFS: progression-free survival				

Table 41: KM and parametric survival landmark estimates for PFS for cabozantinib and BSC (epNETs)

Category	Curve	PFS %		
		Year 1	Year 2	Year 5
Cabozantinib				
KM data	Cabozantinib	40.6% (30.2%, 50.8%)	6.9% (1.5%, 18.2%)	6.9%* (NR, NR)
Extrapolations	Exponential	40.1%	16.1%	1.0%
	Weibull	38.6%	7.7%	<0.1%
	Log-logistic	35.7%	12.7%	2.4%
	Lognormal	36.1%	12.8%	1.5%
	Generalised gamma	36.2%	11.9%	1.01%
	Gompertz	40.9%	8.5%	<0.1%
BSC				
KM data	Placebo	10.3% (2.1%, 26.1%)	10.3%* (NE, NE)	NR (NR, NR)
Cabozantinib curve + HRs	Exponential	9.0%	0.8%	<0.1%
	Weibull	8.2%	0.1%	<0.1%
	Log-logistic	6.6%	0.4%	<0.1%
	Lognormal	6.8%	0.4%	<0.1%
	Generalised gamma	6.9%	0.4%	<0.1%
	Gompertz	9.5%	0.2%	<0.1%
* DCO 32.20 months cabo, 16.56 months BSC				
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; pNET: pancreatic neuroendocrine tumour; ITT: intent-to-treat; PFS: progression-free survival				

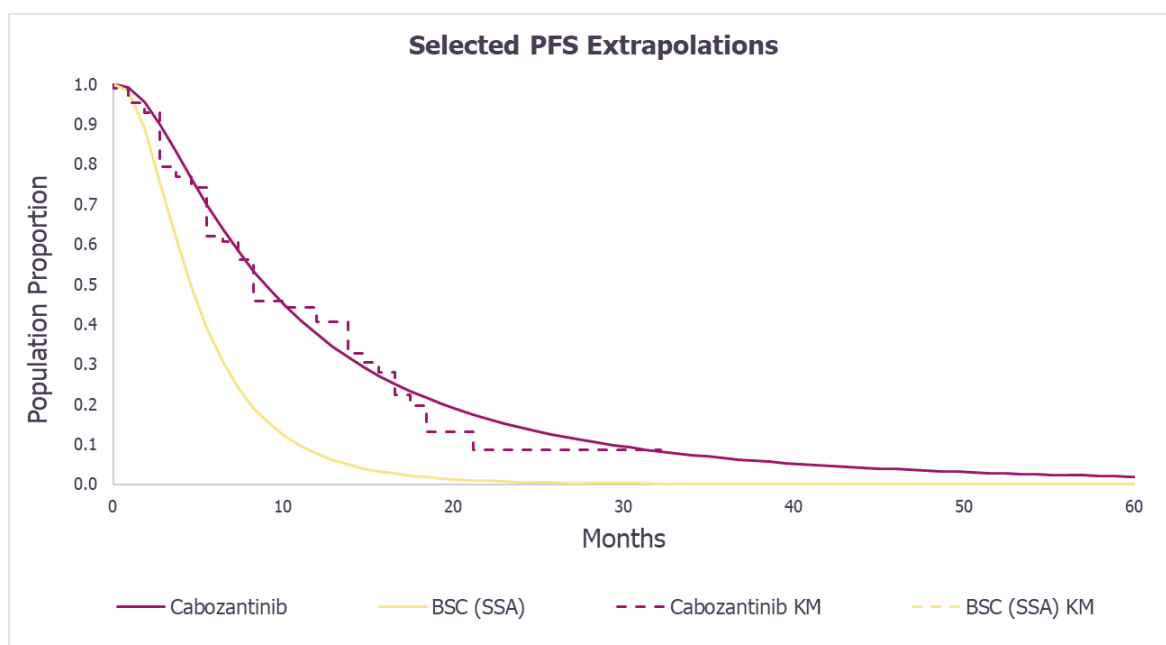
At clarification the EAG requested that the company analysed the lung NET and the epNET without lung populations separately. The company provided this for the cabozantinib arms (and used a HR to estimate the BSC arms) whilst caveating that using a post-hoc analysis breaks randomisation, generates imbalances in baseline characteristics and may be underpowered due to small patient numbers. The company's extrapolation is shown in Figure 18 for lung epNETs and Figure 19 epNETs without lung. As with the company base case, lognormal curves were selected and had the lowest AIC and BIC scores.

Figure 18. Selected PFS curves epNET (lung)



Abbreviations: BSC, best supportive care; epNET: extra-pancreatic neuroendocrine tumour; KM, kaplan meier; PFS: progression free survival.

Figure 19. Selected PFS curves epNET (without-lung)



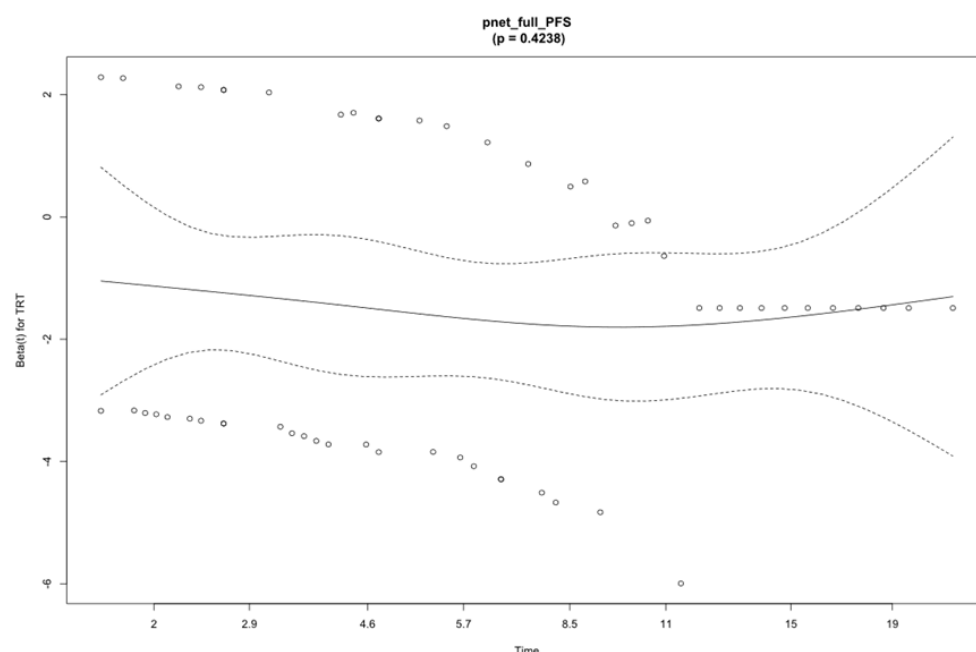
Abbreviations: BSC, best supportive care; epNET: extra-pancreatic neuroendocrine tumour; KM, kaplan meier; PFS: progression free survival.

4.2.3.1.3 EAG critique

At clarification, the EAG raised its concerns around the assumption that PH holds for the pNET and epNET PFS data. Whilst the p-value for both Schoenfeld residual curves was not sufficient to reject the null hypothesis at 95% CI, this is insufficient justification for accepting the null hypothesis.

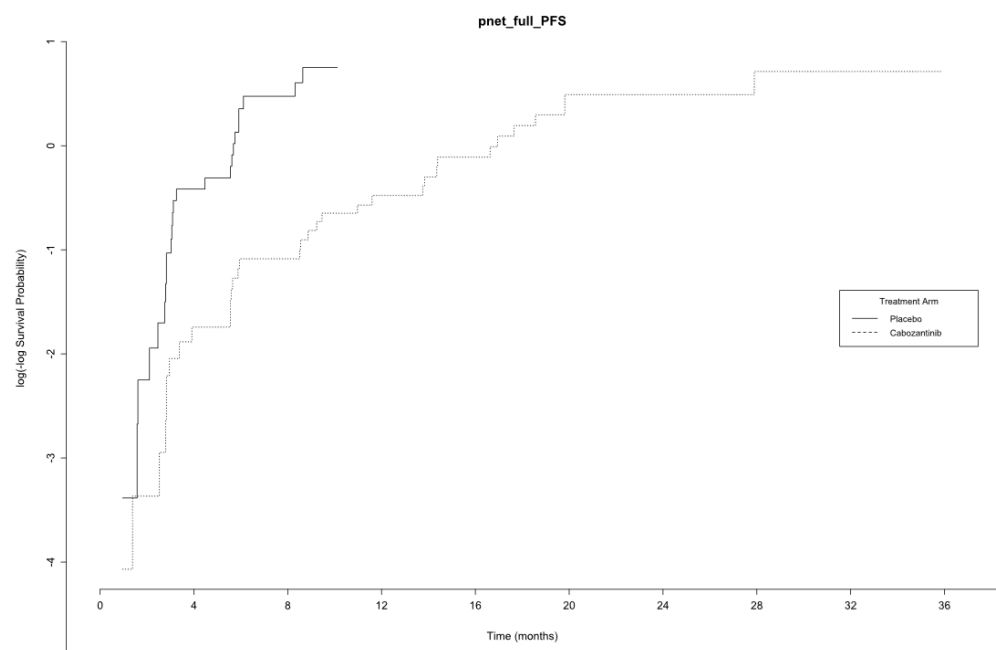
Inspecting the plots reveals a downwards trend (albeit based on 11 patients at risk at month 11), therefore suggesting a decrease in the HR between treatment arms. Looking at the pNET evidence of PH first, the Schoenfeld residual plot, in Figure 20, demonstrates there is a trend downwards to the 11 months point though the curve predictably flattens when data for PFS ends. In line with this, the log cumulative hazards plot, in Figure 21, does not show parallel curves. Specifically, the HR does not appear constant over time: cabozantinib seems less effective early on, with the relative benefit increasing later. Finally, the smoothed hazard plots for placebo and cabozantinib in Figure 22 also appear to show slightly different trends. but the large error margins make it difficult to interpret for evidence either way.

Figure 20. PFS pNET: Schoenfeld residual plot (reproduced from Figure 14 of the company appendix)



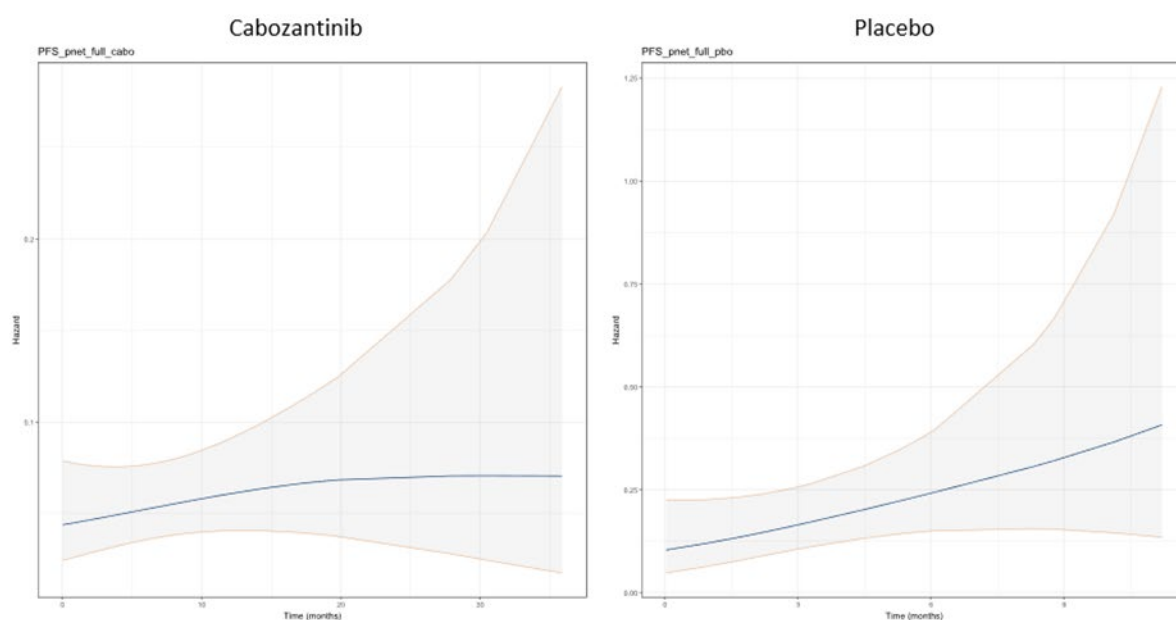
Abbreviations: pNET: pancreatic neuroendocrine tumour; PFS: progression free survival.

Figure 21. PFS pNET: log cumulative hazard plot (reproduced from Figure 15 of the company appendix)



Abbreviations: pNET: pancreatic neuroendocrine tumour; PFS: progression free survival.

Figure 22. PFS pNET: smoothed hazard plots (reproduced from Figure 16 of the company appendix)



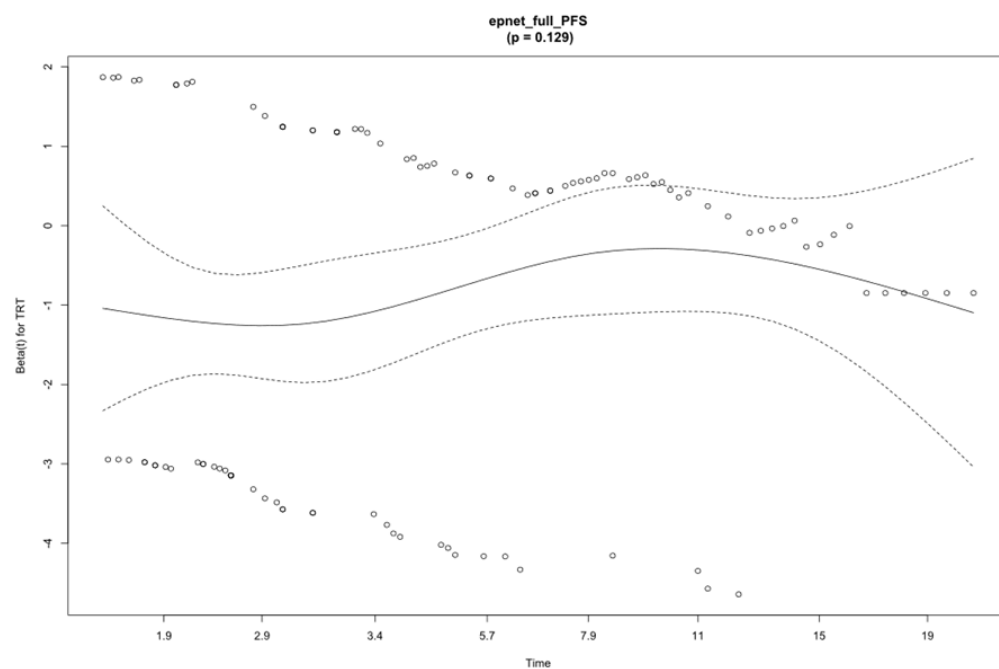
Abbreviations: pNET: pancreatic neuroendocrine tumour; PFS: progression free survival.

Similar to the pNET population, the Schoenfeld residual plot for the epNET population does not show a flat line, with a slight rise and fall implying time-varying effects. The EAG notes that the wide confidence intervals add uncertainty to the interpretation of the assessment of PH. In line with this, the log cumulative hazards plot, in Figure 24, does not show parallel curves. Cabozantinib seems more effective early on compared with placebo, but the advantage narrows later. Finally, the smoothed hazard plots for placebo and cabozantinib in Figure 25 show considerably different hazard trends.

Overall, given the small number of patients (particularly for pNETs with 64 patients in the cabozantinib arm, and 31 in the placebo arm), there is a large amount of uncertainty in interpreting these results. This issue combined with the apparent trend of an increase in the relative treatment effect of cabozantinib vs placebo in CABINET, leads to the EAG's conclusion that the most appropriate and robust approach to compare cabozantinib with BSC is to independently fit survival curves to CABINET data and to not rely on the PHs assumption.

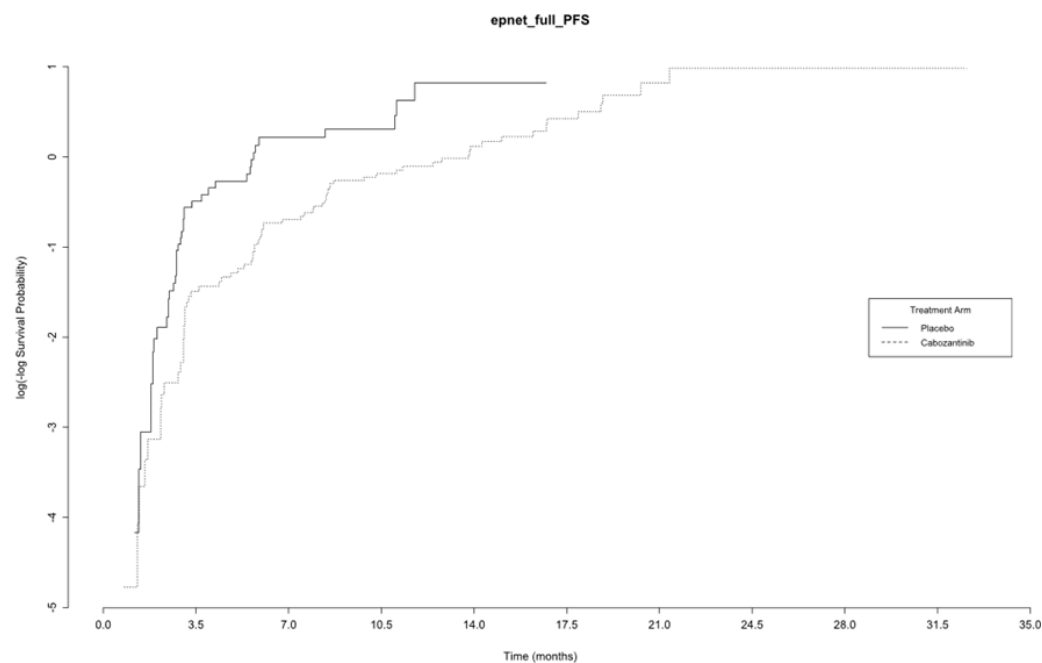
On a final technical note, the EAG notes that the company's approach of using the Cox model HR from the trial is not appropriate or justified, and that (when appropriate to use), HRs should be derived from the same parametric models used to estimate the respective survival curves, to maintain internal validity.

Figure 23. PFS epNET: Schoenfeld residual plot (reproduced from Figure 17 of the company appendix)



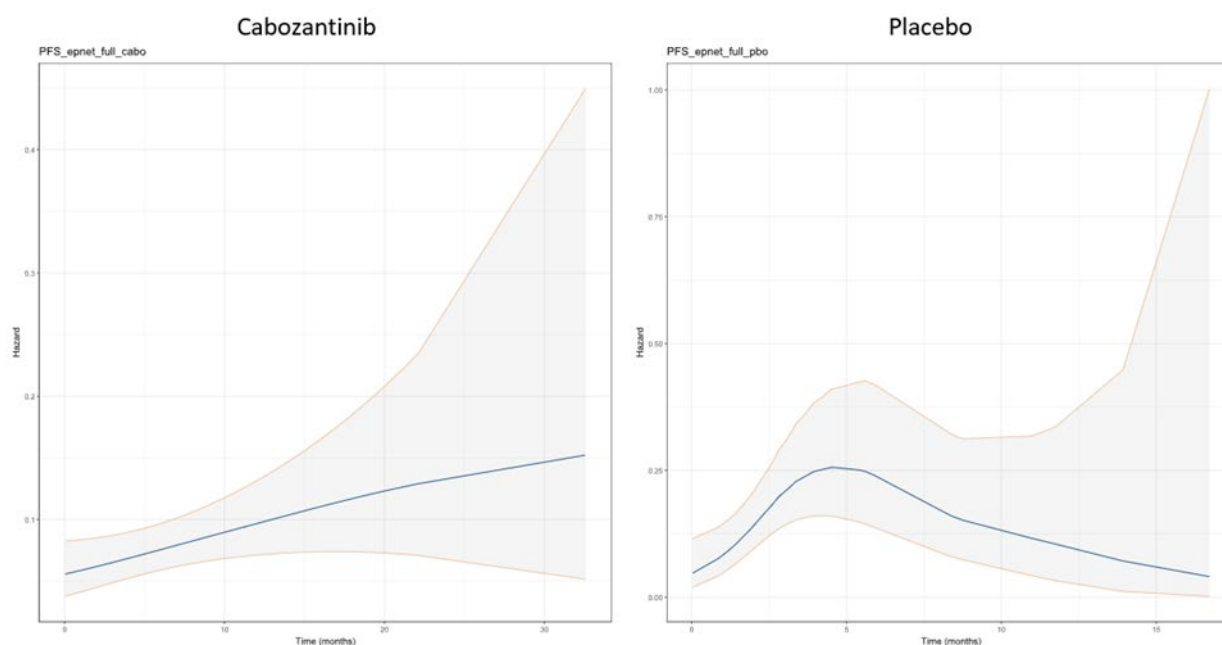
Abbreviations: epNET: extra pancreatic neuroendocrine tumour; PFS: progression free survival.

Figure 24. PFS epNET: log cumulative hazard plot (reproduced from Figure 18 of the company appendix)



Abbreviations: epNET: extra pancreatic neuroendocrine tumour; PFS: progression free survival.

Figure 25. PFS epNET: smoothed hazard plots (reproduced from Figure 19 of the company appendix)



Abbreviations: epNET: extra pancreatic neuroendocrine tumour; PFS: progression free survival.

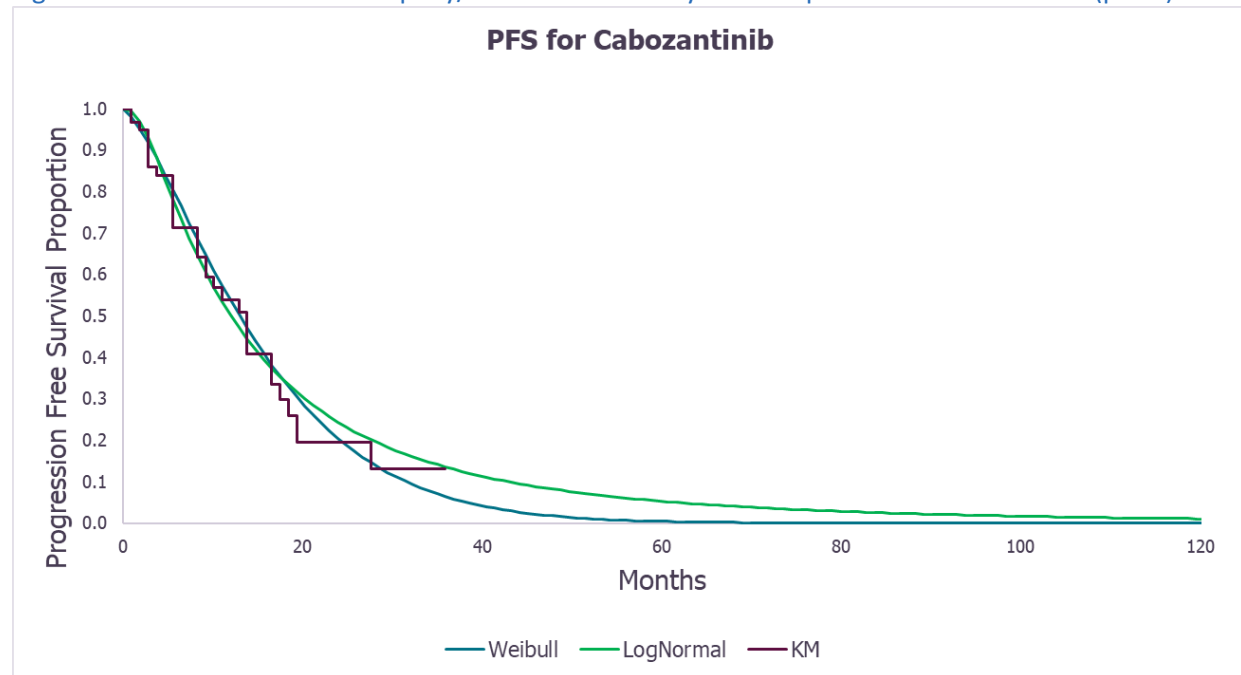
The company provided a scenario analysis where the cabozantinib and BSC curves were independently fitted with lognormal curves in both populations. The issue of violated PH assumption is part of **key issue 4** as the impact of using independent extrapolations on the cost-effectiveness results is minor.

The EAG was also concerned that the company's choice of a lognormal PFS curve overpredicted survival with cabozantinib between approximately 18 and 28 months (Figure 26 for pNET and Figure 27 for epNET). To attempt to resolve this issue, and in line with DSU TSD 21⁴³, the EAG requested the company explored more flexible modelling approaches for both pNETs and epNETs. The company provided spline models fitted to the PFS KM data, however these resulted in overfitted models and did not provide a better fit to the 18-to-28-month period of KM data.

In the company's response to clarification, it was also noted that the tails of KM curves have significant uncertainty due to low numbers at risk, with only 8 and 3 patients at risk at 18 and 24 months respectively in the pNET and epNET population. The company also pointed out that the estimated curves were within the 95% CIs demonstrated (Figure 10 in company's response to clarification).

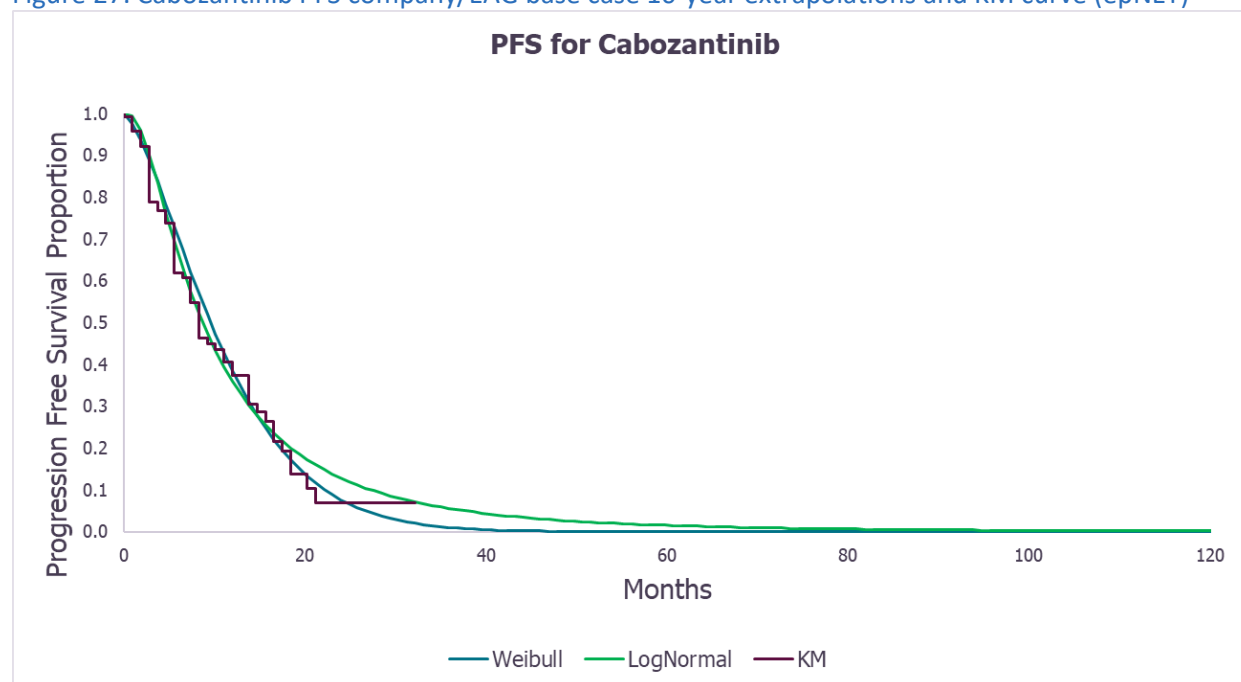
The EAG preference is to use the r Weibull model for both the pNET and epNET populations. Even though the AIC and BIC for this model is higher than the company's base case lognormal choice, it provides a more conservative fit to the underlying PFS KM data. The EAG acknowledges the uncertainty around the tails of the KM curves, however, notes that this further justifies taking the more conservative approach and the one that better reflects the underlying KM PFS curves, which relies on using the Weibull curve. This is **key issue 4**.

Figure 26. Cabozantinib PFS company/EAG base case 10-year extrapolations and KM curve (pNET)



Abbreviations: epNET: extra pancreatic neuroendocrine tumour; KM: Kaplan-Meier, PFS: progression free survival.

Figure 27. Cabozantinib PFS company/EAG base case 10-year extrapolations and KM curve (epNET)



Abbreviations: epNET, extra pancreatic neuroendocrine tumour; KM, Kaplan-Meier; PFS, progression free survival.

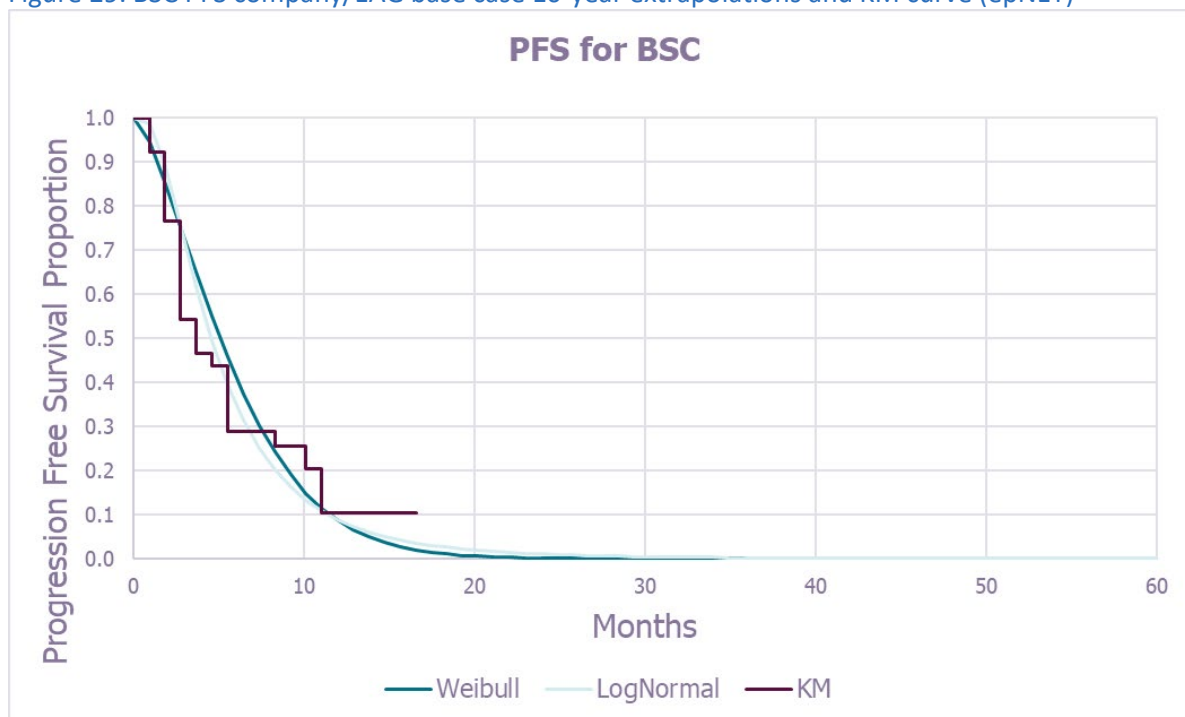
The EAG has added a scenario which applies independently fit weibull curves to the BSC arm to match cabozantinib, though the EAG preference is for the company selected lognormal curves there is little difference in applying the weibull curves as shown in Figure 28 for pNET and Figure 29 for epNET. It should also be noted that it is valid to use a HR with the weibull extrapolation. The lognormal provides the better fit according to AIC and BIC but the weibull matches the EAG preference for the cabozantinib curve.

Figure 28. BSC PFS company/EAG base case 10-year extrapolations and KM curve (pNET)



Abbreviations: epNET: extra pancreatic neuroendocrine tumour; KM: Kaplan-Meier, OS: overall survival.

Figure 29. BSC PFS company/EAG base case 10-year extrapolations and KM curve (epNET)



Abbreviations: epNET: extra pancreatic neuroendocrine tumour; KM: Kaplan-Meier, OS: overall survival.

4.2.3.2 Additional analysis requested by the EAG

The company only provided KM data for the cabozantinib arm for the lung NET and epNET without lung subgroups. The equivalent KM data were not provided for the BSC arm, and a HR was applied to derive the BSC arms. The chosen HR was taken from the pooled I epNET population. This is inappropriate as one of the key purpose of subgroup analysis is to observe how (and if) effectiveness differs in these two groups. Following a post-clarification request the company was able to provide the HRs for the specific subgroups with lung having a HR of [REDACTED] and w/o lung having a HR of [REDACTED]

To note is that there was no option in the model to independently fit curves in the lung NET and the epNET without lung populations in the model.

The EAG’s preferences to model subgroups and treatments are listed in Table 42. Results of the EAG’s analysis can be found in Section 6.

Table 42: EAG and company preferred PFS curves summary

Subgroup	Company base case		EAG base case	
	Cabozantinib	BSC	Cabozantinib	BSC
pNET	lognormal	HR (pNET)	Weibull	lognormal
epNET	lognormal	HR (epNET)	Weibull	lognormal
epNET (lung)	lognormal	HR (epNET)	Weibull	HR (epNET lung)
epNET (w/o lung)	lognormal	HR (epNET)	Weibull	HR (epNET w/o lung)

Abbreviations: BSC, best supportive care; EAG, external assessment group; HR, hazard ratio; w/o, without.

4.2.3.2.1 Overall survival

As discussed in the clinical sections, the company’s base case analysis uses OS data from the first data cut-off (DCO) from August 2023. The company provided scenario analyses from the updated DCO, from September 2024, but stated that it was more appropriate to use the prespecified first DCO rather than the updated OS data sweep data.

4.2.3.2.1.1 Curve selection first DCO

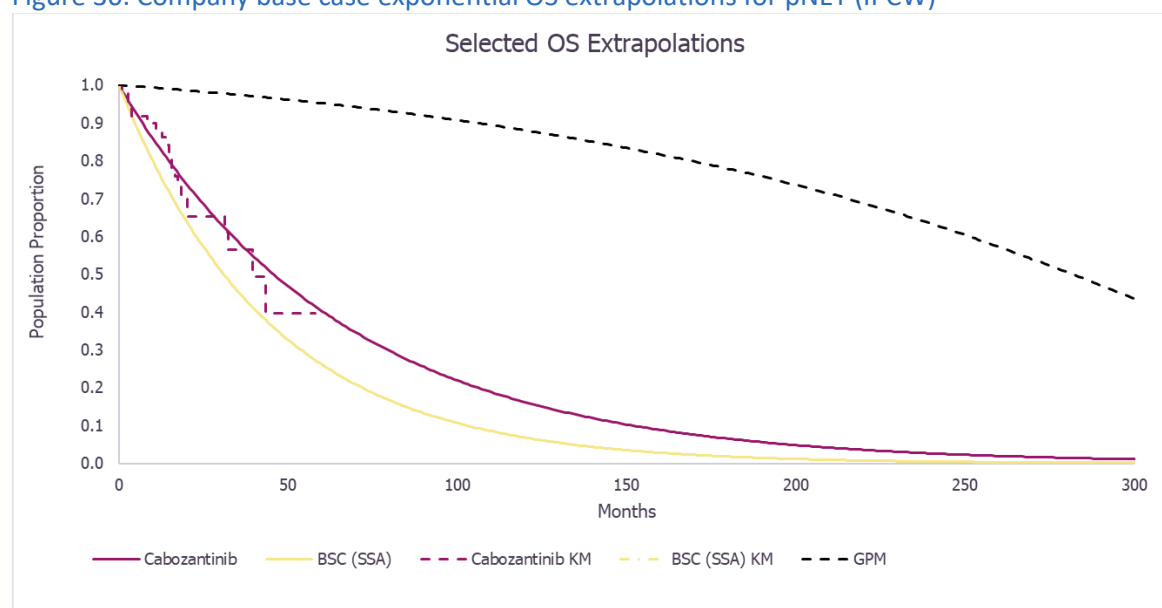
As discussed in Section 3.3.2.1, the company used the inverse probability of censoring weights (IPCW) method to adjust OS trial data for crossover. This involves artificially censoring patients who

switched to cabozantinib, at time of patient switch, and reweighting remaining observations, using prognostic factors, based on probability of being censored. Further details relating to this analysis are found in the company appendix L.

An IPCW crossover-adjusted HR was applied to the cabozantinib arm to derive the BSC treatment OS curve, therefore only the cabozantinib arm required the process of a survival curve selection. The choice of curve was based on statistical fit, visual fit to the cabozantinib arm and clinical validation of the resulting OS curve for BSC. Based on this, the company selected the exponential distribution for cabozantinib pNET OS and the loglogistic distribution for cabozantinib epNET OS. Figure 30 for pNET and Figure 31 for epNET presents the company's preferred OS curves alongside age and sex adjusted general population mortality (GPM) OS.

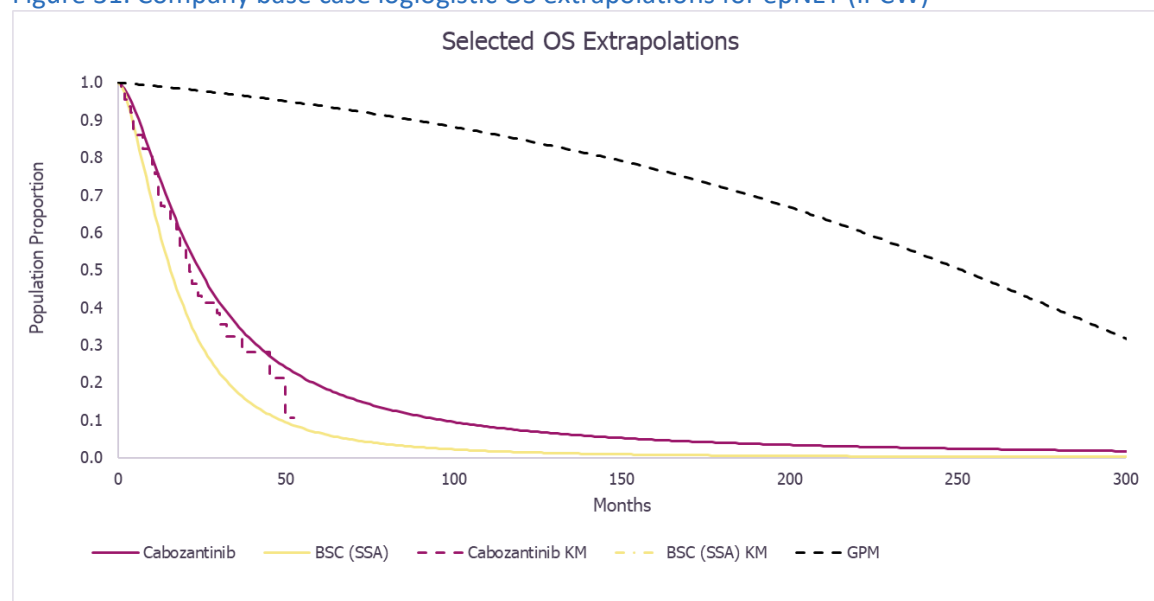
The company provided Schoenfeld residuals for the ITT (in company appendix K.2) and IPCW-adjusted (in clarification response B10) data supporting the non-violation of the PH assumption between the cabozantinib and BSC arms. The EAG agrees that the evidence supplied indicates that the PH assumption is likely to hold. The company's base case IPCW adjusted HR used was 0.74 (95% CI 0.36 to 1.52) for pNET and 0.65 (95% CI 0.39 to 1.07) for epNET.

Figure 30. Company base case exponential OS extrapolations for pNET (IPCW)



Abbreviations: BSC, best supportive care; GPM, general population mortality; KM, Kaplan Meir; OS, overall survival.

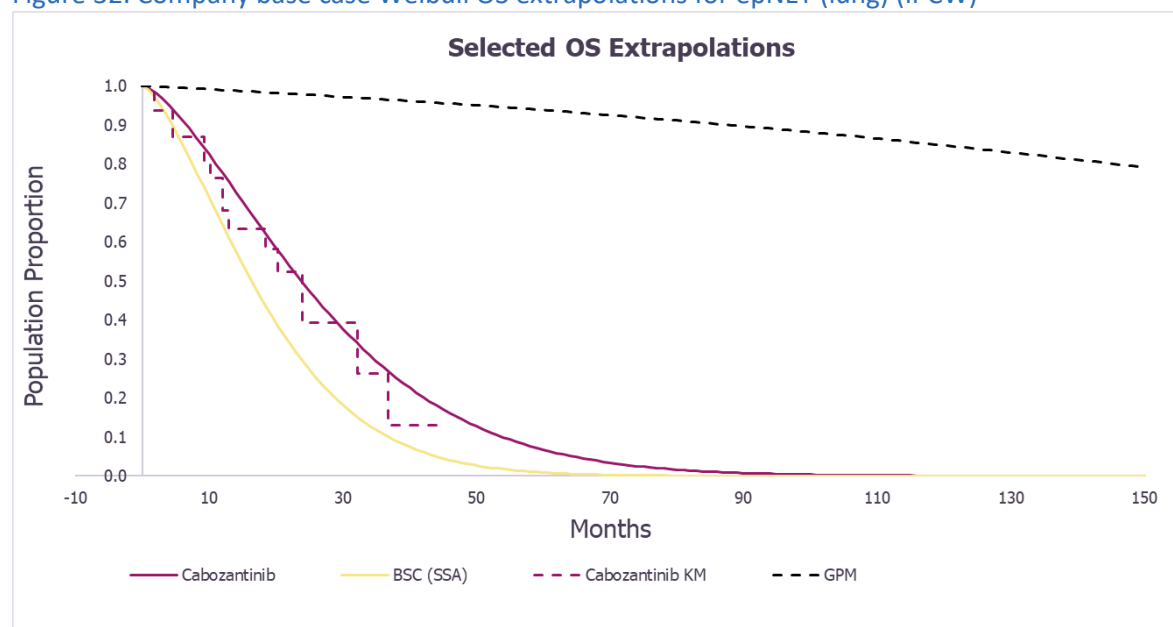
Figure 31. Company base case loglogistic OS extrapolations for epNET (IPCW)



Abbreviations: BSC, best supportive care; GPM, general population mortality; KM, Kaplan Meir; OS, overall survival.

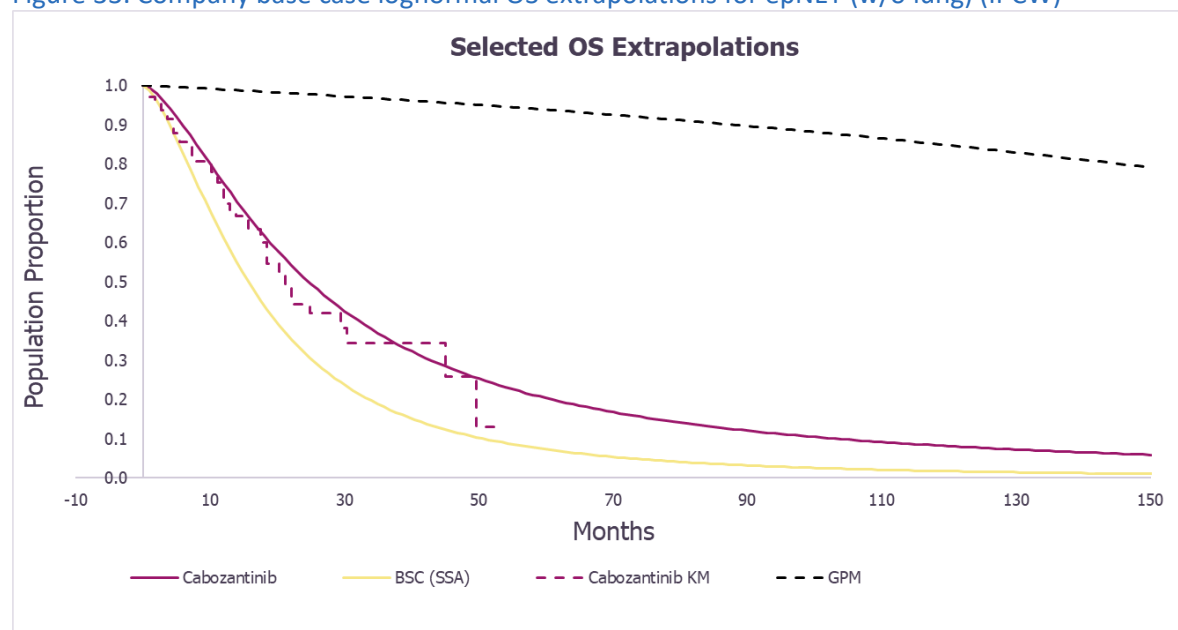
The company's curve selection for epNET lung and epNETs without lung scenarios was Weibull and loglogistic, respectively, for the cabozantinib arm, as these had the best fits visually the best AIC and BIC ranking. A HR of [REDACTED] was applied to estimate survival in the BSC arms for both subgroups. These curves can be observed in Figure 32 and Figure 33.

Figure 32. Company base case Weibull OS extrapolations for epNET (lung) (IPCW)



Abbreviations: BSC, best supportive care; GPM, general population mortality; KM, Kaplan Meir; OS, overall survival.

Figure 33. Company base case lognormal OS extrapolations for epNET (w/o lung) (IPCW)



Abbreviations: BSC, best supportive care; GPM, general population mortality; KM, Kaplan Meir; OS, overall survival.

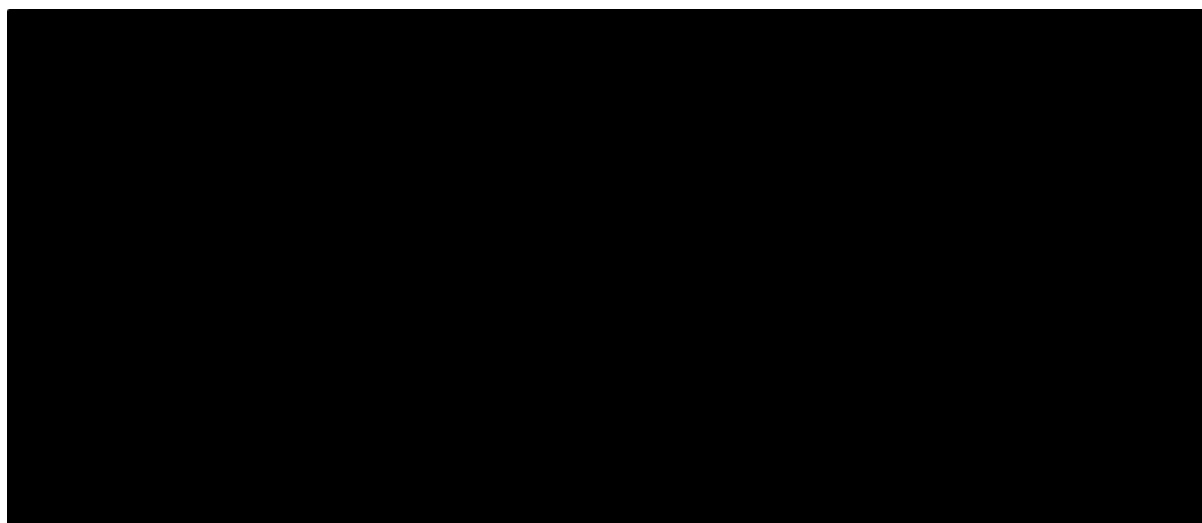
4.2.3.2.1.2 Curve selection with updated DCO

Following clarification, at the request of the EAG, the company provided an updated OS DCO from September 2024. As with the first DCO their base case used IPCW crossover adjustment but RPSFTM and ITT was presented.

For the updated DCO, the company base case used loglogistic for pNET and epNET. This was based partly on the AIC and BIC ranking, seen in Figure 34 and Figure 35, and due to these curves matching clinician landmark survival estimates for OS in cabozantinib. Differences in AIC and BIC were minor (<5) so preference was given for the curves that matched the clinician estimates (provided in Table 7 of CQ response addendum).

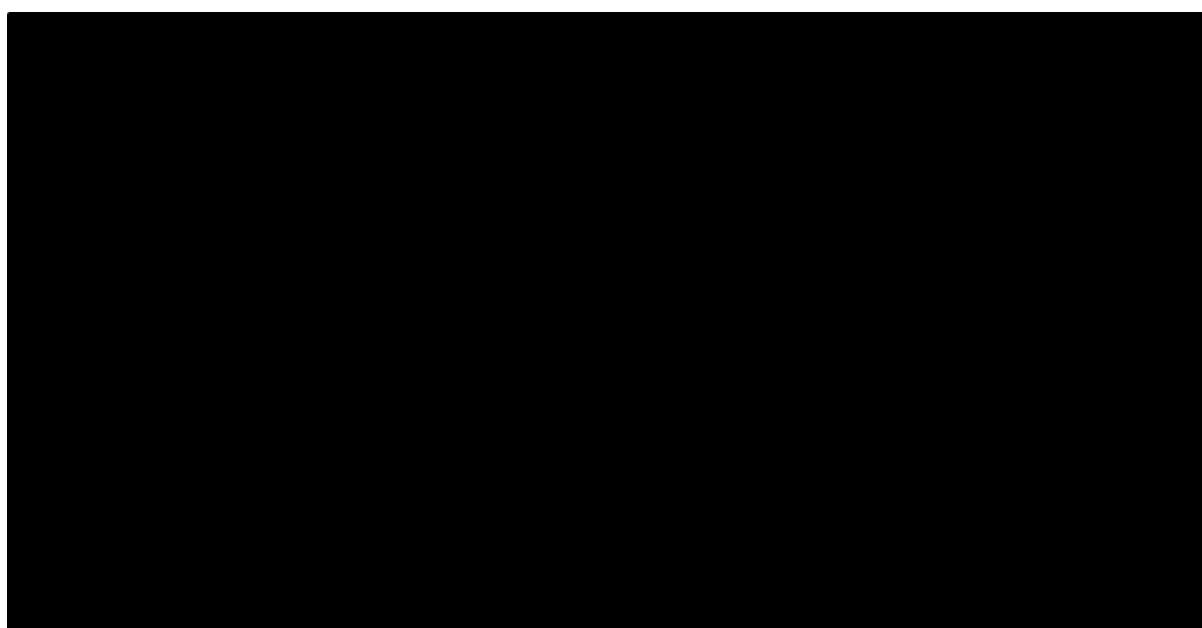
For lung NETs the Gompertz extrapolation was selected as it had the lowest AIC and BIC (Figure 36). For epNET without lung, a loglogistic curve was selected as it had low AIC and BIC, (Figure 37). The company added that the loglogistic curve fitted the 5;10; and15 year survival estimates for the epNET population given by clinical experts.

Figure 34. Cabozantinib OS extrapolations (pNETs) (copy of Figure 1 company's response addendum)



Abbreviations: KM: Kaplan-Meier; OS: overall survival; pNET: pancreatic neuroendocrine tumour.

Figure 35. Cabozantinib OS extrapolations (epNETs) (copy of Figure 2 company response addendum)

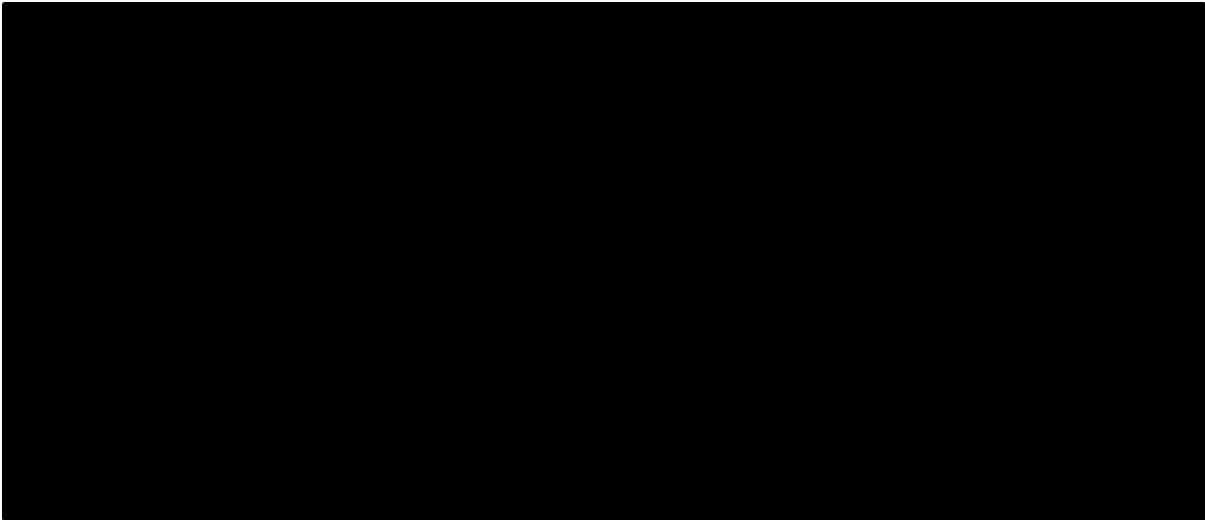


Abbreviations: epNET: extra pancreatic neuroendocrine tumour; KM: Kaplan-Meier, OS: overall survival.

Figure 36. Cabozantinib OS extrapolations (lung NETs) (copy of Figure 5 company response addendum)

Abbreviations: KM: Kaplan-Meier; OS: overall survival; epNET: extra-pancreatic neuroendocrine tumour.

Figure 37. Cabozantinib OS extrapolations (epNETs; without lung) (copy of Figure 6 company response addendum)



Abbreviations: KM: Kaplan-Meier; OS: overall survival; epNET: extra-pancreatic neuroendocrine tumour.

The company assessed proportional hazards in the ITT population of the updated DCO and considered that the proportional hazards assumption was reasonable, based on Schoenfeld residuals analysis. Therefore, as with the original DCO, an IPCW adjusted HR was applied to the cabozantinib curve to generate the BSC survival.

The IPCW, RPSFTM and ITT HRs (and 95% CI) for all relevant populations can be found in Table 43. Updated RPSFTM KM curves were provided for lung NETs and w/o lung epNETs for the updated DCO but were not provided for the pooled epNET population or pNETs. As discussed in the clinical section, for the updated DCO, effect estimates numerically favoured placebo (with the exception of the IPCW HR for the pooled epNETs population), but differences were [REDACTED].

Table 43. OS HRs for cabozantinib vs placebo for updated DCO in CABINET

Population/Subgroup	Crossover adjustment	HR value	95% CI lower	95% CI upper
pNETs	IPCW	[REDACTED]	[REDACTED]	[REDACTED]
	RPSFTM	[REDACTED]	[REDACTED]	[REDACTED]

	ITT HR (no adjustment)	■	■	■
epNETs	IPCW	■	■	■
	RPSFTM	■	■	■
	ITT HR (no adjustment)	■	■	■
Lung NETs	IPCW	■	■	■
	RPSFTM	■	■	■
	ITT HR (no adjustment)	■	■	■
epNETs without lung	IPCW	■	■	■
	RPSFTM	■	■	■
	ITT HR (no adjustment)	■	■	■

Abbreviations: BSC, best supportive care; CI, confidence interval; EAG, external assessment group; HR, hazard ratio; IPCW, inverse probability coefficient weighting; ITT, intention to treat; RPSFTM, rank preserving structural failure time model

4.2.3.2.1.3 EAG critique

As discussed in clinical section 3.3.2.1 the EAG considers that the updated DCO should be used to estimate OS in the model. This is **key issue 3**. Even though the EAG preference is to use the more mature OS data in the analysis, for completeness, the EAG included a critique of the company's approach to incorporating the original August 2023 DCO in the economic model in Appendix 9.2 of the EAG report.

The EAG has some concerns with the company's selected loglogistic curves for the OS updated DCO. The latter are not compatible with using fixed hazard ratios as loglogistic curves imply time varying hazards.

Given the minimal difference in AIC and BIC values, the EAG has selected the best fitting survival curves which are compatible with using a HR in the model. This is the exponential in the pNET population and the Weibull in the epNET population. As the company stated, the difference in AIC and BIC is minimal, with the Weibull AIC and BIC scores in pNET and epNET being less than 1 different to the best fitting curve.

In the lung NET population, the Weibull is also the best fitting and HR-compatible curve and the exponential provides the better fit in the epNET without lung group (for a HR-compatible curve).

Both these curves have AICs/BICs within 1 of the best fitting curves. These curves can be seen alongside additional comparators in section 4.2.3.3.

In reviewing the HRs provided by the company and the evidence given for the proportional hazards assumption, the collective evidence suggests a high degree of uncertainty around the existence of an OS benefit associated with cabozantinib except in lung NET population, where the HRs suggest a survival benefit associated with cabozantinib. For all other groups (pNETs; epNETs; and epNETs without lung), the RPSFTM (and the majority of the IPCW) HRs are above 1, suggesting a numerical survival benefit associated with placebo.

The EAG considered the apparent discrepancy in the direction of the PFS and OS results in the CABINET trial, particularly when the updated DCO OS data are used. The EAG's preference remains to use the more mature OS data, and notes that 12 months of additional OS trial data should not be ignored (as is the company's preference in their base case). The EAG acknowledges that the number of patients in CABINET is considerably small, leading to a small number of patients crossing over and a reduced number of OS events in patients who crossed over. Consequently, OS results with different adjustment methods are uncertain.

After consideration of the evidence, the EAG concluded that assuming equal survival for cabozantinib and BSC in the economic model was a more plausible approach than using the ITT or the RPSFTM HRs for the updated DCO. The latter imply a survival advantage for placebo against cabozantinib, which lacks clinical validity. Results of the EAG's exploratory analysis are reported in Section 6.

The EAG base case and company preferences, using the updated DCO, is laid out in Table 44. Results of the EAG analysis can be found in Section 6.

Table 44: EAG and company preferred OS curves summary updated DCO

Subgroup	Company preferences (using updated DCO)		EAG base case	
	Cabozantinib	BSC	Cabozantinib	BSC
pNET	Loglogistic	Stratified IPCW adjusted HR (pNET) [REDACTED]	Weibull	Assumed 1
epNET	Loglogistic	Stratified IPCW adjusted HR (epNET)	Weibull*	Assumed 1*

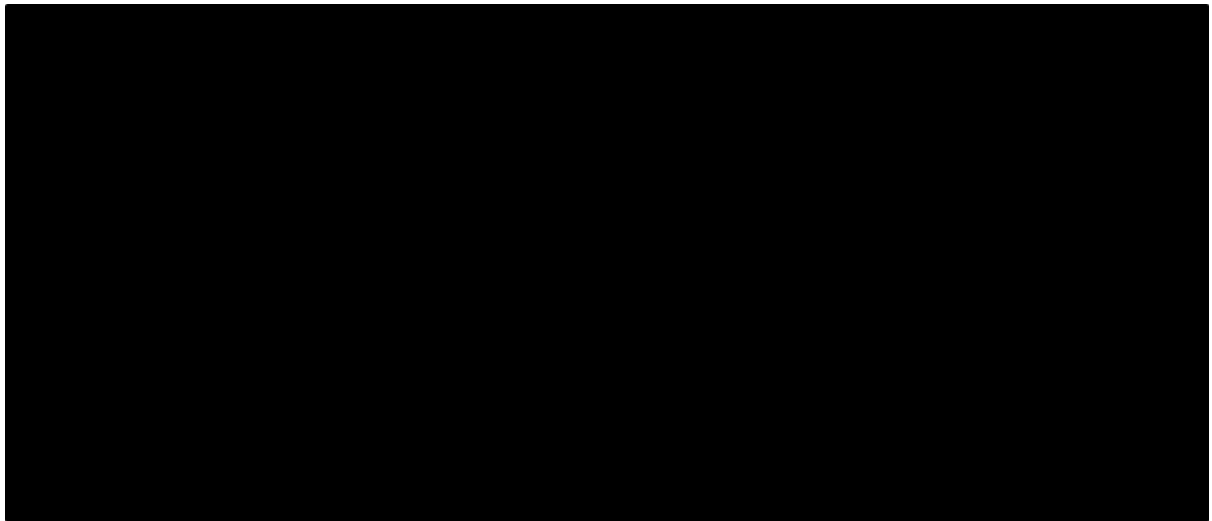
Lung NET	Gompertz**	Stratified IPCW adjusted HR (epNET)	Weibull	Unstratified RPSFTM adjusted HR
epNET (w/o lung)	Loglogistic**	Stratified IPCW adjusted HR (epNET)	exponential	Assumed 1
*EAG base case assumes epNET lung and epNET without lung should be separated **company base case assumes epNET should be assessed as whole population Abbreviations: BSC, best supportive care; EAG, external assessment group; HR, hazard ratio; w/o, without.				

4.2.3.2.2 TTD

In the base case analysis, time to treatment discontinuation (TTD) was based on data from the CABINET trial, with the PH assumption assessed in accordance with NICE TSD 14. Diagnostic plots showed no significant violation of the PH assumption for either the pNET or epNET cohorts, supporting the use of a HR-based approach to model BSC TTD by applying the CABINET Cox model HR to the cabozantinib TTD curve. Independent extrapolations for each arm were also explored as a scenario analysis. TTD curves were bounded by PFS curves, reflecting clinical guidance that treatment would not extend beyond progression.

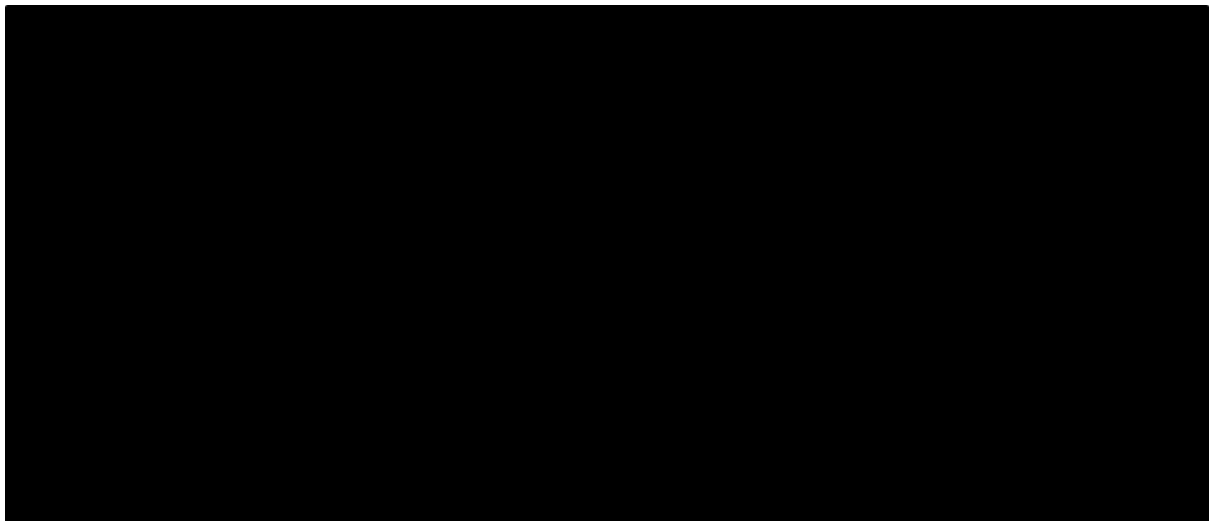
Two key assumptions were made by the company for modelling TTD; the first is that discontinuation of SSAs occurred in line with placebo discontinuation in the trial; and the second is that discontinuation of cabozantinib meant discontinuation of concomitant SSAs. The company base case TTD extrapolations are shown in Figure 38 and Figure 39 for pNET and epNET. Figure 40 and Figure 41 show the company's scenario analyses for lung NETs and epNETs without lung.

Figure 38. company base case TTD extrapolations (pNET)



Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; KM, Kaplan-Meier; QALY, quality adjusted life year; TTD, time to treatment discontinuation; WTP, willingness to pay.

Figure 39. company base case TTD extrapolations (epNET)



Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; KM, Kaplan-Meier; QALY, quality adjusted life year; TTD, time to treatment discontinuation; WTP, willingness to pay.

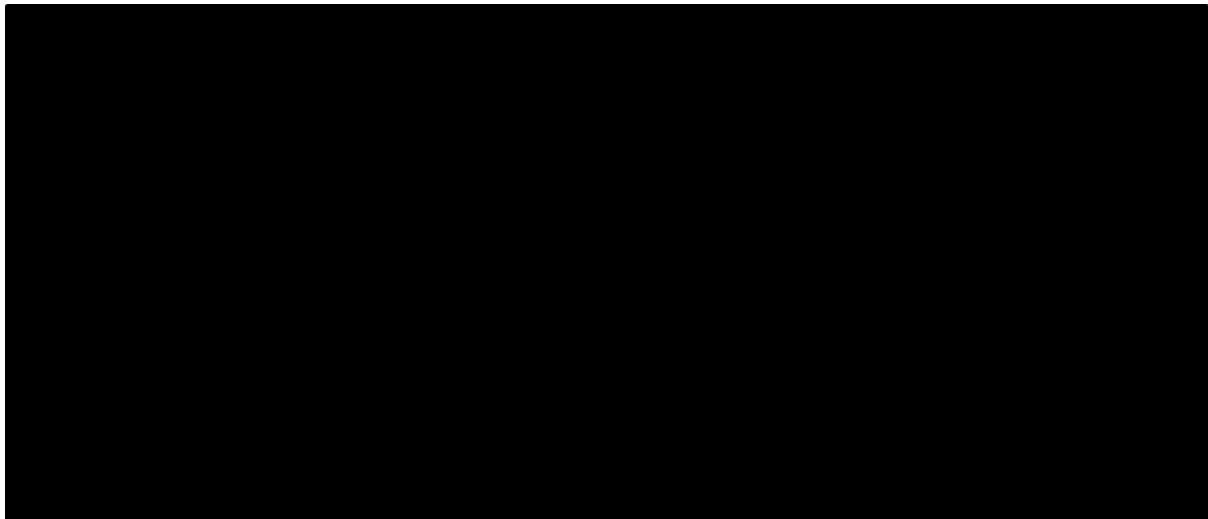
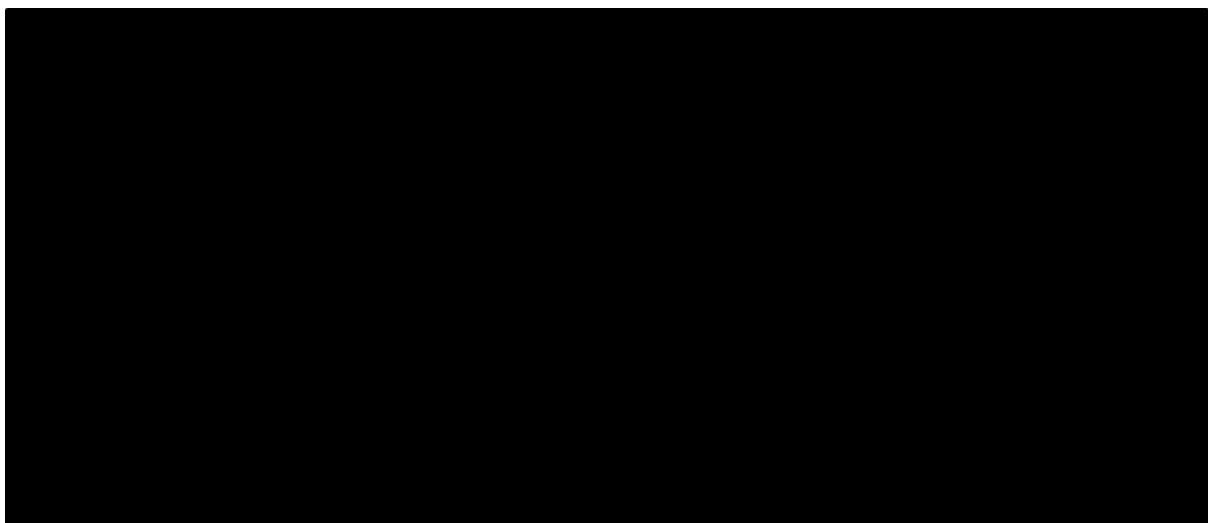


Figure 40. company base case TTD extrapolations (lung NETs)

Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; NETs, neuroendocrine tumours; QALY, quality adjusted life year; TTD, time to treatment discontinuation; WTP, willingness to pay.

Figure 41. company base case TTD extrapolations (epNET without lung NET)



Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; KM, Kaplan-Meier; QALY, quality adjusted life year; TTD, time to treatment discontinuation; WTP, willingness to pay.

4.2.3.2.3 EAG critique

Given the maturity of the KM TTD data, the EAG considers that directly using the KM curves to estimate TTD in the model would present a more accurate depiction of discontinuation in the CABINET trial and remove unnecessary uncertainty from the analysis. This approach also does not need to rely on the PH assumption. The KM curves also show sharp declines at assessment points

which may be more reflective of real-world practice than a smoothed decline represented by parametric models.

The EAG considers that both key assumptions made by the company around SSA treatment duration are inappropriate. This is further discussed in Section 4.2.6 and forms **key issue 8**.

4.2.3.3 The less heavily pretreated population – everolimus and sunitinib as comparators

Modelling PFS

The exploratory ITC conducted by the EAG (described in section 3.4.2) has been used to estimate the relative treatment effect of cabozantinib vs. everolimus and sunitinib in the model. As previously noted, everolimus is a relevant comparator not only for pNETs but also in non-functional epNET lung patients who have received prior chemotherapy as a first systemic line of treatment. Applying the exploratory HRs reported in Table 45 to the EAG- preferred cabozantinib PFS curves results in the PFS extrapolations shown in Figure 42 for pNET, Figure 43 for epNET,

As can be seen from the figures, results of the EAG’s exploratory ITCs indicate that cabozantinib has a numerical benefit for PFS compared to everolimus and sunitinib. Nonetheless, none of the PFS HRs in the EAG’s exploratory analysis were statistically significant, which is not unexpected, given the Bucher method used for the exploratory analysis.

As can be seen in the table, the HR for cabozantinib vs. everolimus for the pooled epNET population was used for the epNET without lung subgroup.

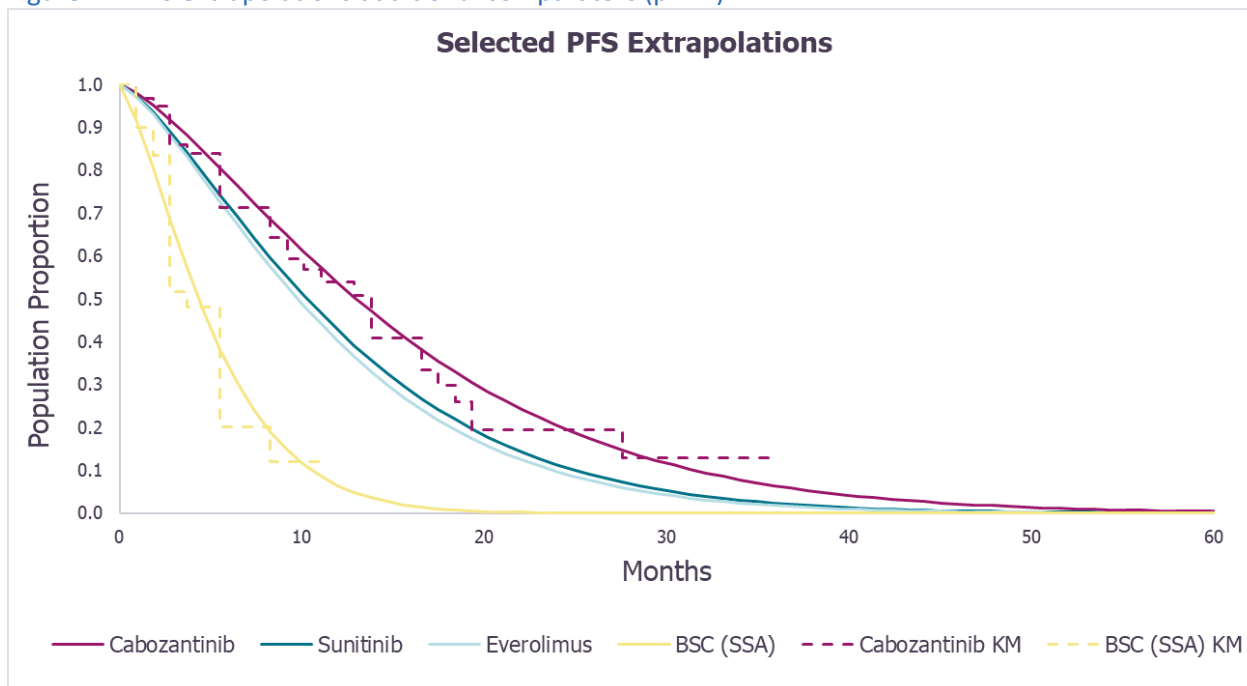
Table 45. PFS HR ratios used in EAG’s exploratory analysis

treatment	HR	SE	95% CI lower	95% CI upper
pNETs				
BSC	■	■	■	■
Everolimus	■	■	■	■
Sunitinib	■	■	■	■
epNETs				
BSC	■	■	■	■
Everolimus	■	■	■	■
epNETs (lung)				
BSC	■	■	■	■
Everolimus	■	■	■	■
epNETs (without lung)				

BSC	■	■	■	■
Everolimus	■	■	■	■

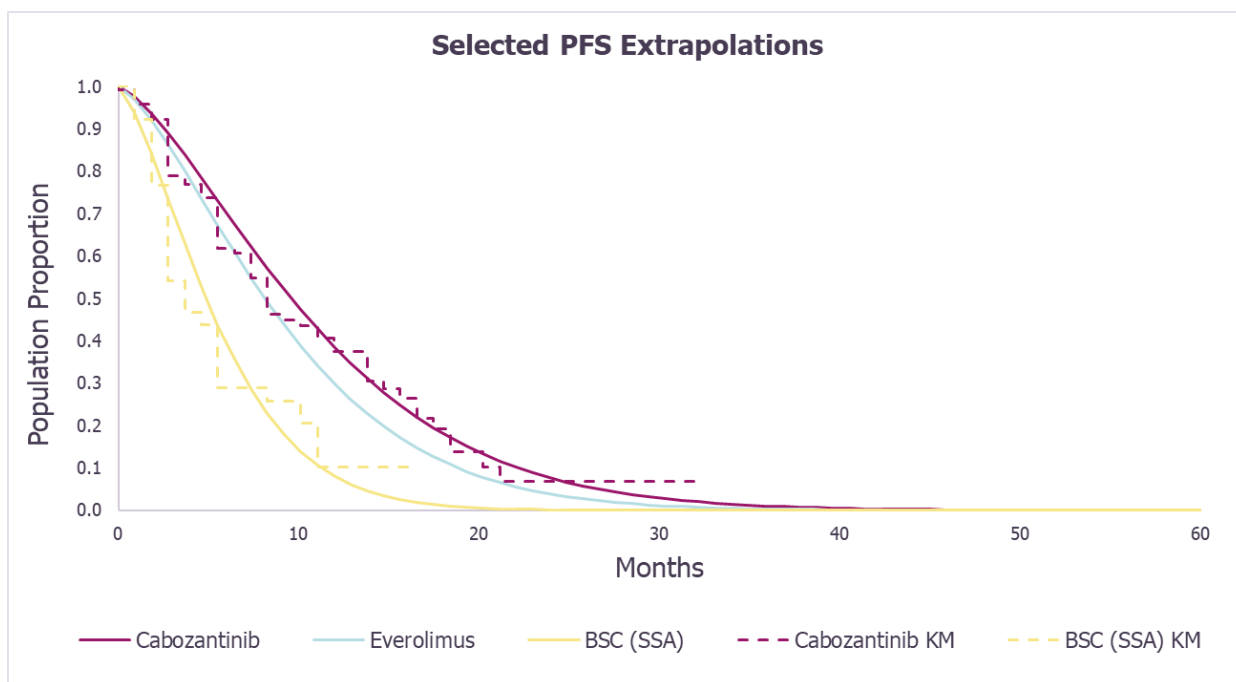
Abbreviations: epNET: extra-pancreatic neuroendocrine tumour; pNET: pancreatic neuroendocrine tumour; TRAE: treatment-related adverse event.

Figure 42. PFS extrapolations additional comparators (pNET)



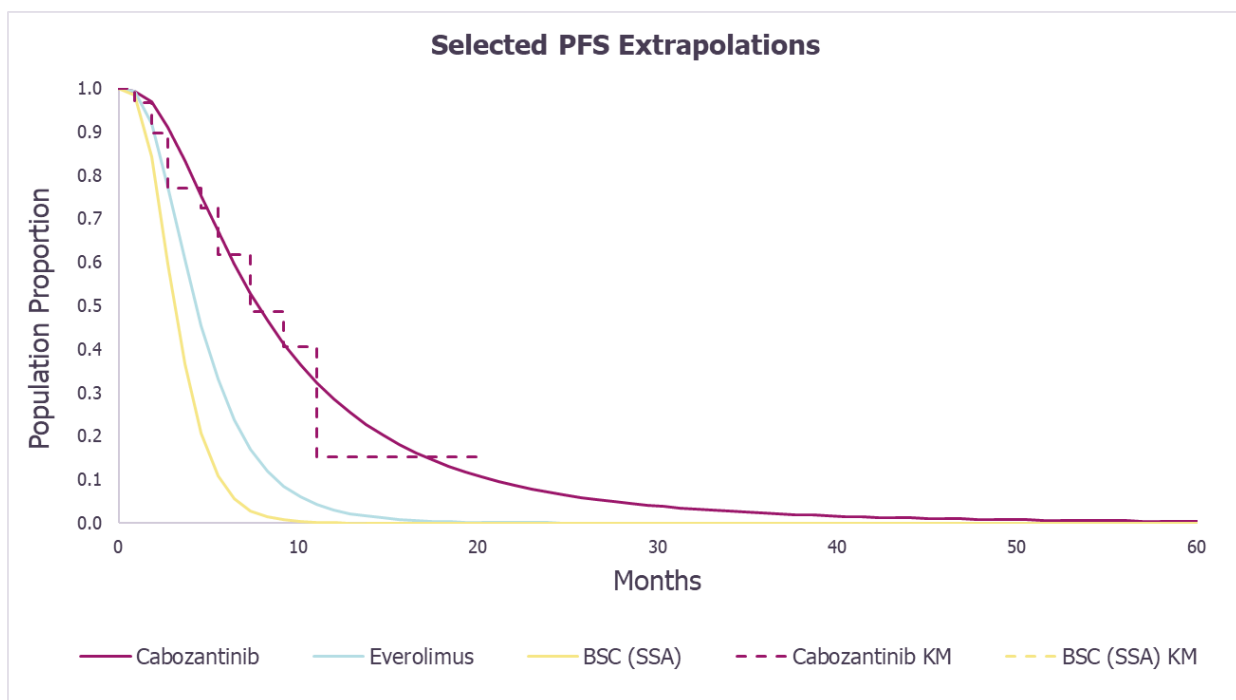
Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; PFS, progression free survival; pNETs, pancreatic neuroendocrine tumours; QALY, quality adjusted life year; WTP, willingness to pay.

Figure 43. PFS extrapolations additional comparators (epNET)



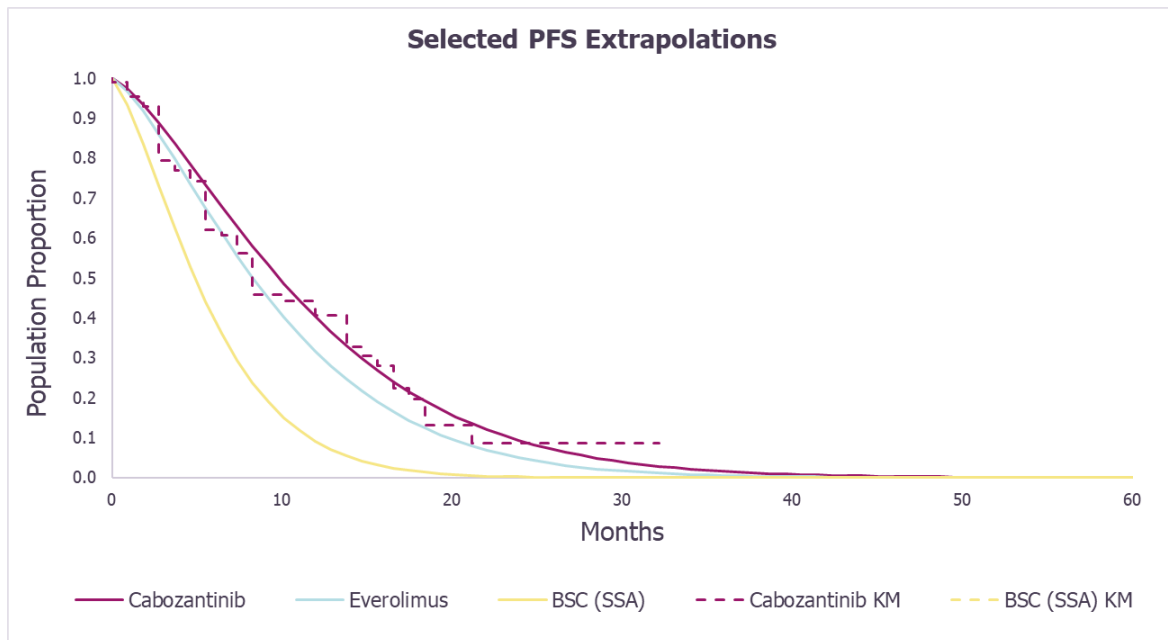
Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; KM, Kaplan-Meier; PFS, progression free survival; QALY, quality adjusted life year; WTP, willingness to pay.

Figure 44. PFS extrapolations additional comparators (lung NETs)



Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; NETs, neuroendocrine tumours; PFS, progression free survival; QALY, quality adjusted life year; WTP, willingness to pay.

Figure 45. PFS extrapolations additional comparators (epNET without lung)



Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; KM, Kaplan-Meier; PFS, progression free survival; QALY, quality adjusted life year; WTP, willingness to pay.

Modelling OS

The EAG notes that these results are being driven by the direct evidence from CABINET, particularly with the updated OS DOC, where placebo shows a numerical survival advantage to cabozantinib. The EAG notes that all OS results in this section use the updated DCO. For additional comparator analysis using the original DCO please refer to Appendix 9.2.1.

The EAG considered the apparent discrepancy in the direction of the PFS and OS results in its exploratory analysis. Furthermore, the EAG considered external evidence showing that cabozantinib has a statistically significant survival advantage over everolimus in previously treated advanced renal cell carcinoma (METEOR trial) and a numerical but not statistically significant OS benefit against sunitinib (CABOSUN trial). After consideration of the evidence, the EAG considered that assuming equal survival for cabozantinib, everolimus and sunitinib in the economic model was a more plausible approach than using the exploratory ITC results showing a PFS advantage for cabozantinib and an OS disadvantage for the treatment against everolimus and sunitinib. Results of the EAG's exploratory analysis are reported in Section 6.

Modelling TTD

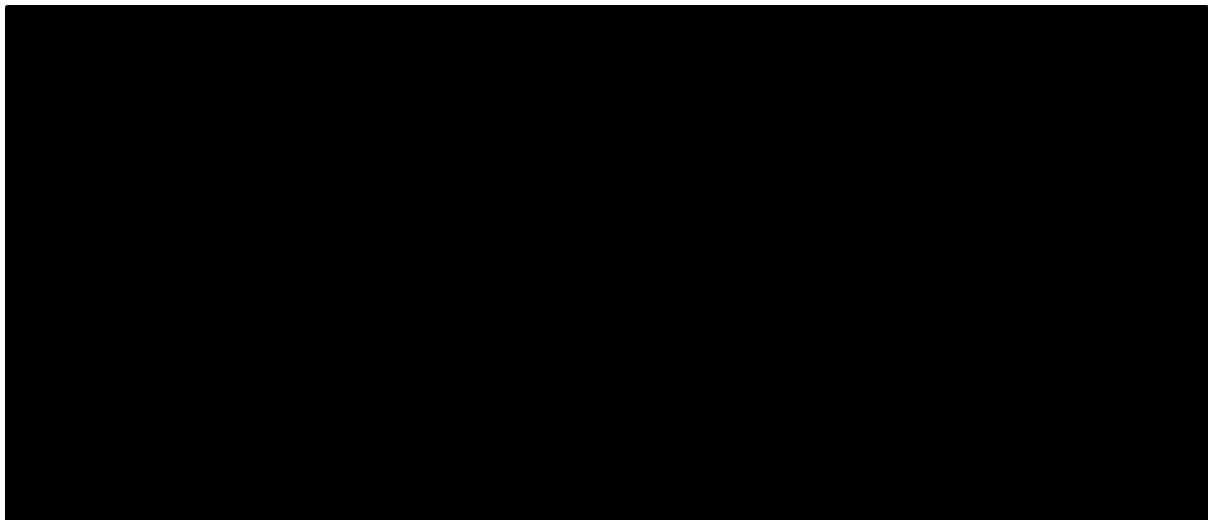
Only median TTD was available for everolimus and sunitinib. Therefore, TTD curves for sunitinib and everolimus were modelled using an exponential function, derived from the median duration of treatment taken from RADIANT-3^{37, 45}, RADIANT-4^{37, 46} and A6181111^{37, 47}. The durations of treatment are found in section 4.2.6.3.

The exponential function; $S(t) = e^{-t\theta}$ with θ being a constant, can be derived using median treatment duration as $t = \text{median survival}$ when $S(t) = 0.5$. Therefore, the equation can be reorganised to: $\theta = \frac{\ln(2)}{\text{median survival}}$

TTD extrapolations are shown in Figure 46 for pNET, Figure 47 for epNET, Figure 48 for lung NETs and Figure 49 for epNET without lung.

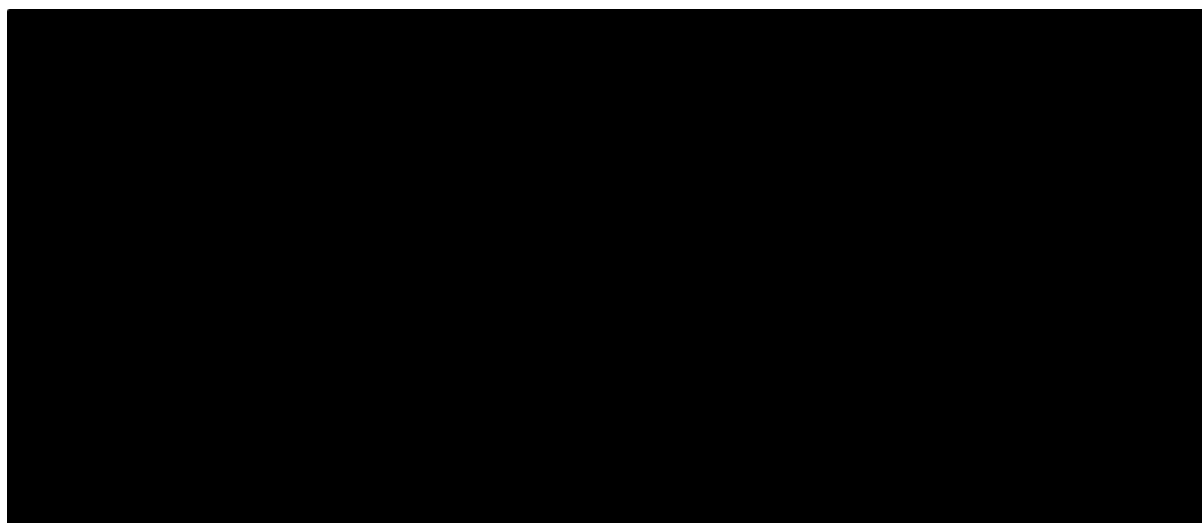
In iterations of the model using epNET (without lung) population the HR applied to BSC is assumed equal to lung NETs. The smoothed curve for cabozantinib is for illustrative purposes only as the EAG base case is to apply the KM curve directly.

Figure 46. TTD extrapolations additional comparators (pNET)



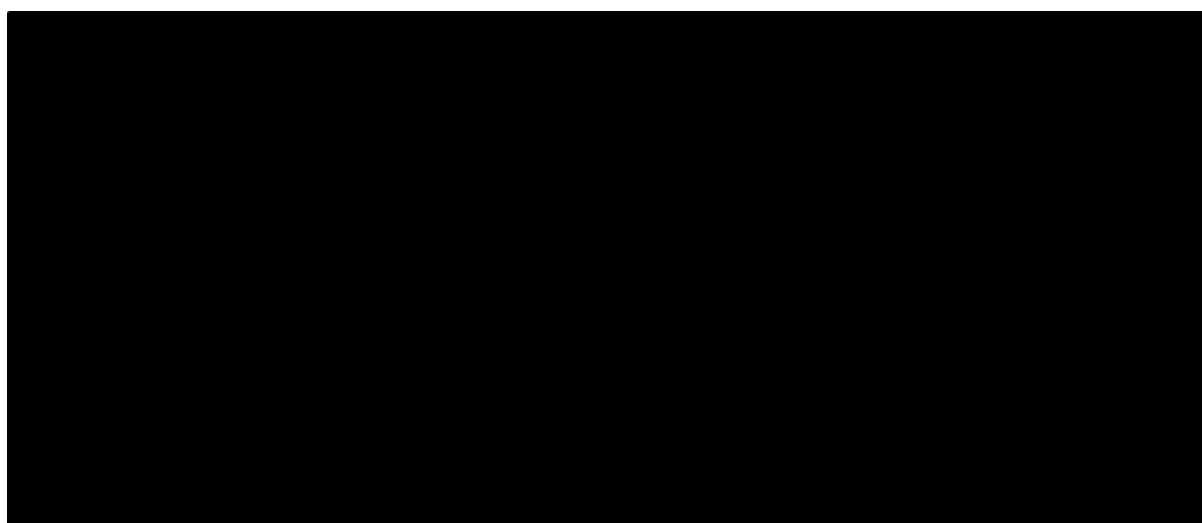
Abbreviations: BSC, best supportive care; pNETs, pancreatic neuroendocrine tumours; KM, Kaplan-Meier; QALY, quality adjusted life year; TTD, time to treatment discontinuation; WTP, willingness to pay.

Figure 47. TTD extrapolations additional comparators (epNET)



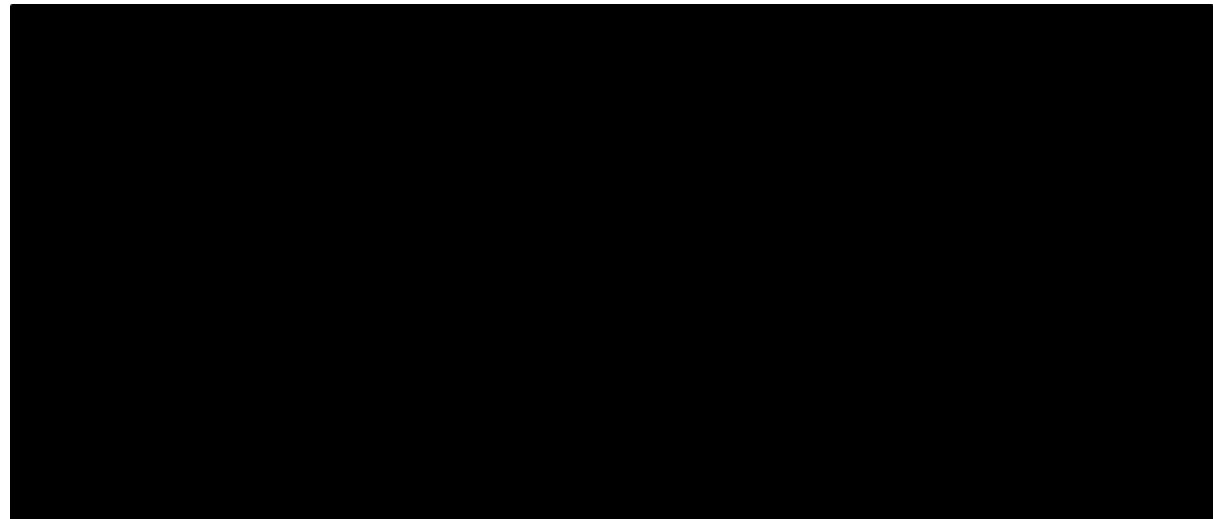
Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; KM, Kaplan-Meier; QALY, quality adjusted life year; TTD, time to treatment discontinuation; WTP, willingness to pay.

Figure 48. TTD extrapolations additional comparators (lung NETs)



Abbreviations: BSC, best supportive care; NETs, neuroendocrine tumours; KM, Kaplan-Meier; QALY, quality adjusted life year; TTD, time to treatment discontinuation; WTP, willingness to pay.

Figure 49. TTD extrapolations additional comparators (epNET without lung)



Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; KM, Kaplan-Meier; QALY, quality adjusted life year; TTD, time to treatment discontinuation; WTP, willingness to pay.

The treatment costs for sunitinib and everolimus were taken from the company's model, where the treatments were costed as subsequent treatments (Section 4.2.6.3).

Adverse events were incorporated in the model based on tables provided by the company at clarification (see Section 4.2.4.1).

Subsequent treatments for cabozantinib, everolimus and sunitinib were excluded in the EAG base case less heavily pretreated population analysis.

4.2.4 Adverse events

All treatment-related AEs that occurred in CABINET in either the cabozantinib or placebo arm, in more than 5% of patients and were Grade 3 or above, were incorporated into the model. The observed probability of AEs over the trial follow-up period (approximately 26 months) are shown in Table 46. These were then converted to rates (r), in order to estimate per 28-day cycle probabilities (p) for the model using the standard formula $p = 1 - \exp(-rt)$ with t being the follow-up duration. The AEs were applied on a per-cycle bases to patients currently on treatment with disutilities and costs applied based on this.

Table 46. Adverse event rates and follow up (copy of table 41 in company submission)

Adverse Event	pNETs		epNET	
	Cabozantinib (n=63)	BSC (n=83)	Cabozantinib (n=63)	BSC (n=83)
Mean follow-up (months)	25.7	27.6	24.4	24.21
Fatigue	11.1%	3.2%	12.9%	7.5%
Diarrhoea	6.4%	0.0%	10.6%	4.5%
Hypertension	19.1%	9.7%	20.5%	3.0%
Stomatitis	6.4%	0.0%	0.0%	0.0%
PPE syndrome	9.5%	0.0%	0.0%	0.0%
Nausea	8.0%	3.2%	0.0%	0.0%
Vomiting	6.4%	0.0%	0.0%	0.0%
Small intestinal obstruction	0.0%	6.5%	0.0%	0.0%
Embolism	6.4%	0.0%	0.0%	0.0%

Abbreviations: epNET: extra-pancreatic neuroendocrine tumour; pNET: pancreatic neuroendocrine tumour; TRAE: treatment-related adverse event.

4.2.4.1 EAG critique

The company's implementation of the probability of adverse events has failed to consider the impact of treatment discontinuation and/or mortality occurring in every cycle of the model. The probability was applied to the number of patients on treatment, every 28-day cycle in the model; however, the same probability was derived from the frequency of AEs observed in the whole trial population over approximately 26 months. This resulted in fewer AEs being estimated in the model lifetime than those observed in the trial follow-up period. For an example of this, see Table 47 which shows that over the lifetime model time horizon there are fewer than half the AEs occurring in the model compared to during the follow-up period of the trial.

Table 47. Example of cabozantinib epNET population modelled AEs compared to trial observed AEs

	Fatigue	Diarrhoea	Hypertension
Model time horizon % AE	4.60%	3.74%	7.62%
Follow-up period % AE	12.88%	10.61%	20.45%

Abbreviations: AE, adverse event;

Therefore, the EAG has made a simplifying assumption of applying all AE-related costs and QALYs in the first cycle of the model.

AEs for everolimus and sunitinib were assumed equivalent to the rates for cabozantinib in the CABINET trial, shown in Table 46.

4.2.5 Health-related quality of life

The economic model captured health-related quality of life by assigning a utility value to the PFS and PD health states, as well as applying a disutility for any adverse events on a per-cycle basis. The overall utility for patients was age-adjusted as outlined in the NICE DSU report on estimating EQ-5D by age and sex in the UK.⁴⁸ Further details are given in the following subsections.

4.2.5.1 Health state utility values

In the company's base case, the health state utility value (HSUV) for the PF health state was derived from the European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire (EORTC QLQ-C30) data collected in the HRQoL sub-study of the CABINET trial. Individual patient data (IPD) were mapped to EQ-5D using the Longworth *et al.* 2014 mapping algorithm.⁴⁹ The mapped IPD were then fitted to a regression analysis to derive a utility value for use in the economic model. Regression analyses were fitted separately for the pNETs and epNETs populations.

The company fitted two linear mixed models for repeated measures (MMRMs) to the IPD; the first of these models (hereafter referred to as the 'simplified' model) included only fixed effect terms for health state and baseline utility, and a random effect term for patient ID. The second model (hereafter, the 'full' model) additionally included the following fixed effect terms:

- Primary tumour site (epNETs only);
- Tumour grade;
- Hormone syndrome/functional status;
- Prior therapy;
- ECOG performance status;
- Age.

The company selected these fixed effect terms for inclusion as these were considered to be relevant prognostic factors based on an informal review of literature and medical input received by the company.

Both models showed similar goodness of fit; the full model including additional prognostic factors had slightly higher R^2 values for both pNETs and epNETs but also had a considerably higher AIC value. As a result, the company selected the simplified model to inform the model base case. The results of the analysis using the full model were not given in the CS, and were not explored in a scenario analysis in the economic model by the company. Full details of the MMRMs, as well as goodness of fit statistics and residual plots, are given in the company's response to clarification questions (B22).

The company considered that the HRQoL sub-study data from the CABINET trial were not appropriate for informing the HSUV for the PD health state, due to the limited availability of data for post-progression patients. Therefore, the company used an estimate sourced from existing literature to inform this model input. In the company's base case, the PD HSUV was informed by Swinburn *et al.* 2012, a vignette study of utility values in NETs; the PD HSUV was calculated by multiplying the PF HSUV by the proportional decrease in utility value observed in Swinburn *et al.* 2012 following disease progression.⁵⁰ The EAG notes that Swinburn *et al.* 2012 was also used to inform scenario analyses in TA449 and TA539 for pancreatic NETs.^{1, 36, 37}

As a scenario analysis, the company used the proportional decrease in utility following progression informed by the proportional difference between a PF utility value derived from a study of the Guy's and St Thomas' (UK) hospital registry, and a PD utility value derived from the ERASMUS trial, both for patients treated with 177Lu dotatate.^{36, 37} The EAG notes that this approach was also used in a scenario analysis in TA539.

The company also presented scenarios in which the absolute values of PD HSUVs from Swinburn *et al.* 2012, and from the ERASMUS trial, were used directly, rather than applying a proportional decrease to the PF HSUV.

In the base case and all scenario analyses, the same HSUVs were assumed for pNETs and epNETs. The company has also assumed the same HSUVs for cabozantinib and BSC. A summary of input values is given in Table 48.

Table 48. Health state utility inputs used in the company's model

Input	pNETs	epNETs	Source
Base case: CABINET (PF) + Swinburn <i>et al.</i> 2012 decrement (PD)			
PF	■	■	CABINET: simplified regression model (Ipsen data on file) ⁵¹
PD	■	■	Swinburn <i>et al.</i> (2012) ⁵⁰
Scenario: CABINET (PF) + Swinburn <i>et al.</i> 2012 absolute value (PD)			
PF	■	■	CABINET: simplified regression model (Ipsen data on file) ⁵¹
PD	0.612	0.612	Swinburn <i>et al.</i> (2012) ⁵⁰
Scenario: CABINET (PF) + TA539 decrement (PD)			
PF	■	■	CABINET: simplified regression model (Ipsen. Data on File) ⁵¹
PD	■	■	TA539 (Guy's and St Thomas' [UK] hospital registry, ERASMUS) ³⁷
Scenario: CABINET (PF) + TA539 absolute value (PD)			
PF	■	■	CABINET: simplified regression model (Ipsen. Data on File) ⁵¹
PD	0.790	0.740	TA539 (ERASMUS) ³⁷
Abbreviations: epNETs, extra-pancreatic neuroendocrine tumours; PD, progressed disease; PF, progression-free; pNETs, pancreatic neuroendocrine tumours.			

4.2.5.1.1 EAG critique

The EAG does not consider that the company's approach to sourcing HSUVs is currently fit for purpose. This is **key issue 7**.

While in general it is preferable to source HSUVs from the key trial informing clinical effectiveness, the EAG considers that the PF utility estimated with the company's regression analysis from the HRQoL sub-study of the CABINET is currently not appropriate for decision-making, for the following reasons:

- Limited justification was given for the use of a linear MMRM structure, which may not be appropriate for modelling HSUVs; in particular, HSUVs are generally constrained to lie between zero and one, which is not reflected in a linear MMRM.
- The company has not provided the utility values resulting from using the full model in the CS, or in a scenario analysis;

- The company has not provided fitted coefficients for either the simplified or the full model, or p-value estimates for the coefficients (the EAG acknowledges that deriving p-values for mixed effects models is not straightforward, but this could be accomplished, for example, by approximating the number of degrees of freedom);
- The EAG has not seen any evidence that the choice of terms to be included in the statistical models was based on a systematic approach (for example, a stepwise variable selection procedure);
- Neither the simplified or the full models included terms to adjust for key factors which would be expected to affect patient quality of life, including whether the patient was receiving treatment with cabozantinib, and whether the patient was experiencing AEs;

These concerns, allied with the EAG's concerns around the data collection process in the HRQoL sub-study of CABINET render the company's base case utilities unfit for decision making. The EAG's concerns with the HRQoL sub-study are as follows:

- Enrolment of trial participants in the HRQoL sub-study was optional, which resulted in some patient characteristics not being balanced across study arms, notably, Eastern Cooperative Oncology Group (ECOG) performance status and number of prior systemic anticancer regimens at baseline; further details are given in the company's response to clarification question A10.
- Limited data are available on missing data in the sub-study, and a large proportion of patients included in the sub-study did not report QLQ-C30 scores at later timepoints (particularly in placebo arms from week 24 onwards). Given that no data are available on reasons for dropout from the HRQoL sub-study, the EAG considers that the QLQ-C30 data are at risk of bias.

In order to mitigate the EAG's concerns with the use of data from the CABINET HRQoL sub-study to parametrise utility values in the model, the company should provide the following:

- Details for the rationale for drop-out and missing data from the HRQoL sub-study;
- Updated regression analyses (simplified and full models) including terms for treatment and/or AEs;

- Fitted coefficients, estimated p-values, goodness-of-fit statistics, and diagnostic plots for the updated regression analyses;
- Full justification for selection of covariates in the full regression model;
- Justification for use of a linear MMRM rather than a generalised linear model.

The EAG acknowledges that there are limited available alternative data sources to parametrise the PF utility value in patients with NETs; in particular, the company's SLR of HRQoL studies did not identify any data sources which would be appropriate for use in the model (few UK-specific studies were identified, and all of these were relevant only to small subpopulations of the overall NETs population). Another alternative approach would be to explore using one of the approaches proposed in TA449 and TA539, which were not captured in the company's HRQoL SLR; the PF input values and sources used in these appraisals are summarised in Table 49.

Table 49. Summary of approach to parametrising PF utility in TA449 and TA539

Population and treatment	Base case		Scenario	
	PF utility value	Source	PF utility value	Source
pNETs, everolimus	Redacted	Assumed equal to sunitinib	0.749	Swinburn <i>et al.</i> 2012 (adjusted for treatment effect) ⁵⁰
pNETs, sunitinib	Redacted	Analysis of IPD from A6181111 ^{37, 47}	0.749	Assumed equal to everolimus
pNETs, BSC	Redacted	Analysis of IPD from A6181111 ^{37, 47}	0.771	Swinburn <i>et al.</i> 2012 ⁵⁰
epNETs, everolimus	0.767	Treatment arm analysis of RADIANT-4 ^{37, 46}	0.779	Pooled analysis of IPD from RADIANT-4 ^{37, 46}
epNETs, 177Lu dotatate	0.770	ERASMUS study ^{37, 52}	0.790	Guy's and St Thomas' (UK) hospital registry ³⁷
epNETs, BSC	0.807	Treatment arm analysis of RADIANT-4 ^{37, 46}	0.779	Pooled analysis of IPD from RADIANT-4 ^{37, 46}

Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; IPD, individual patient data; PF, progression-free; pNETs, pancreatic neuroendocrine tumours.

The EAG notes that there are limitations to using all of the PF utility values considered in TA449 and TA539 in the current appraisal:

- The utility values sourced from A6181111 are not publicly available, and insufficient details of the analyses used to derive these values are given in the existing appraisals to assess whether they are relevant to the current appraisal;
- The utility values sourced from the RADIANT-4 trial may not be directly applicable to the current appraisal, due to the fact that the subsequent treatments available differ from current clinical practice (for example, availability of PRRT was limited), which may affect the utility values for the PD health state;⁴⁶
- The utility values sourced from the ERASMUS study and the Guy's and St Thomas' (UK) hospital registry are specific to patients currently receiving treatment with 177Lu dotatate, and have not been adjusted to take into account the effect of treatment on HRQoL (for example, AEs);³⁷
- Utility values sourced from Swinburn *et al.* 2012 were informed by a vignette study, which is likely to be less robust than data derived from an RCT. Furthermore, while some of the EAG's experts did not have an issue with using utility data from 2012, some of the company's and some of the EAG's other clinical experts stated that it may not be appropriate to use utility data from 2012, as these may not be reflective of current UK clinical practice.⁵⁰

Even though the EAG acknowledges there are limitations associated with using any of the data sources discussed above, as an exploratory interim analysis, the EAG used the PF utility value from the BSC arm of RADIANT-4 (0.807) to inform PF utility for both cabozantinib and BSC for the epNET population. The BSC arm was selected rather than the everolimus arm as the HSUVs from TA449 and TA539 are inclusive of the effect of AEs, and patients experienced fewer AEs in the BSC arm (in the company's economic model in the current appraisal, AEs are accounted for separately, so it is more appropriate to use a utility value with reduced AEs). The EAG's preference for the epNETs PD utility value is to use the pooled analysis of IPD from RADIANT-4 data for the PD HSUV, since at this point patients would not be receiving first-line treatment, and therefore no further treatment-related AEs would be expected. The same approach was used in the base case in TA449 and TA539.^{1, 36, 37}

For the pNET population, the EAG considers that utility values sourced from absolute values reported in Swinburn *et al.* 2012 would be the most appropriate for use in the model at the present time.

The EAG notes that ideally separate utility values would be used for lung NETs, and epNETs excluding lung NETs; however, the EAG were unable to identify relevant data to parametrise this approach.

The utility values used in the EAG's base case, as well as the utilities used in the scenarios undertaken by the EAG (including the EAG's exploratory analysis in the less heavily pretreated population), are given in Table 50. These values were used both in the analysis for the CABINET population and the exploratory analysis for the less heavily pretreated population. The EAG reinforces its view that the company should provide further details of its regression analysis of the CABINET data, together with additional analysis of the raw data, in order for the trial utility values to be used in any future analysis.

Table 50. Summary of EAG's preferred utility value inputs

Input	pNETs	epNETs	Source
Base case: Swinburn et al. 2012 (pNETs), RADIANT-4 treatment arm analysis (epNETs)			
PF	0.771	0.807	pNETs: Swinburn et al. 2012 ⁵⁰ epNETs: RADIANT-4 ^{37, 46}
PD	0.612	0.725	pNETs: Swinburn et al. 2012 ⁵⁰ epNETs: RADIANT-4 ^{37, 46}
Scenario (company base case): CABINET (PF) + Swinburn <i>et al.</i> 2012 decrement (PD)			
PF	■	■	CABINET: simplified regression model (Ipsen data on file) ⁵¹
PD	■	■	Swinburn et al. 2012 ⁵⁰
Scenario: CABINET (PF) + Swinburn <i>et al.</i> 2012 decrement (pNETs PD) / RADIANT-4 decrement (epNETs PD)			
PF	■	■	CABINET: simplified regression model (Ipsen. Data on File) ⁵¹
PD	■	■	pNETs: Swinburn et al. 2012 ⁵⁰ epNETs: RADIANT-4 ^{37, 46}
Abbreviations: epNETs, extra-pancreatic neuroendocrine tumours; PD, progressed disease; PF, progression-free; pNETs, pancreatic neuroendocrine tumours.			

4.2.5.2 Adverse events

The HRQoL impact of AEs was modelled by applying a per-cycle QALY decrement to a proportion of patients based on the expected per-cycle incidence of each AE (further details are given in Section 4.2.4.1). The QALY decrement for each AE was derived by multiplying the expected disutility by the expected duration of the AE; both the disutility and duration were sourced from existing literature.

The majority of these inputs were sourced either from the previously-described vignette study of HRQoL for patients with NETs (Swinburn *et al.* 2012), or from previous NICE TAs.⁵⁰

A summary of the input values used in the company's base case is given in Table 51.

Table 51. AE disutility and duration inputs used in the company's base case

AE	Disutility		Duration	
	Input value	Source	Input value (days)	Source
Fatigue	-0.073	Nafees <i>et al.</i> 2008 ⁵³	23.80	TA911 (Table 51, CS) ⁵⁴
Diarrhoea	-0.171	Swinburn <i>et al.</i> 2012 ⁵⁰	5.50	TA911 (Table 51, CS) ⁵⁴
Hypertension	-0.085	TA911 (Table 51, CS) ⁵⁴	15.00	TA911 (Table 51, CS) ⁵⁴
Stomatitis	-0.214	Swinburn <i>et al.</i> 2012 ⁵⁰	18.12	Assumed equal to average of other AEs
PPE syndrome	-0.188	Swinburn <i>et al.</i> 2012 ⁵⁰	18.12	Assumed equal to average of other AEs
Nausea	-0.061	Swinburn <i>et al.</i> 2012 ⁵⁰	10.50	TA789 (Table 49, CS) ⁵⁵
Vomiting	-0.061	Swinburn <i>et al.</i> 2012 ⁵⁰	2.00	TA789 (Table 49, CS) ⁵⁵
Small intestinal obstruction	-0.255	TA1011 (Table 78, CS); assumed same as 'other genitourinary complications' ⁵⁶	18.12	Assumed equal to average of other AEs
Embolism	-0.370	TA476 (Table 53, CS); assumed same as pulmonary embolism ⁵⁷	51.90	TA476 (Table 55, CS); assumed same as pulmonary embolism ⁵⁷

Abbreviations: AE, adverse event; CS, company submission; PPE, palmar-plantar erythrodysesthesia.

4.2.5.2.1 EAG critique

As described in Section 4.2.4.1 the EAG considers that it is more appropriate to apply a one-off QALY decrement capturing the impact of AEs at baseline, rather than applying a per-cycle decrement.

The EAG also considers that some of the input values for disutilities used in the company's base case were not appropriate, as follows:

- Hypertension: the disutility used in the company's base case was derived from an analysis in TA428, in which it was assumed that all AEs had the same disutility. Therefore, the value used is unlikely to be reflective of hypertension specifically.⁵⁸

- Small intestinal obstruction: the disutility used in the company's base case was a disutility for genitourinary complications, and is therefore unlikely to be reflective of small intestinal obstruction.⁵⁶
- Embolism: the EAG were unable to trace the original source for this disutility.

A summary of the EAG's preferred disutilities is given in Table 52.

Table 52. EAG's preferred AE disutility input values

AE	Disutility	Source
Hypertension	-0.153	Swinburn <i>et al.</i> 2010 ⁵⁹
Small intestinal obstruction	-0.360	Kimpe <i>et al.</i> 2024 ⁶⁰
Embolism	-0.330	Locadia <i>et al.</i> 2004 ⁶¹
Abbreviations: AE, adverse event.		

The EAG also has some concerns with the values used for the duration of AEs. In particular, the duration for hypertension was sourced from TA911, and was based on an assumption, with no justification given.⁵⁴ The company also assumed that durations for stomatitis, palmar-plantar erythrodysesthesia (PPE) syndrome, and small intestinal obstruction were equal to the mean of other durations, since no appropriate values could be identified in existing literature, although there is no clinical rationale for this approach. However, the EAG were unable to source more appropriate alternatives, so these values are retained in the EAG base case. However, to investigate the impact of these inputs on overall results, the EAG investigated a scenario in which the durations for hypertension, stomatitis, PPE syndrome and small intestinal obstruction were set equal to the average dose hold duration in the CABINET trial, pooled across trial arms (■ days for pNETs and ■ days for epNETs, based on tables 14.3.1.1.6.a.1 and 14.3.1.1.6.b.1 in the CSR).⁵¹ This was considered to be potentially more reflective of the experience of patients with NETs, since dose holds are often used to manage AEs before recommencing treatment.

The EAG acknowledges that the impact of the changes described above on model results are minimal, and therefore the parametrisation of HRQoL impact of AEs is not considered a key issue.

In order to implement the exploratory analysis in the less heavily pretreated population, the EAG applied disutilities for patients receiving sunitinib and everolimus in line with the frequencies presented in Section 4.2.4.1.

4.2.6 Resource use and costs

The company's economic model includes the following costs:

- Treatment acquisition for the intervention, comparators, concomitant SSAs, and subsequent treatments;
- Management of AEs;
- Disease management;
- End-of-life care.

Further details are given in the following sections. For all costs, the most recent available costs were used; in particular, costs sourced from the NHS reference costs were taken from the 2023/24 dataset.⁶² In the company's base case, costs sourced from the Personal Social Services Research Unit (PSSRU) unit costs were taken from the 2023 manual.⁶³

4.2.6.1 Treatment costs: intervention and comparators

Cabozantinib has a list price of £5,143.00 per pack of 30 tablets; packs are available with 20 mg, 40 mg, or 60 mg tablets, but flat pricing is used (i.e. the cost is the same regardless of the dosage per tablet). A simple PAS discount is available, resulting in a pack price (and cost per 30-day cycle) of [REDACTED]. All results presented in this report use the PAS price rather than the list price for cabozantinib.

Costs for cabozantinib use were applied in the economic model to patients in the cabozantinib arm on a per-cycle basis, up to the modelled TTD for cabozantinib (further details are given in Section 4.2.3.2.2). In line with the SmPC, patients were assumed to receive cabozantinib once daily, until disease progression or unacceptable toxicity.⁶⁴ The company noted that, although 20 mg/day, 40 mg/day, and 60 mg/day dosing regimens are permitted, with patients receiving lower doses to manage toxicity, the flat pricing of cabozantinib results in the same total costs regardless of dosing regimen; therefore, the treatment acquisition cost was assumed the same for all patients. As a result, a relative dose intensity of 100% was assumed. However, the company incorporated reduction in costs due to dose holds into the economic model by adjusting the cost per cycle of cabozantinib based on the proportion of the mean total exposure time for which a patient was on a dose hold. The cost per cycle was adjusted as follows:

$$\text{Adjusted cost per cycle} = \text{unadjusted cost per cycle} \times \left(1 - \frac{\text{mean total hold length per patient}}{\text{mean duration of exposure}}\right)$$

The mean total hold length per patient, and mean duration of exposure, were derived from IPD from the CABINET trial; adjustments were calculated separately for the pNETs and epNETs populations. The inputs used to calculate the dose hold adjustment are given in Table 53.

Table 53. Dose hold input values

Input	pNETs	epNETs
Mean total hold length per patient	■	■
Mean duration of exposure	■	■
Proportional reduction of costs per cycle	■	■
Abbreviations: epNETs, extra-pancreatic neuroendocrine tumours; pNETs, pancreatic endocrine tumours.		

As an alternative, the company also presented a scenario analysis in which dose holds were not accounted for.

Since cabozantinib is administered orally, a dispensing cost of £16.20 was applied once per cycle, corresponding to 12 minutes of hospital pharmacist time, based on the cost per hour for band 8b hospital-based staff in the PSSRU 2023 manual.⁶³ However, the company also included a scenario in which no administration costs were applied for treatments administered orally.

The only comparator included in the company's model was BSC. Patients in the BSC arm accrued no treatment acquisition or administration costs (with the exception of concomitant SSA costs and subsequent treatment costs).

4.2.6.1.1 EAG critique

The EAG considers that the company's approach to modelling treatment acquisition and administration costs was broadly appropriate.

However, the EAG notes that adjustments to treatment costs to account for dose holds are not commonly used. Furthermore, while the EAG's clinical experts confirmed that dose holds are commonly used to manage toxicity in this patient population, and that the duration and frequency of dose hold use in the CABINET trial were reasonably reflective of UK clinical practice, the EAG considers that the company's approach to implementing dose holds in the economic model may lead to unwarranted uncertainty. The approach of reducing costs by a fixed proportion per cycle is simplistic, and not reflective of how dose holds work in clinical practice; in particular, assuming a

consistent percentage of time per cycle in which treatment is not received is clinically implausible, and is likely to result in inaccuracies in discounting. 86% of pNET cabozantinib dose holds and 80% of epNET cabozantinib dose holds were the result of AEs, with these lasting between 2 and 52 days (according to company base case inputs). Since AEs occur mostly at the start of treatment{Lipitz-Snyderman, 2017 #47366}, it is not valid to apply a consistent per cycle value for dose hold. . Furthermore, although dose holds are used in clinical practice, it is unclear to what extent dose holds would be expected to result in direct cost reductions, especially since the economic model does not account for the effect of wastage.

Finally, dose hold data are not available for the additional comparators added to the model by the EAG for exploratory analyses. Therefore, the EAG’s preferred approach is to exclude adjustment of treatment acquisition costs for dose holds; while this may overestimate costs for treatment with cabozantinib, the EAG considers that this approach may be more in line with clinical practice if wastage is taken into account, and is at worst a conservative approach to estimating cabozantinib treatment costs.

The EAG also preferred to use an administration cost of £17.20 per month for cabozantinib, informed by the PSSRU 2024 manual.⁶⁵

For exploratory analyses in the less heavily pretreated population including sunitinib and everolimus as comparators, the EAG applied a per-cycle treatment cost for sunitinib and everolimus based on dosages from the relevant SmPCs, and acquisition costs based on the electronic market information tool (eMIT).⁶⁶⁻⁶⁸ A summary of the relevant costs is given in Table 54. Since both sunitinib and everolimus are administered orally, the same treatment administration cost was applied as for cabozantinib.

Table 54. Treatment acquisition costs for additional comparators

Comparator	Administration	Dose per administration	Total cost per 28-day cycle
Sunitinib	Oral administration once daily	37.5 mg	£89.07
Everolimus	Oral administration once daily	10 mg	£264.80

The total duration of treatment was informed by the median duration of treatment, which was aligned with the values used in TA449; details are given in Table 55, with the median duration of treatment with cabozantinib given for context.^{1, 37} The median duration of treatment was used to parametrise an exponential curve, as described in Section 4.2.3.3.

Duration of treatment was considered separately for pNETs and epNETs, but was not considered separately for lung NETs and epNETs excluding lung NETs, due to lack of available data.

The EAG also assumed that the proportion of patients receiving concomitant treatment with SSAs alongside everolimus and sunitinib was the same as for patients treated with cabozantinib.

Table 55. Duration of treatment for additional comparators

Comparator	Median duration of treatment	Source
Cabozantinib (pNETs)	8.28 months	CABINET CSR ⁶⁹
Cabozantinib (epNETs)	5.37 months	CABINET CSR ⁶⁹
Everolimus (pNETs)	8.79 months	RADIANT-3 ^{37, 45}
Everolimus (epNETs)	9.29 months	RADIANT-4 ^{37, 46}
Sunitinib	4.64 months	A6181111 ^{37, 47}

Abbreviations: epNETs, extra-pancreatic neuroendocrine tumours; pNETs, pancreatic neuroendocrine tumours.

4.2.6.2 Treatment costs: concomitant SSAs

Costs for concomitant treatment with SSAs were included in the economic model. In the company's base case, the proportion of patients receiving concomitant treatment with SSAs was assumed equal to the proportion receiving SSAs at baseline in the CABINET trial, stratified by pNETs/epNETs and also by trial arm; details are given in Table 56.

Table 56. Proportion of patients using concomitant SSA therapy

Treatment arm	pNETs	epNETs
Cabozantinib	54.7%	68.7%
BSC	54.8%	69.6%

Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; pNETs, pancreatic neuroendocrine tumours.

In the company's base case, all patients treated with concomitant SSAs were assumed to receive SSAs up to treatment discontinuation for cabozantinib in the cabozantinib arm, or treatment discontinuation (estimated with TTD data) for placebo in the BSC arm (further details of how TTD was estimated are given in Section 4.2.3.2.2). The cost of SSA use at later stages was captured by the inclusion of SSAs as a subsequent treatment (see Section 4.2.6.3 for further details).

However, at the EAG's request, the company also added the following scenarios during clarification:

- Scenario in which concomitant SSA costs were applied while patients were in a progression-free state;
- Scenario in which concomitant SSA costs were applied while patients were alive.

Patients receiving concomitant treatment with SSAs were assumed to receive either lanreotide or octreotide; the company assumed ■ of patients would receive lanreotide, and the remainder of patients would receive octreotide, based on the company's data on file. Lanreotide and octreotide both have three recommended dosages (120 mg, 90 mg or 60 mg per cycle for lanreotide, and 30 mg, 20 mg or 10 mg for octreotide); the company assumed that for both lanreotide and octreotide, ■ of patients would receive the highest dosage, ■ of patients would receive the intermediate dose, and ■ of patients would receive the lowest dose, with no rationale given for these assumptions. Prior to clarification, these values were 'hard-coded' in the economic model, and could not be adjusted by the user, or varied in probabilistic analyses or deterministic sensitivity analyses (DSAs); at the EAG's request, the company updated the economic model to allow the value of these inputs to be adjusted by the user.

Patients were assumed to receive one long-acting administration of SSAs per four-week treatment cycle. Acquisition costs for lanreotide and octreotide were obtained from the BNF website. A full breakdown of the acquisition costs for concomitant SSA use is given in Table 57.

Confidential medicines procurement and supply chain (MPSC) prices are available for lanreotide and octreotide. As such, the EAG has produced a confidential appendix to the EAG report. Analyses included in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses. Please refer to Appendix 9.1 for details on the source of the confidential price for each treatment.

Table 57. Acquisition costs for SSAs

SSA	Vial size	Cost per vial*	Proportion of patients	Average cost per cycle*
Lanreotide	120 mg	£937.00	■	■
	90 mg	£736.00	■	
	60 mg	£551.00	■	
Octreotide	30 mg	£898.57	■	■
	20 mg	£719.40	■	
	10 mg	£494.74	■	

Abbreviations: SSA, somatostatin analogue

The economic model also included administration costs for lanreotide and octreotide. Patients receiving lanreotide were assumed to receive one deep subcutaneous injection per treatment cycle, and patients receiving octreotide were assumed to receive one intramuscular injection per treatment cycle. The company assumed that these treatments would be administered at home; therefore, the cost of administration was assumed to consist of an hour of nurse time, and cost for reimbursement of 5 miles of travel. This assumption was informed by Thorn *et al.* 2020, a cost-effectiveness analysis of a patient-centred approach to managing multimorbidity in primary care; this was identified as an appropriate source to inform homecare costs on the basis of a targeted literature review conducted by the company.⁷⁰

Overall, this resulted in an administration cost of £55.95 per cycle for both lanreotide and octreotide. A breakdown of the administration costs for SSAs is given in Table 58.

Table 58. Administration costs for SSAs

Cost input	Value	Source
1 hour of nurse time	£53.00	PSSRU 2023; cost for one hour of band 6 community-based scientific and professional staff time ⁶³
Reimbursement for 5 miles of travel	£2.95	Reimbursement of 59p per mile, NHS Employers website ⁷¹
Abbreviations: NHS, National Health Service; PSSRU, Personal Social Services Research Unit; SSA, somatostatin analogue.		

4.2.6.2.1 EAG critique

The EAG has several concerns about the company's approach to costing concomitant treatment with SSAs.

The EAG considers that the company's assumption that patients would discontinue treatment of concomitant SSAs upon discontinuation of cabozantinib is inappropriate. This is because patients receiving concomitant SSAs are those who need SSAs for continued symptom management. Furthermore, the use of TTD data for placebo is also inappropriate to cost the use of concomitant SSAs in the BSC arm. Based on the company's own assertion that '*concomitant SSAs would be continued indefinitely throughout the PF and PD health states*' (page 120, Section 3.5.1 of the CS), which is supported by the EAG's clinical experts, the EAG's preferred approach is to apply the costs for concomitant SSA use while patients are alive. **This is key issue 8.**

The EAG also considers that the proportions of patients assumed to receive concomitant SSAs in the model may not be appropriate, since the proportion of patients receiving SSAs at baseline in the CABINET trial may not be a reasonable proxy for the proportion of patients receiving concomitant treatment with SSAs while receiving treatment with cabozantinib. The EAG’s clinical experts stated that, in UK clinical practice, the majority of patients receiving systemic treatment with SSAs would discontinue treatment upon starting another systemic treatment, with only patients using SSAs to manage symptoms of functional NETs continuing to receive treatment concomitantly.

However, no data informing the proportion of patients receiving concomitant treatment with SSAs during the CABINET trial was available from the CSR, so the EAG considers that this approach may be a necessary simplification. The EAG did identify a table entitled ‘Concomitant Medications’ for both the epNETs and pNETs populations in the CSR (Tables 14.3.1.2.1.a and 14.3.1.2.1.b), but at clarification the company stated that these tables in fact represented ‘subsequent treatment only’.⁶⁹ The EAG is still unclear of the purposes of these tables in the CSR, and notes that the values reported in this table were much lower than the proportions of patients receiving SSAs at baseline (Table 59).

Table 59. Potential alternative concurrent SSA proportions reported in CABINET CSR

Concurrent SSA	pNETs		epNETs	
	Cabozantinib	Placebo	Cabozantinib	Placebo
Lanreotide	■	■	■	■
Octreotide	■	■	■	■

Abbreviations: epNETs, extra-pancreatic neuroendocrine tumours; pNETs, pancreatic neuroendocrine tumours; SSA, somatostatin analogue.

To explore the impact of this assumption on results, the EAG also explored a scenario in which the proportion of patients receiving concomitant treatment with SSAs was aligned with the proportion of patients with functional NETs in the CABINET trial, pooled between treatment arms (■ in the epNETs population and ■ in the pNETs population; lung NETs and w/o lung epNETs were not considered separately due to lack of data).⁵¹

The EAG notes that the proportion of patients receiving lanreotide or octreotide, as well as the proportion of patients receiving each dosage of these treatments, are based on assumptions, with no rationale given for the values used. The company have since clarified that these were based on internal market share data from the company (who are also the primary manufacturer of

lanreotide). As the EAG has been unable to identify appropriate alternatives, the impact of these assumptions was explored by varying the values in scenario analyses (see Section 6.3).

Finally, the EAG is also concerned with the company's approach for estimating administration costs for SSAs. While the company reports that the cost of administration was based on Thorn *et al.* 2020, the latter assumed 27 minutes of total nurse time per appointment (15 minute visit and 12 minute travelling) rather than an hour of total nurse time.⁷⁰ Therefore, the EAG adjusted the administration cost to align with the approach described in Thorn *et al.* 2020, and used PSSRU 2024 costs, which gave a cost per administration of £28.60 compared to the £55.95 used in the company's base case. Results of the EAG's correction are reported in Section 6.^{65, 70}

The EAG notes that the approach used in TA449 and TA539 sourced a different cost for the administration of both lanreotide and octreotide, assuming that patients would receive treatment in hospital. The former was taken from the NHS reference costs (SB15Z), while the latter was derived by applying a cost of 15 minutes for hospital nurse time based on the PSSRU manual.³⁷ The company provided a scenario investigating the impact of using updated versions of these costs instead of the homecare-based costing approach.

4.2.6.3 Treatment costs: subsequent treatments

The costs for subsequent treatments in the economic model were estimated by applying a one-off treatment cost to all patients upon entering the PD health state; this one-off cost was an estimate of the average subsequent treatment cost per patient, incorporating both treatment acquisition and administration, based on the expected distribution and duration of subsequent treatments.

The costs arising from management of any adverse events due to subsequent treatments were not considered. Subsequent treatment with systemic therapies was assumed to not include active treatment with SSAs, although continued treatment with concomitant SSAs after discontinuation of the initial treatment was considered. In the company base case, the proportion of patients receiving subsequent treatment with SSAs for symptom management was aligned with the proportion of patients receiving SSAs at baseline in the CABINET trial, (see Section 4.2.6.2); however, the company also considered a scenario in which the proportion of patients receiving subsequent treatment with SSAs was aligned with the proportion of patients receiving subsequent treatment with SSAs in the CABINET trial, pooled between the cabozantinib and placebo arms.

The choice of subsequent systemic treatments included in the economic model was based on treatments received by at least 5% of patients in the CABINET trial, with the exception of radiation therapy, since this is not commonly used in UK clinical practice. The included treatments were as follows:

- Sunitinib (pNETs only);
- Everolimus;
- Peptide receptor radionuclide therapy (PRRT);
- Capecitabine and temozolomide (CAPTEM);
- Folinic acid, fluorouracil and oxaliplatin (FOLFOX).

The overall proportion of patients receiving subsequent systemic treatments was informed by the proportion of patients receiving any subsequent treatment in the relevant treatment arm of the CABINET trial; these are shown in Table 60 below.

Table 60. Proportion of patients receiving any subsequent treatment

Treatment arm	pNETs	epNETs
Cabozantinib	51.02%	40.54%
BSC	35.29%	45.00%

Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; pNETs, pancreatic neuroendocrine tumours.

The proportion of patients receiving each individual systemic treatment was informed by clinical expert opinion in the company's base case, since the company considered that the distribution of subsequent treatments in the CABINET trial was not reflective of UK clinical practice. The input values used in the base case are given in Table 61.

Table 61. Proportion of patients receiving individual subsequent treatments, company base case

Subsequent treatment	pNETs		epNETs	
	Cabozantinib	BSC	Cabozantinib	BSC
Sunitinib	22.50%	22.50%	N/A	N/A
Everolimus	10.00%	10.00%	10.00%	10.00%
PRRT (177Lu dotatate)	22.50%	22.50%	30.00%	30.00%
CAPTEM	22.50%	22.50%	30.00%	30.00%
FOLFOX	22.50%	22.50%	30.00%	30.00%

Abbreviations: CAPTEM, capecitabine and temozolomide; FOLFOX, folinic acid, fluorouracil and oxaliplatin; IV, intravenous; PRRT, peptide receptor radionuclide therapy.

The company also provided a scenario analysis in which the proportion of patients receiving each systemic treatment was informed by the CABINET trial data.

In both the base case and scenario analysis, the company rescaled the proportions receiving each treatment to sum to 100% of the patients receiving any systemic treatment, implicitly assuming that patients could only receive one subsequent systemic treatment.

Per-cycle acquisition costs for subsequent treatments were estimated based on the recommended dosages given in the relevant SmPCs.^{66, 67, 72} The costs for sunitinib and everolimus as subsequent treatments were the same as the costs for sunitinib and everolimus as comparators (see Section 4.2.6.1.1); a summary of the acquisition costs for other subsequent systemic treatments is given in Table 62. All costs were sourced from eMIT with the exception of PRRT, which cost was sourced from TA539, as no cost was available from eMIT or BNF.^{36, 68}

A confidential PAS discount price is available for Lu dotatate; discounts are not available for the other subsequent treatments. Please refer to the confidential appendix for results of analyses including the PAS discount for Lu dotatate.

Table 62. Subsequent treatment costs

Subsequent treatment	Component	Administration	Dose per administration	Total cost per 28-day cycle
PRRT (Lu dotatate)	N/A	IV administration once per eight weeks; four administrations total	7.40 GBq	£8,937.50*
CAPTEM	Capecitabine	Oral administration twice daily on days 1-14 in 28-day cycle	750 mg/m ²	£53.57
	Temozolomide	Oral administration twice daily on days 10-14 in 28-day cycle	100 mg/m ²	
FOLFOX	Folinic acid	IV administration on day 1 in 28-day cycle	100 mg/m ²	£59.89
	Fluorouracil	IV administration (initial 10-minute administration followed by 46-hour infusion) on day 1 in 28-day cycle	400 mg/m ² (initial infusion) 2,400 mg/m ² (46-hour infusion)	
	Oxaliplatin	IV administration on day 1 in 28-day cycle	85 mg/m ²	

*Costs are not inclusive of confidential discounts; discounted costs are available in the confidential appendix.

Abbreviations: CAPTEM, capecitabine and temozolomide; FOLFOX, folinic acid, fluorouracil and oxaliplatin; IV, intravenous; PRRT, peptide receptor radionuclide therapy.

A summary of the administration costs used in the company's base case for PRRT and FOLFOX is given in Table 63; the administration costs for sunitinib, everolimus and CAPTEM, which are administered orally, were assumed the same as the administration cost for cabozantinib, i.e. £16.20 per 28-day cycle (see Section 4.2.6.1).

Table 63. Administration costs for subsequent treatments

Cost input	Value	Source
IV administration (PRRT)	£1,237.70	NHS reference costs 2023/24, RN52Z (Delivery of Other Radionuclide Therapy), Total HRG ⁶²
IV administration FOLFOX	£755.35	NHS reference costs 2023/24, SB14Z (Delivery of More Complex Parenteral Chemotherapy at First Attendance), Total HRG and WF01A (Non-Admitted Face-to-Face Attendance, Follow-up, Medical Oncology [Non-Consultant Led]) ⁶²

Abbreviations: FOLFOX, folinic acid, fluorouracil and oxaliplatin; HRG, healthcare resource group; IV, intravenous; NHS, National Health Service; PRRT, peptide receptor radionuclide therapy.

Acquisition and administration costs for SSAs as subsequent treatments were the same as costs for SSAs as concomitant treatments (see Section 4.2.6.2).

The assumed duration of treatment for each subsequent treatment was derived from existing literature; the duration of treatment was assumed to be independent of treatment arm, and the same for the pNETs and epNETs populations. A summary of the durations used in the company's base case is given in Table 64.

Table 64. Subsequent treatment durations

Subsequent treatment	Treatment duration (weeks)	Source
Sunitinib	43.48	Rinzivillo <i>et al.</i> 2018 ⁷³
Everolimus	39.13	Dasari <i>et al.</i> 2019 ⁷⁴
PRRT	32.00	Lutathera SmPC; assumed all patients receive maximum duration of treatment ⁷²
CAPTEM	54.79	Arrivi <i>et al.</i> 2022 ⁷⁵
FOLFOX	54.79	Assumed same as CAPTEM
SSA (lanreotide/octreotide)	26.09	Dasari <i>et al.</i> 2019 ⁷⁴

Abbreviations: CAPTEM, capecitabine and temozolomide; FOLFOX, folinic acid, fluorouracil and oxaliplatin; PRRT, peptide receptor radionuclide therapy; SmPC, summary of product characteristics.

4.2.6.3.1 EAG critique

The EAG considers that the company's approach to modelling subsequent treatment costs is not appropriate. This is **key issue 9**.

The EAG is concerned with the robustness of the company's estimation of the proportion of patients receiving each subsequent systemic treatment based on clinical expert opinion, as the input values were not informed using an appropriate structured elicitation approach. Furthermore, the EAG's clinical experts were of the opinion that the distribution of subsequent treatments used in the company's base case is not reflective of UK clinical practice.

The EAG also considers that some of the inputs used in the company's economic model for duration of treatment for subsequent treatments were not appropriate. In particular:

- The duration of treatment with sunitinib was aligned with the mean PFS rather than the mean duration of treatment in the stated source (Rinzivillo *et al.* 2018⁷³).
- The durations of treatment with everolimus and SSAs were taken from Dasari *et al.* 2019, a study conducted in a population of patients with lung NETs only, which the EAG does not consider to be representative of the overall NETs population.⁷⁴ Furthermore, the company stated that the input values used were extracted from a figure in Dasari *et al.* 2019, but the EAG has been unable to validate the values cited.
- The duration of treatment with FOLFOX was assumed to be the same as the duration of treatment with CAPTEM; the company provided minimal justification for this assumption.

The EAG also considers that the implementation of costing subsequent treatments in the economic model was insufficiently robust. In particular, it is inappropriate to scale the individual proportions of patients receiving each subsequent systemic treatment to sum to 100%, since some patients would be expected to receive multiple lines of subsequent systemic treatment.

The EAG also notes that the company's approach to applying subsequent treatment costs upon entering the PD health state underestimates the overall subsequent treatment costs. Since time-to-progression data is not included in the economic model, for a given cycle, subsequent treatment costs are applied to either the difference in occupancy of the PD health state between the current and previous cycles (or to no patients, if the difference is negative); however, the difference in

health occupancy is less than the number of patients entering the health state, since patients may also leave the health state to enter the death state.

The EAG considers that it is appropriate to exclude SSAs from subsequent treatment altogether, since the EAG's preferred approach to modelling concomitant SSA use is to apply costs until death occurs for all patients receiving concomitant SSAs (further details are given in Section 4.2.6.2).

As a minor point, the EAG noted that the NHS reference cost used by the company as an administration cost used for PRRT included both directly accessed diagnostic services and nuclear medicine. The EAG's preference is for the specific cost for nuclear medicine to be used.

Finally, the EAG was unable to identify data on subsequent treatment usage for the additional comparators added to the model (sunitinib and everolimus); therefore, subsequent treatment costs could not be estimated for these comparators.

Therefore, the following updates to the company's modelling methodology were applied in the EAG base case:

- For cabozantinib and BSC, the proportions of patients receiving each systemic subsequent treatments were sourced from the CABINET trial CSR, without rescaling the proportions to sum to 100% of patients receiving any subsequent treatment.⁵¹
 - The proportion of patients receiving sunitinib in the epNET population was assumed to be 0%.
 - Proportions were calculated as a proportion of all patients who left the PF health state (due to death or progression), rather than a proportion of patients who discontinued cabozantinib or placebo treatment.
 - The same proportions were used for the epNETs and epNETs without lung populations, as more granular data were not available. In the lung NETs population, the same values were also used, albeit with the proportion receiving PRRT set to zero, since PRRT is not recommended for use in this population; the proportions for other treatments were rescaled so the total proportion of patients receiving any subsequent treatment was unchanged.

The proportions used are given in Table 65.

- Subsequent treatment costs were applied upon leaving the PF health state, rather than entering the PD health state.

- The administration cost for PRRT was aligned with the NHS reference cost for nuclear medicine administration only (£1,242.39).⁶²
- In line with intervention and comparator costs, administration costs for orally administered subsequent treatments were set to £17.20 based on the PSSRU 2024 manual.⁶⁵

Given the lack of availability of appropriate subsequent treatment data for the additional comparators added by the EAG subsequent treatment were excluded altogether for the exploratory analysis of the less heavily pretreated population. A similar approach was taken in TA449 and TA539.^{1, 36, 37} However, the EAG-preferred approach described above was applied in a scenario analysis, with proportions receiving each subsequent treatment assumed to align with cabozantinib. However, the proportions receiving subsequent sunitinib and everolimus in the sunitinib and everolimus arms respectively were set to zero, since it was assumed that patients would not be rechallenged with the same treatment, and the other proportions were rescaled accordingly. Subsequent treatment duration for sunitinib was informed by Mujica-Mota *et al.* 2018 (7.51 months), and subsequent treatment duration for everolimus was aligned with RADIANT-3 (8.79 months).^{37, 45}

Table 65. Proportion of patients receiving individual subsequent treatments, EAG analysis

Subsequent treatment	pNETs				epNETs, epNETs without lung			Lung NETs		
	Cabozantinib	BSC	Sunitinib	Everolimus	Cabozantinib	BSC	Everolimus	Cabozantinib	BSC	Everolimus
Sunitinib	6.3%	15.4%	0%	6.8%	0%	0%	0%	0%	0%	0%
Everolimus	6.3%	0%	6.8%	0%	5.6%	15.0%	0%	9.0%	24.4%	0%
PRRT (177Lu dotatate)	18.8%	23.1.0%	20.5%	20.5%	18.3%	25.0%	20.7%	0%	0%	0%
CAPTEM	31.3%	7.7%	34.1%	34.1%	16.9%	5.0%	19.1%	26.9%	8.1.1%	32.9%
FOLFOX	12.5%	7.7%	13.6%	13.6%	8.5%	20.0%	9.5%	13.4%	32.5%	16.4%

Abbreviations: CAPTEM, capecitabine and temozolomide; FOLFOX, folinic acid, fluorouracil and oxaliplatin; IV, intravenous; PRRT, peptide receptor radionuclide therapy.

4.2.6.4 Costs for management of AEs

Costs for management of AEs were captured in the economic model as a one-off cost applied in the cycle in which the AE was assumed to occur. The values used are summarised in Table 66.

Table 66. AE management costs

AE	Cost	Source
Fatigue	£766.57	NHS reference costs 2023/24, weighted average of SA01G–SA01K (Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia), non-elective inpatient short stay ⁶²
Diarrhoea	£566.83	NHS reference costs 2023/24, weighted average of FD10A–FD10M (Non-Malignant Gastrointestinal Tract Disorders with and without Interventions), non-elective inpatient short stay ⁶²
Hypertension	£404.67	NHS reference costs 2023/24, EB04Z (Hypertension), non-elective inpatient short stay ⁶²
Stomatitis	£519.16	NHS reference costs 2023/24, weighted average of CB02A–CB02F (Non-Malignant, Ear, Nose, Mouth, Throat, Head or Neck Disorders, with and without Interventions), non-elective inpatient short stay ⁶²
PPE syndrome	£511.89	NHS reference costs 2023/24, weighted average of JD07A–JD07K (Skin Disorders with and without Interventions), non-elective inpatient short stay ⁶²
Nausea	£508.69	NHS reference costs 2023/24, FD10M (Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2), non-elective inpatient short stay ⁶²
Vomiting	£508.69	NHS reference costs 2023/24, FD10M (Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2), non-elective inpatient short stay ⁶²
Small intestinal obstruction	£4,584.00	NHS reference costs 2023/24, weighted average of FF20A–FF22D (Complex/Very Major/Major Small Intestine Procedures), non-elective inpatient short stay ⁶²
Embolism	£663.75	NHS reference costs 2023/24, weighted average of DZ09J–DZ09Q (Pulmonary Embolus with and without Interventions), non-elective inpatient short stay ⁶²

Abbreviations: AE, adverse event; NHS, National Health Service; PPE, palmar-plantar erythrodysesthesia.

The EAG considers that the company's approach for estimating the cost of AEs is appropriate. The same AE costs were used for sunitinib and everolimus in the exploratory analysis of the less heavily pretreated population, with frequencies of AEs as described in Section 4.2.4.1.

4.2.6.5 Disease management costs

The economic model included costs for disease management based on health state-specific resource use frequencies sourced from existing literature. In the company's base case, resource use estimates were informed by Casciano *et al.* 2013, an international study of resource use in patients with advanced NETs.⁴⁰ This source reported the proportion of patients who used each specified resource category during the periods prior to the first disease progression, and between first and second disease progressions. The former period had an average follow-up time of 13 months, while the later period had an average follow-up time of nine months.

Different frequencies were used for the pNET and epNET populations, as well as for the PFS and PD health states; however, disease management costs were assumed to be independent of the primary treatment received. The input values used in the economic model are given in Table 60, page 124 of the CS.

Costs for disease management were informed by relevant costs from the NHS reference costs 2023/24.⁶² Details of the input values used are given in Table 67.

Table 67. Unit cost inputs for disease management

Resource	Unit cost	Cost source
CT scan	£142.33	NHS Reference Costs 2023/24, RD22Z (Computerised Tomography Scan of One Area, with Pre and Post Contrast), total HRGs ⁶²
Hospitalisation	£792.05	NHS Reference Costs 2023/24, average of non-elective inpatient short stays ⁶²
Laboratory test	£3.10	NHS Reference Costs 2023/24, PATH05 (Haematology, Directly Accessed Pathology Services) ⁶²
Ultrasound	£70.49	NHS Reference Costs 2023/24, weighted average of RD40Z - RD43Z (Ultrasound Scan with and without Contrast), total HRGs ⁶²
Other imaging	£38.63	NHS Reference Costs 2023/24, 812 (Diagnostic Imaging, Outpatient Attendance) ⁶²
Visit	£174.37	NHS Reference Costs 2023/24, weighted average 370 (Medical Oncology Service), WF01A/C (Non-Admitted Face-to-Face Attendance/Non-Face-to-Face Attendance, Follow-Up, Outpatient Attendance) ⁶²
Abbreviations: CT, computed tomography; HRG, healthcare resource group; NHS, National Health Service.		

The overall disease management costs per cycle are given in Table 68.

Table 68. Disease management costs per cycle: company base case

Health state	Cost per cycle	
	pNETs	epNETs
PFS	£93.72	£85.69
PD	£129.65	£120.85
Abbreviations: epNETs, extra-pancreatic endocrine tumours; PD, progressed disease; PF, progression-free; pNETs, pancreatic neuroendocrine tumours.		

4.2.6.5.1 EAG critique

The EAG considers the unit costs used in the economic model to be appropriate. However, the EAG considers that Casciano *et al.* 2013 is not an appropriate source to estimate the resource use in the model. Firstly, resource use in this study was analysed from the time of first diagnosis of advanced NETs until first progression and in between first and second progression; therefore, the data collected during the two follow-up periods do not align with the PF and PD health states in the economic model. This is true for both the company's proposed positioning of cabozantinib as a potential second-line systemic treatment; and in the CABINET context, where patients had received previous lines of treatments, and had had multiple disease progressions

Secondly, this study reports the number of patients using particular resources, rather than the frequency of use of resources. The EAG's clinical experts stated that patients would require use of most resources multiple times a year; therefore, conflating the number of patients using resources with the number of instances of resource use results in an underestimation of the overall resource use frequency estimates. The EAG's clinical experts confirmed that the frequency of resource use for all categories in the company's base case considerably underestimates the frequency of resource use that would be expected in UK clinical practice.

The EAG's preferred approach is to align resource use frequency with TA449 and TA539; in both TAs, resource use was informed by an unpublished study conducted by Novartis, based on a survey of UK clinicians.^{1, 36, 37} These estimates were also more in line with the EAG's clinical experts' opinions on the likely frequency of resource use. For ease of incorporation into the company's model, active treatment estimates were used for the PF health state and off-treatment estimates were used for the PD health state. The EAG also consolidated all hospitalisations, CT scans and blood tests into single categories.

The following resource categories were excluded, as the expected usage was less than 0.01 per 28-day cycle for all health states:

- Pulmonary angiogram, conventional;
- Chest radiography;
- Iodine-131 meta-iodobenzylguanidine (I-131 mIBG) scan;
- Fluorodeoxyglucose positron emission tomography (FDG PET).

The same resource use estimates were used for both lung NETs and epNETs excluding lung NETs, as only aggregated data for all epNETs were reported.

The resource use frequency inputs and associated costs used in the EAG's base case are given in Table 69. The overall disease management costs per cycle are given in Table 70. The same resource use costs were also used in the EAG's exploratory analysis of the less heavily pretreated population. This is **key issue 9**.

Table 69. Resource use frequency and costs: EAG base case

Resource	Resource use per 28 days: pNETs		Resource use per 28 days: epNETs		Unit cost	Cost source
	Pre-progression	Post-progression	Pre-progression	Post-progression		
Hospitalisation	0	0.0577	0.0714	0.0400	£792.05	NHS Reference Costs 2023/24, average of non-elective inpatient short stays ⁶²
Outpatient clinic consultation						
Primary physician	0.2737	0.7437	N/A	N/A	£45.00	PSSRU 2024; cost for 10-minute GP consultation ⁶⁵
Other physician	0.0805	1.3846	N/A	N/A	£174.37	NHS Reference Costs 2023/24, weighted average 370 (Medical Oncology Service), WF01A/C (Non-Admitted Face-to-Face Attendance/Non-Face-to-Face Attendance, Follow-Up, Outpatient Attendance) ⁶²
Medical oncologist	N/A	N/A	0.4137	0.3958	£193.39	NHS Reference Costs 2023/24, 370 (Medical Oncology Service) ⁶²
Surgeon	N/A	N/A	0.0463	0.0182	£180.99	NHS Reference Costs 2023/24, 100 (General Surgery Service) ⁶²
Palliative care	N/A	N/A	0	0.1041	£242.83	NHS Reference Costs 2023/24, 315 (Palliative Medicine Service) ⁶²
Respirologist	N/A	N/A	0	0.0189	£195.64	NHS Reference Costs 2023/24, 340 (Respiratory Medicine Service) ⁶²
Nurse specialist	N/A	N/A	0.0750	0	£6.20	PSSRU 2024; 10 minutes of band 6 hospital-based nurse time, costed at £62/hour ⁶⁵
Dietitian	N/A	N/A	0.0444	0.0129	£133.09	NHS Reference Costs 2023/24,654 (Dietetics Service) ⁶²
Procedure/test						
Abdominal ultrasound	0.0241	0.0321	0.0073	0.0091	£70.49	NHS Reference Costs 2023/24, weighted average of RD40Z - RD43Z (Ultrasound Scan With and Without Contrast), total HRGs ⁶²
CT scan	0.1449	0.1731	0.1166	0.2200	£142.33	NHS Reference Costs 2023/24, RD22Z (Computerised Tomography Scan of One Area, With Pre and Post Contrast), total HRGs ⁶²
Octreoscan/SRS	0.0080	0	0.0771	0.0372	£930.31	NHS Reference Costs 2023/24, RDN10 (Octreotide Scan), total HRGs ⁶²

Resource	Resource use per 28 days: pNETs		Resource use per 28 days: epNETs		Unit cost	Cost source
	Pre- progression	Post- progression	Pre- progression	Post- progression		
MRI	0.0241	0.0192	0.0989	0.0894	£172.70	NHS Reference Costs 2023/24, weighted average of RD01A, RD02A, RD03Z, RD04Z, RD05Z, RD06Z, RD07Z (Magnetic Resonance Imaging Scan With or Without Contrast, 19 Years and Over), total HRGs ⁶²
Blood test	0.7969	1.0384	4.3142	3.9699	£3.10	NHS Reference Costs 2023/24, PATH05 (Haematology, Directly Accessed Pathology Services) ⁶²

Abbreviations: CT, computed tomography; epNETs, extra-pancreatic neuroendocrine tumours; HRG, healthcare resource group; MRI, magnetic resonance imaging; NHS, National Health Service; pNETs, pancreatic neuroendocrine tumours; PSSRU, Personal Social Services Research Unit; SRS, somatostatin receptor scintigraphy.

Table 70. Disease management costs per cycle: EAG base case

Health state	Cost per cycle	
	pNETs	epNETs
PF	£62.64	£270.25
PD	£353.95	£236.12

Abbreviations: epNETs, extra-pancreatic endocrine tumours; PD, progressed disease; PF, progression-free; pNETs, pancreatic neuroendocrine tumours.

4.2.6.6 End-of-life care

The model applied a single cost covering additional resource use associated with end-of-life care to all patients in the cycle in which they moved into the death state. A cost of £13,314.00 was used, informed by the PSSRU 2023 handbook.⁶³ The EAG considers that the use of this end-of-life cost is appropriate, but updated the input value in the EAG base case to align with the 2024 handbook (£13,964.00).⁶⁵ The same cost was applied in the exploratory analysis of the less heavily pretreated population.

5 Cost effectiveness results

5.1 Company's cost effectiveness results

Table 71 and Table 72 present the cost-effectiveness results of the company's updated (i.e., post clarification) base case deterministic and probabilistic analyses for pNET and epNET, respectively. The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around base case results. Incremental results from the company's PSA are based on 1,000 simulations.

In the base case probabilistic analysis, incremental quality-adjusted life-year (QALY) gains for cabozantinib are similar in pNET and epNET patients with [REDACTED] and [REDACTED] over BSC respectively. Lower incremental costs in the epNET population of [REDACTED], compared to [REDACTED] in pNET patients, results in a lower ICER in the epNET population. In the pNET population, the probabilistic ICER amounts to £23,534 per QALY gained, whereas the ICER for the epNET population amounts to £13,187 per QALY gained.

Table 71. Company's base case results (pNET)

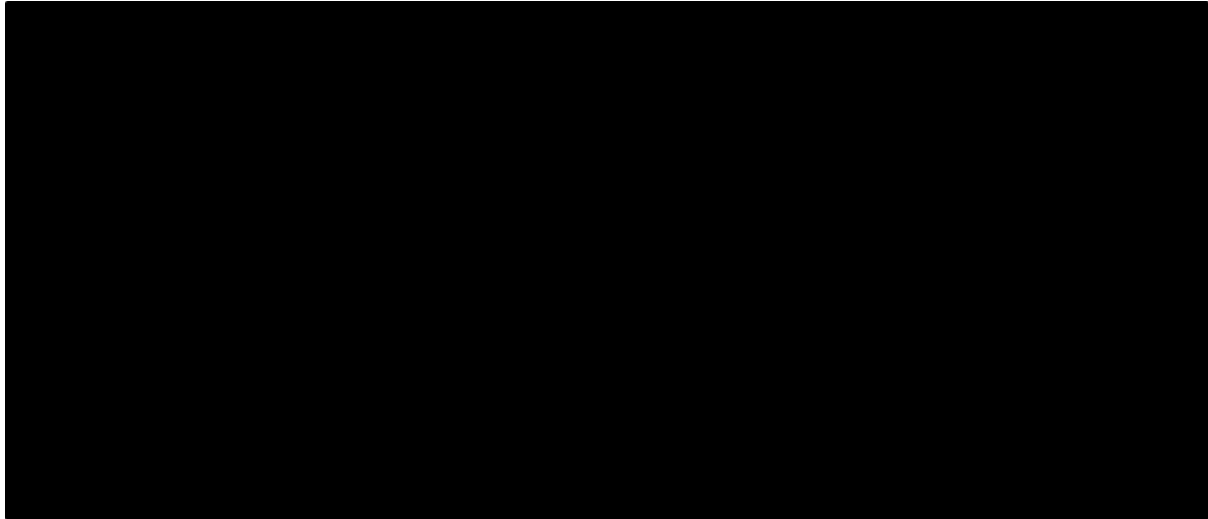
Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Cabozantinib	[REDACTED]	4.38	[REDACTED]	-	-	-	-
BSC	[REDACTED]	3.36	2.23	[REDACTED]	1.02	[REDACTED]	£24,815
Probabilistic results							
Cabozantinib	[REDACTED]	4.46	[REDACTED]	-	-	-	-
BSC	[REDACTED]	3.35	2.20	[REDACTED]	1.11	[REDACTED]	£23,534
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year							

Table 72. Company's base case results (epNET)

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Cabozantinib	[REDACTED]	2.95	[REDACTED]	-	-	-	-
BSC	[REDACTED]	1.84	1.13	[REDACTED]	1.11	[REDACTED]	£12,849
Probabilistic results							
Cabozantinib	[REDACTED]	2.96	[REDACTED]	-	-	-	-
BSC	[REDACTED]	1.86	1.13	[REDACTED]	1.09	[REDACTED]	£13,187
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year							

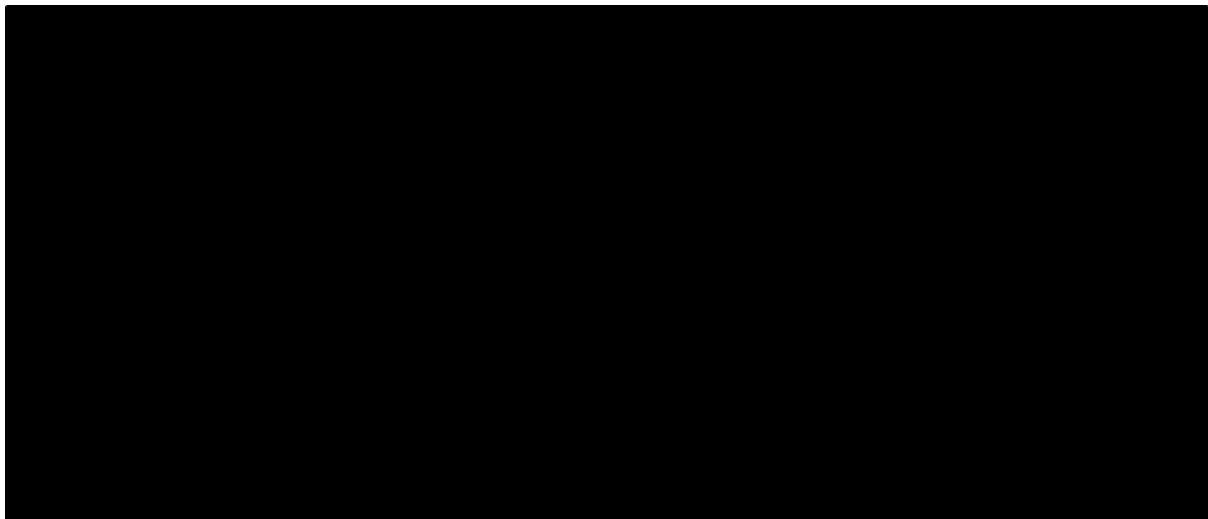
A PSA scatterplot for pNET patients is presented in Figure 50 and a cost-effectiveness acceptability curve (CEAC) is presented in Figure 51 for the same population. The CEAC notably does not go above a 85-90% probability of cost-effectiveness, despite the increase in the WTP threshold, due to a number of scenarios producing outcomes where cabozantinib is less effective than BSC.

Figure 50. Scatterplot of PSA estimates on a cost-effectiveness plane pNET



Abbreviations: BSC, best supportive care; pNETs, pancreatic neuroendocrine tumours; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; WTP, willingness to pay.

Figure 51. Cost-effectiveness acceptability curve pNET



Abbreviations: BSC, best supportive care; pNETs, pancreatic neuroendocrine tumours.

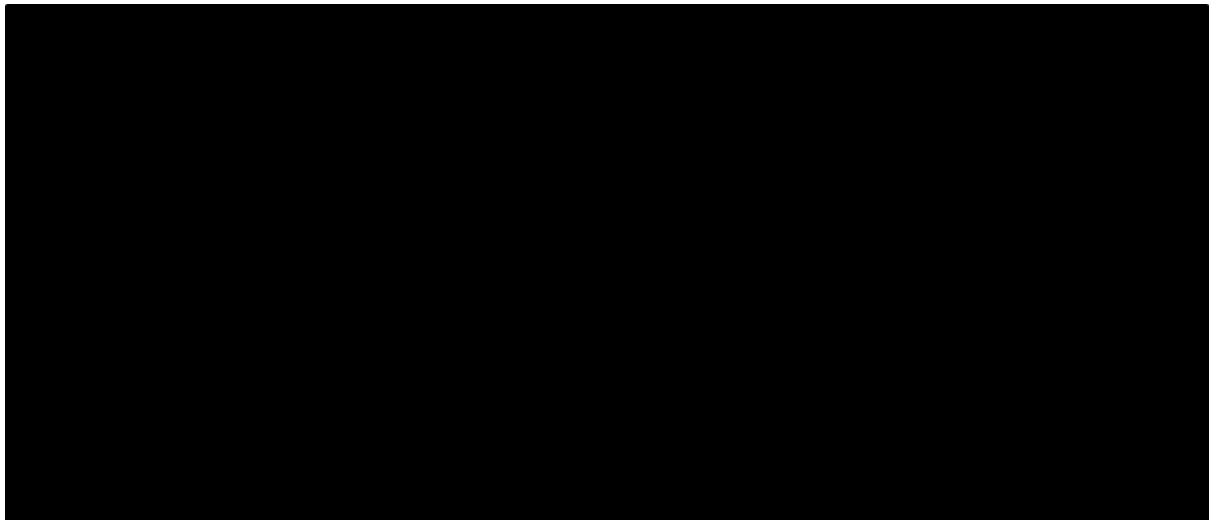
PSA scatterplot for pNET patients is presented in Figure 52 and a CEAC is presented in Figure 53.

Figure 52. Scatterplot of PSA estimates on a cost-effectiveness plane epNET



Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; WTP, willingness to pay.

Figure 53. Cost-effectiveness acceptability curve epNET



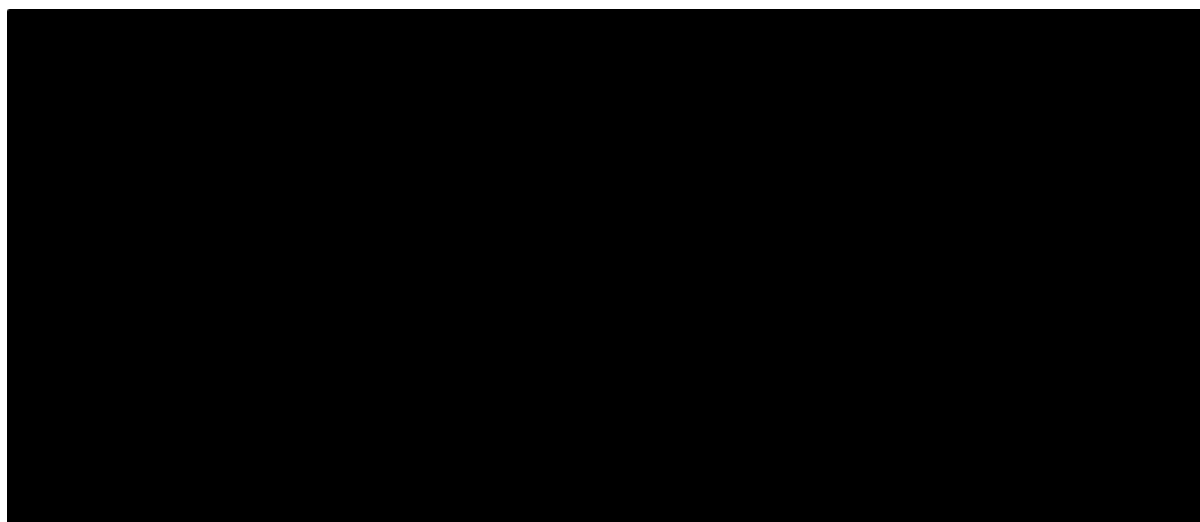
Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours.

5.2 Company's sensitivity analyses

5.2.1 One-way sensitivity analysis

The company conducted one-way sensitivity analyses (OWSAs) to assess the impact on the ICER of varying specific parameters in isolation and to identify the main model drivers. The results are illustrated in the tornado diagram presented in Figure 54. The ICER was most sensitive to varying the OS HR for the BSC arm vs cabozantinib (IPCW adjusted).

Figure 54. Tornado plot pNET



Abbreviations: BSC, best supportive care HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NET, neuroendocrine tumour; TTD, time to treatment discontinuation; OS, overall survival; pNETs, pancreatic neuroendocrine tumours; PFS, progression free survival; QALY, quality-adjusted life year; RPSFTM, Rank preserving structural failure time model; WTP, willingness-to-pay.

Figure 55. Tornado plot epNET

Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NET, neuroendocrine tumour; TTD, time to treatment discontinuation; OS, overall survival; PFS, progression free survival; QALY, quality-adjusted life year; RPSFTM, Rank preserving structural failure time model; WTP, willingness-to-pay.

5.2.2 Scenario analysis

The company undertook a series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters, presented in Table 73 for pNET and Table 74 for epNET. In addition, the company conducted several additional scenario analyses requested by the External Assessment Group (EAG), also presented in the tables below. The deterministic ICERs were most sensitive to the method used to derive the OS BSC curve for both the epNET and the pNET populations.

Table 73. Company deterministic scenario analysis pNET

No.	Scenario	Incremental costs (£)	Incremental QALYs	ICER
0	Company base case	■	■	£24,815
1	Discount rate for costs and benefits: 6.0%	■	■	£27,210
2	Discount rate for costs and benefits: 1.5%	■	■	£22,869
3	CABINET trial (PF) and Swinburn Vignettes (PD) utility values	■	■	£24,662
4	CABINET trial (PF) and ERASMUS relative decrement (PD) utility values	■	■	£25,452

5	CABINET trial (PF) and ERASMUS (PD) utility values	■	■	£25,394
6	AE disutilities: exclude	■	■	£24,730
7	Alternative PFS/TTD curve selection for cabozantinib: PFS: Gompertz, TTD: Weibull	■	■	£26,845
8	Alternative OS curve selection for cabozantinib (based on clinical validation): loglogistic	■	■	£20,850
9	PFS/TTD: Direct extrapolation: PFS: Lognormal, TTD: Weibull	■	■	£24,759
10	Administration costs for orally administered drugs: £0	■	■	£24,587
11	Subsequent treatment distribution source: Ipsen Data on File, CABINET CSR	■	■	£20,722
12	CCT in PD distribution source: Ipsen Data on File, CABINET CSR (pooled SSA use alongside subsequent treatment)	■	■	£25,490
13	Resource use source: Casciano et al. 2013 (adjusted frequency)	■	■	£27,677
EAG requested scenarios				
QB12:	Fitting a survival curve to OS BSC instead of using a HR	■	■	£41,413
QB13:	Adjustment for crossover RPSFTM	■	■	£43,974
QB13:	No adjustment for crossover (ITT)	■	■	£45,953
QB18:	Cabozantinib TTD Method	■	■	£30,875
QB23:	Utilities sources: PF from Swinburn PD from relative decrement Swinburn	■	■	£26,366
QB23:	Utilities sources: PF from Swinburn PD from relative decrement ERASMUS trial	■	■	£27,043
QB24:	Alternative disutility (hypertension, embolism)	■	■	£24,817
QB27:	Concomitant treatment duration scenario using PFS duration	■	■	£28,778
QB27:	Concomitant treatment duration scenario using OS duration	■	■	£28,982
QB35d:	Subsequent treatment duration Mujica-Mota <i>et al.</i> 2018 for sunitinib and PRRT and RADIANT-3 trial for everolimus.	■	■	£24,818
QB38:	Update costs based on PSSRU 2024 report	■	■	£24,805
QB40B:	Administration cost approach for SSAs	■	■	£26,021
QB41:	Administration cost for PRRT excluding diagnostic services	■	■	£24,815
Abbreviations: AE, adverse events; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; KM, Kaplan-Meier; OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; QALY, quality-adjusted life-year; RWE, real-world evidence; TTD, time-to-treatment discontinuation.				

Table 74. Company deterministic scenario analysis epNET

No.	Scenario	Incremental costs (£)	Incremental QALYs	ICER
0	Company base case	■	■	£12,849
1	Discount rate for costs and benefits: 6.0%	■	■	£13,783
2	Discount rate for costs and benefits: 1.5%	■	■	£12,067
3	CABINET trial (PF) and Swinburn Vignettes (PD)	■	■	£12,578
4	CABINET trial (PF) and ERASMUS relative decrement (PD)	■	■	£12,016
5	CABINET trial (PF) and ERASMUS (PD)	■	■	£11,590
6	AE disutilities: exclude	■	■	£12,841
7	Alternative PFS/TTD curve selection for cabozantinib: PFS: Gompertz, TTD: Weibull	■	■	£13,809
8	Alternative OS curve selection for cabozantinib (based on clinical validation): loglogistic	■	■	£12,956
9	PFS/TTD: Direct extrapolation: PFS: Lognormal, TTD: Weibull	■	■	£13,273
10	Administration costs for orally administered drugs: £0	■	■	£12,711
11	Subsequent treatment distribution source: Ipsen Data on File, CABINET CSR	■	■	£10,507
12	CCT in PD distribution source: Ipsen Data on File, CABINET CSR (pooled SSA use alongside subsequent treatment)	■	■	£13,522
13	Resource use source: Casciano et al. 2013 (adjusted frequency)	■	■	£15,431
EAG requested scenarios				
QB2:	epNET subgroups lung nets	■	■	£23,525
QB2:	epNET subgroups without lung nets	■	■	£13,718
QB12:	Fitting a survival curve to OS BSC instead of using a HR	■	■	£12,102
QB13:	Adjustment for crossover RPSFTM	■	■	£20,588
QB13:	Adjustment for crossover ITT	■	■	£13,606
QB18:	Cabozantinib TTD Method	■	■	£12,384
QB23:	Utilities sources: PF from Mujica-Mota base case PD from relative decrement Swinburn	■	■	£11,638
QB23:	Utilities sources: PF from Mujica-Mota base case PD from relative decrement ERASMUS	■	■	£10,884
QB23:	Utilities sources: PF from Mujica-Mota base case PD from absolute value Swinburn	■	■	£11,847
QB23:	Utilities sources: PF from Mujica-Mota base case PD from absolute value ERASMUS	■	■	£10,967

QB23:	Utilities sources: PF from Mujica-Mota alternative values PD from relative decrement Swinburn	■	■	£12,057
QB23:	Utilities sources: PF from Mujica-Mota alternative values PD from relative decrement ERASMUS	■	■	£11,276
QB23:	Utilities sources: PF from Mujica-Mota alternative values PD from absolute value Swinburn	■	■	£12,106
QB23:	Utilities sources: PF from Mujica-Mota alternative values PD from absolute value ERASMUS	■	■	£11,188
QB24:	Disutility (hypertension, embolism)	■	■	£12,853
QB27:	Concomitant treatment duration scenario using pfs	■	■	£15,753
QB27:	Concomitant treatment duration scenario using OS	■	■	£21,553
QB35d:	Subsequent treatment duration Mujica-Mota <i>et al.</i> 2018 for sunitinib and PRRT and RADIANT-3 trial for everolimus.	■	■	£12,850
QB38:	Update costs based on PSSRU 2024 report	■	■	£12,828
QB40B:	Administration cost approach for SSAs	■	■	£13,417
QB41:	Administration cost for PRRT excluding diagnostic services	■	■	£12,848

Abbreviations: AE, adverse events; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; KM, Kaplan-Meier; OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; QALY, quality-adjusted life-year; RWE, real-world evidence; TTD, time-to-treatment discontinuation.

5.3 Model validation and face validity check

Section 3.14 in the company submission outlines the company's approach to the validation of the economic model. Generally, the EAG is satisfied that the company's approach to model validation was robust.

6 Additional economic analysis undertaken by the EAG

6.1 Model corrections

The EAG did not find any errors in the company's model that needed correcting after clarification. As a small note, the curves for OS extrapolations for cabozantinib on the "Efficacy" sheet of the model were using model cycle length rather than time to inform the X axis values, which was leading to slightly odd curves being produced. This has been updated in all curves present here.

6.2 Exploratory and sensitivity analyses undertaken by the EAG

The analyses conducted by the EAG were explained throughout the report. The results provided are for all the relevant comparators considered in the EAG's report: BSC; everolimus and sunitinib.

The EAG notes that changes made in the CABINET population analysis affected the estimated curves for cabozantinib. This affected results in the exploratory analysis for the less heavily pretreated population, where cabozantinib curves were used to apply the exploratory ITC HRs to estimate the relative cost-effectiveness of everolimus and sunitinib.

The EAG also notes that even though the analyses for the CABINET and the less heavily pretreated populations have been considered separately in the EAG report, it is the combined CABINET and less heavily pretreated populations that constitute the overall population eligible to receive cabozantinib. Therefore, results for the EAG analysis present comparisons of cabozantinib vs BSC; everolimus and sunitinib. In the interest of aiding the discussion of results, the EAG summarises the treatment pathway and the appropriateness of each comparator in the analysis according to the available evidence below:

- Heavily pretreated population (reflected in CABINET), where cabozantinib is given as a fourth (or later) line of systemic treatment for pNET patients (excluding previous SSAs); and as a third (or later) line of systemic treatment for epNET patients, excluding previous SSAs. The main comparator to cabozantinib is BSC.
- Functional lung NETs. BSC is the most relevant comparator, as chemotherapy is the only available systemic treatment (excluding SSAs) which would be given before cabozantinib.
- Patients receiving cabozantinib as a second (or later) systemic treatment (excluding SSAs as a prior treatment). The comparators included in this analysis are everolimus and sunitinib.
- Lung NET patients who have received chemotherapy as a first-line active treatment (other than SSAs). Everolimus is the relevant comparator.

The EAG notes that it was not possible to differentiate lung NET patients with functional and non-functional NETs in its analysis due to lack of effectiveness data available for each of these groups. The evidence for cabozantinib is based on CABINET, where ■ of patients in the epNETs population and ■ in the pNETs population had functional tumours.

The analysis conducted by the EAG consisted of the following:

1. Scenario 1. EAGs preference is for population-specific HRs for lung NETs and epNET without lung. The company used epNET total population HR for both analyses.
2. Scenario 2. EAG's preference for modelling PFS: The EAG has a preference for independently fitted curves where available (for the pNET and epNET populations). The EAG had to use HRs to estimate BSC curves for lung NETs and epNETs without lung, as there was no option in the model to independently fit curves for these populations.

The EAG's preference is also for the use of the Weibull over the lognormal curve for modelling the cabozantinib PFS curves, in all populations. In addition, For the pNET and the epNET BSC PFS curves, the EAG preference is to use a lognormal curve.
3. Scenario 3. Use of updated DCO: This scenario uses the company updated DCO OS data.
4. Scenario 4. EAG's preferences for modelling OS (with updated DCO): This scenario uses the company's updated DCO data and a Weibull curve for modelling cabozantinib in pNET, epNET, and lung NET. An exponential curve was used to model cabozantinib for the epNET without lung population. In addition, the EAG assumed equal effectiveness for OS between cabozantinib and BSC; everolimus; and sunitinib in the pNET; pooled epNET; and epNET without lung populations. The RPSFTM-adjusted HR was applied to the cabozantinib OS curve to derive the BSC OS curve in the epNET lung population. This isn't relevant in other populations as HRs are capped at 1.
5. Scenario 5. TTD modelled with KM: The EAG preference is to model the time to treatment discontinuation using the KM TTD data over an exponential model preferred by the company.
6. Scenario 6. Concomitant treatment duration with SSAs: Concomitant SSA costs were applied up to death in the model for the proportion of patients taking them in CABINET.
7. Scenario 7. AEs applied in first cycle: The EAG applied all costs and QALY related to AEs in the first cycle of the model.
8. Scenario 8. EAG health state utility preferences: The EAG's preference is to use Swinburn Vignettes (PF and PD relative decrement) for pNETs and RADIANT-4 (PF and PD) for epNETs.

9. Scenario 9. Disutilities applied to AEs: The EAG used alternative AE disutilities for hypertension and embolism in the model.
10. Scenario 10. Dose hold: The EAG does not consider that a dose hold reduction in treatment with cabozantinib should be included in the analysis.
11. Scenario 11. Using PSSRU 2024 costs and correction to cost estimate: The EAG used the latest version of the PSSRU costs. In addition, the EAG PSSRU correction more accurately reflects treatment times by healthcare professionals.
12. Scenario 12. Disease management costs: The EAG has used different sources for resource use for disease management costs.
13. Scenario 13. Subsequent treatment excluded (less heavily pretreated population): The EAG's exploratory analysis for the less heavily pretreated population excluded subsequent treatments from the analysis (when comparing cabozantinib to everolimus or sunitinib).
14. Scenario 14. EAG preferred subsequent treatment (CABINET population): The EAG preference is to use the subsequent treatments given in CABINET in the model for the CABINET population analysis (when comparing cabozantinib to BSC).

6.3 EAG scenario analysis

The impact of the scenarios described in Section 6.2 on the company's base case are shown below in Table 75, Table 76 and Table 77 for pNET, lung NET and epNET without lung respectively.

The assumptions with the highest impact on the company's base case ICERs were the use of the updated DCO, use of independent HRs for lung/epNETs without lung populations and the use of EAG OS preferences, particularly capping hazard in pNET and epNET without lung.

Table 75. Deterministic results of the EAG's scenario analyses pNETs

	Incremental		ICER
	Costs	QALYs	
Company base case*			
Sunitinib	████	██	£261,066
Everolimus	████	██	£148,095
BSC	████	██	£24,815
Scenario 2: EAG preferred PFS curves			
Sunitinib	████	██	£453,345
Everolimus	████	██	£267,478

BSC	■■■■	■	£27,506
Scenario 3: Use of updated DCO			
Sunitinib	■■■■	■	£259,051
Everolimus	■■■■	■	£146,094
BSC	■■■■	■	Dominated (NW quadrant ICER -£119,524)
Scenario 4: EAG's preferences for modelling OS (with updated DCO)			
Sunitinib	■■■■	■	£261,677
Everolimus	■■■■	■	£147,481
BSC	■■■■	■	£98,410
Scenario 5: TTD modelled with KM			
Sunitinib	■■■■	■	£334,184
Everolimus	■■■■	■	£207,649
BSC	■■■■	■	£30,875
Scenario 6: Concomitant treatment duration			
Sunitinib	■■■■	■	£566,612
Everolimus	■■■■	■	£401,328
BSC	■■■■	■	£28,982
Scenario 7: AEs applied in first cycle			
Sunitinib	■■■■	■	£255,862
Everolimus	■■■■	■	£157,092
BSC	■■■■	■	£24,766
Scenario 8: EAG health state utility preferences			
Sunitinib	■■■■	■	£277,645
Everolimus	■■■■	■	£157,315
BSC	■■■■	■	£26,366
Scenario 9: Alternative EAG disutilities			
Sunitinib	■■■■	■	£261,224
Everolimus	■■■■	■	£148,095
BSC	■■■■	■	£24,817
Scenario 10: Dose hold removed			
Sunitinib	■■■■	■	£280,284
Everolimus	■■■■	■	£161,540
BSC	■■■■	■	£26,534
Scenario 11: PSSRU 2024 + correction to costing			
Sunitinib	■■■■	■	£259,735

Everolimus	■■■	■	£147,920
BSC	■■■	■	£24,687
Scenario 12: EAG alternative disease management costs			
Sunitinib	■■■	■	£240,672
Everolimus	■■■	■	£128,092
BSC	■■■	■	£23,866
Scenario 13: Subsequent treatment excluded (less heavily pretreated population)			
Sunitinib	■■■	■	£269,395
Everolimus	■■■	■	£158,311
Scenario 14: EAG preferred subsequent treatment (CABINET population)			
BSC	■■■	■	£29,464
Abbreviations: AE, adverse events; BSC, best supportive care; DCO, data cut-off; EAG, economic assessment group; HR, hazard ratio; HSUV, health state utility; ICER, incremental cost-effectiveness ratio; IPCW, inverse probability of censoring weights; OS, overall survival; PFS, progression free survival; PSSRU, personal social services research unit; QALY, quality adjusted life years; RPSFTM, rank preserving structural failure time model; TTD, time to treatment discontinuation; WTP, willingness to pay.			
*Please note that the company's base case did not include comparisons with everolimus or sunitinib			

Table 76. Deterministic results of the EAG's scenario analyses lung NETs

	Incremental		ICER
	Costs	QALYs	
Company base case			
Everolimus	████	████	£92,200
BSC	████	████	£20,904
Scenario 1: Independent BSC HRs for lung NETs			
Everolimus	████	████	£92,200
BSC	████	████	£7,812
Scenario 2: EAG preferred PFS curves			
Everolimus	████	████	£120,675
BSC	████	████	£22,964
Scenario 3: Use of updated DCO			
Everolimus	████	████	£95,473
BSC	████	████	£32,317
Scenario 4: EAG's preferences for modelling OS (with updated DCO)			
Everolimus	████	████	£92,436
BSC	████	████	£98,316
Scenario 5: TTD modelled with KM			
Everolimus	████	████	£89,172
BSC	████	████	£20,303

Scenario 6: concomitant treatment duration			
Everolimus	████	██	£243,827
BSC	████	██	£28,015
Scenario 7: AEs applied in first cycle			
Everolimus	████	██	£91,744
BSC	████	██	£21,155
Scenario 8: EAG health state utility preferences:			
Everolimus	████	██	£169,673
BSC	████	██	£18,644
Scenario 9: Alternative EAG disutilities			
Everolimus	████	██	£92,240
BSC	████	██	£20,912
Scenario 10: dose hold removed			
Everolimus	████	██	£103,012
BSC	████	██	£23,288
Scenario 11: PSSRU 2024 + correction to costing			
Everolimus	████	██	£91,641
BSC	████	██	£20,820
Scenario 12 EAG: Alternative disease management costs			
Everolimus	████	██	£97,219
BSC	████	██	£23,604
Scenario 13: Subsequent treatment excluded (less heavily pretreated population)			
Everolimus	████	██	£96,469
Scenario 14: EAG preferred subsequent treatment (CABINET population)			
BSC	████	██	£16,799
Abbreviations: AE, adverse events; BSC, best supportive care; DCO, data cut-off; EAG, economic assessment group; HR, hazard ratio; HSUV, health state utility; ICER, incremental cost-effectiveness ratio; IPCW, inverse probability of censoring weights; KM, Kaplan Meir; OS, overall survival; PFS, progression free survival; PSSRU, personal social services research unit; QALY, quality adjusted life years; RPSFTM, rank preserving structural failure time model; TTD, time to treatment discontinuation; WTP, willingness to pay.			

Table 77. Deterministic results of the EAG's scenario analyses epNETs without lung

	Incremental		ICER
	Costs	QALYs	
Company base case			
Everolimus	████	██	£338,698
BSC	████	██	£13,718
Scenario 1: Independent BSC HR for epNETs without lung			
Everolimus	████	██	£338,698

BSC	■	■	Dominated (NW quadrant -£675,850)
Scenario 2: EAG preferred PFS curves			
Everolimus	■	■	£608,056
BSC	■	■	£15,136
Scenario 3: Use of updated DCO			
Everolimus	■	■	£337,102
BSC	■	■	Dominated (NW quadrant-£73,250)
Scenario 4: EAG's preferences for modelling OS (with updated DCO)			
Everolimus	■	■	£283,999
BSC	■	■	£85,864
Scenario 5: TTD modelled with KM			
Everolimus	■	■	£318,063
BSC	■	■	£13,156
Scenario 6: Concomitant treatment duration			
Everolimus	■	■	£1,123,059
BSC	■	■	£22,196
Scenario 7: AEs applied in first cycle			
Everolimus	■	■	£341,500
BSC	■	■	£13,803
Scenario 8: EAG health state utility preferences:			
Everolimus	■	■	£619,154
BSC	■	■	£11,825
Scenario 9: Alternate EAG disutilities			
Everolimus	■	■	£337,860
BSC	■	■	£13,722
Scenario 10: Dose hold removed			
Everolimus	■	■	£387,568
BSC	■	■	£15,380
Scenario 11: PSSRU 2024 + correction to costing			
Everolimus	■	■	£339,513
BSC	■	■	£13,637
Scenario 12: EAG alternate disease management costs			
Everolimus	■	■	£344,717
BSC	■	■	£16,309

Scenario 13: Subsequent treatment excluded (less heavily pretreated population)			
Everolimus	■	■	£330,989
Scenario 14: EAG preferred subsequent treatment (CABINET population)			
BSC	■	■	£9,348
Abbreviations: AE, adverse events; BSC, best supportive care; DCO, data cut-off; EAG, economic assessment group; HR, hazard ratio; HSUV, health state utility; ICER, incremental cost-effectiveness ratio; IPCW, inverse probability of censoring weights; OS, overall survival; PFS, progression free survival; PSSRU, personal social services research unit; QALY, quality adjusted life years; RPSFTM, rank preserving structural failure time model; TTD, time to treatment discontinuation; WTP, willingness to pay.			

The cumulative impact of the EAG preferred assumptions are shown below in Table 78, Table 79 and Table 80 for pNET, lung NET and epNET without lung.

Table 78. EAG's preferred model assumptions pNET (deterministic results)

Scenario number	Preferred assumption	Cumulative ICER vs Sunitinib (£)	Cumulative ICER vs Everolimus (£)	Cumulative ICER vs BSC (£)
0	Company base case	£261,066	£148,095	£24,815
2	Independently modelled PFS BSC curve + EAG choice of cabozantinib PFS curve (Weibull)	£453,345	£267,478	£27,506
3	Latest DCO (Loglogistic)	£448,719	£263,021	Dominated (NW quadrant ICER -£93,177)
4	EAG choice of OS curves (Weibull) Cap OS HRs for BSC at 1 RPSFTM	£448,338	£262,679	£137,495
5	TTD KM curve	£444,572	£259,723	£136,310
6	Concomitant treatment duration	£826,450	£567,063	£114,341
7	AEs applied 1 st cycle	£802,767	£622,371	£115,470

8	EAG HSUV	£852,938	£665,316	£122,937
9	Alternate AE disutilities	£853,026	£663,870	£122,861
10	Dose hold removed	£886,412	£689,900	£133,861
11	PSSRU 2024+correction	£872,394	£678,631	£133,966
12	EAG alternate disease management costs	£851,233	£655,325	£112,131
13	Exclude subsequent treatments (less heavily pretreated population only)	£875,490	£682,374	NA
14	EAG preferred subsequent treatment (CABINET population)	NA	NA	£137,976

Abbreviations: AE, adverse events; BSC, best supportive care; DCO, data cut-off; EAG, economic assessment group; HSUV, health state utility; ICER, incremental cost-effectiveness ratio; IPCW, inverse probability of censoring weights; NA, not available; NMB, net monetary benefit; PSSRU, personal social services research unit; QALY, quality adjusted life years; RPSFTM, rank preserving structural failure time model; WTP, willingness to pay.

Table 79. EAG's preferred model assumptions lung NETs (deterministic results)

Scenario number	Preferred assumption	Cumulative ICER vs Everolimus (£)	Cumulative ICER vs BSC (£)
0	Company base case	£92,200	£20,904
1	Independent BSC HR for epNETs lung	£92,200	£7,812
2	EAG choice of cabozantinib PFS curve (Weibull)	£119,110	£6,085
3	Latest DCO OS (Gompertz)	£124,007	£13,854
4	EAG choice of OS curves (Weibull) RPSFTM	£120,935	£8,576
5	TTD KM curve	£118,734	£8,469
6	Concomitant treatment duration	£313,311	£14,677
7	AEs applied 1st cycle	£312,265	£14,761
8	EAG HSUV	£573,419	£17,725
9	Alternate AE disutilities	£572,905	£17,734
10	Dose hold removed	£597,588	£18,690
11	PSSRU 2024+correction	£585,777	£18,403

12	EAG alternate disease management costs	£594,945	£20,489
13	Exclude subsequent treatments (less heavily pretreated population only)	£620,201	NA
14	EAG preferred subsequent treatment (CABINET population)	NA	£17,455

Abbreviations: AE, adverse events; BSC, best supportive care; DCO, data cut-off; EAG, economic assessment group; HSUV, health state utility; ICER, incremental cost-effectiveness ratio; IPCW, inverse probability of censoring weights; NA, not available; NMB, net monetary benefit; PSSRU, personal social services research unit; QALY, quality adjusted life years; RPSFTM, rank preserving structural failure time model; WTP, willingness to pay.

Table 80. EAG's preferred model assumptions epNETs without lung (deterministic results)

Scenario number	Preferred assumption	Cumulative ICER vs Everolimus (£)	Cumulative ICER vs BSC (£)
0	Company base case	£338,698	£13,718
1	Independent BSC HR for epNETs without lung	£338,698	Dominated (NW quadrant ICER -£675,850)
2	EAG choice of cabozantinib PFS curve (Weibull)	£608,056	Dominated (NW quadrant ICER -£284,164)
3	Latest DCO OS (Loglogistic)	£606,167	Dominated (NW quadrant ICER -£65,639)
4	EAG choice of OS curves (exponential) Cap OS HRs for BSC at 1 (RPSFTM)	£510,741	£159,869
5	TTD KM curve	£490,582	£152,488
6	Concomitant treatment duration	£1,303,432	£127,157
7	AEs applied 1st cycle	£1,311,325	£129,309
8	EAG HSUV	£2,888,346	£289,423
9	Alternate AE disutilities	£2,884,768	£293,822
10	Dose hold removed	£3,027,217	£341,382
11	PSSRU 2024+correction	£2,974,480	£341,910
12	EAG alternate disease management costs	£2,985,498	£353,495
13	Exclude subsequent treatments (less heavily pretreated population only)	£3,042,543	NA
14	EAG preferred subsequent treatment (CABINET population)	NA	£197,483

Abbreviations: AE, adverse events; BSC, best supportive care; DCO, data cut-off; EAG, economic assessment group; HSUV, health state utility; ICER, incremental cost-effectiveness ratio; IPCW, inverse probability of censoring weights; NA, not available; NMB, net monetary benefit; PSSRU, personal social services research unit; QALY, quality adjusted life years; RPSFTM, rank preserving structural failure time model; WTP, willingness to pay.

6.4 EAG preferred assumptions

6.4.1.1 The EAG base case

The EAG base case deterministic and probabilistic results are shown in Table 81, Table 82 and Table 83. The comparisons for BSC are separated from those with everolimus and sunitinib here due to the difference in subsequent treatment costs assumed as the populations involve alternate positioning.

Table 81. EAG's base case results (pNETs)

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results (less heavily pretreated population)							
Cabozantinib	■	3.50	■	-	-	-	-
Sunitinib	■	3.50	2.28	■	0.00	■	£875,490
Everolimus	■	3.50	2.27	■	0.00	■	£682,374
Deterministic results (CABINET population)							
Cabozantinib	■	3.50	■	-	-	-	-
BSC	■	3.50	2.19	■	0.00	■	£137,794
Probabilistic results (less heavily pretreated population)							
Cabozantinib	■	3.56	■	-	-	-	-
Sunitinib	■	3.56	2.30	■	0.00	■	£758,750
Everolimus	■	3.56	2.30	■	0.00	■	£608,767
Probabilistic results (CABINET population)							
Cabozantinib	■	3.58	■	-	-	-	-
BSC	■	3.58	2.23	■	0.00	■	£137,976
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year							

Table 82. EAG's base case results (lung NETs)

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results (less heavily pretreated population)							
Cabozantinib	■	2.05	■	-	-	-	-
Everolimus	■	2.05	1.51	■	0.00	■	£620,201
Deterministic results (CABINET population)							
Cabozantinib	■	2.05	■	-	-	-	-
BSC	■	0.90	0.68	■	1.15	■	£17,758

Probabilistic results (less heavily pretreated population)							
Cabozantinib	■	2.08	■	-	-	-	-
Everolimus	■	2.08	1.53	■	0.00	■	£530,103
Probabilistic results (CABINET population)							
Cabozantinib	■	2.09	■	-	-	-	-
BSC	■	0.91	0.68	■	1.17	■	£17,455
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year							

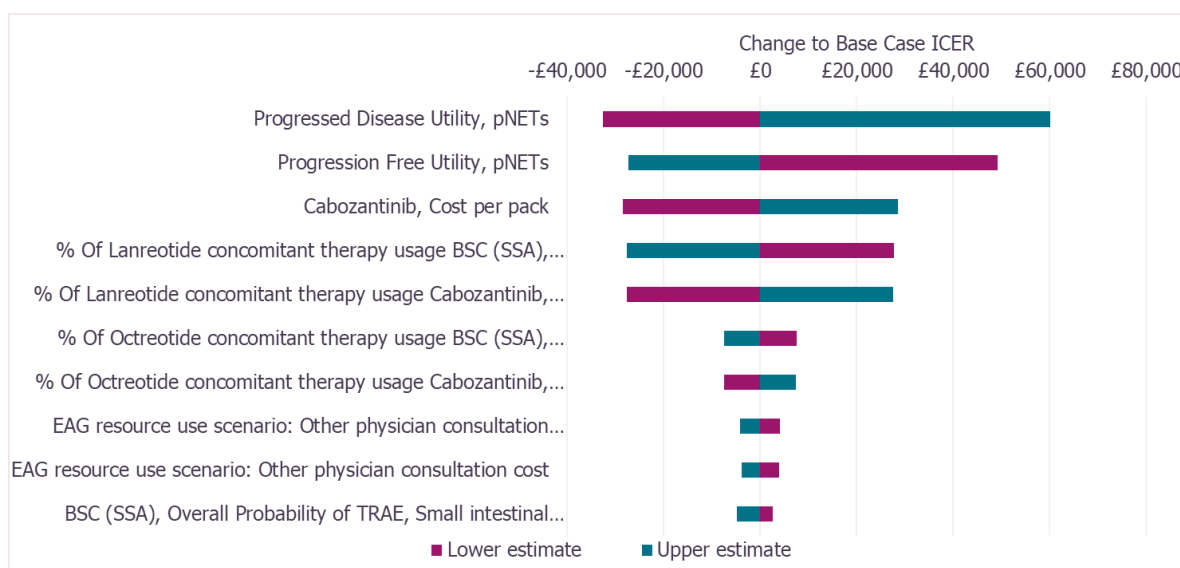
Table 83. EAG's base case results (epNETs without lung)

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results (less heavily pretreated population)							
Cabozantinib	■	2.56	■	-	-	-	-
Everolimus	■	2.56	1.91	■	0.00	■	£3,042,543
Deterministic results (CABINET population)							
Cabozantinib	■	2.56	■	-	-	-	-
BSC	■	2.56	1.89	■	0.00	■	£197,483
Probabilistic results (less heavily pretreated population)							
Cabozantinib	■	2.58	■	-	-	-	-
Everolimus	■	2.58	1.92	■	0.00	■	£2,687,959
Probabilistic results (CABINET population)							
Cabozantinib	■	2.58	■	-	-	-	-
BSC	■	2.58	1.90	■	0.00	■	£195,752
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year							

6.4.1.2 One-way sensitivity analysis EAG base case

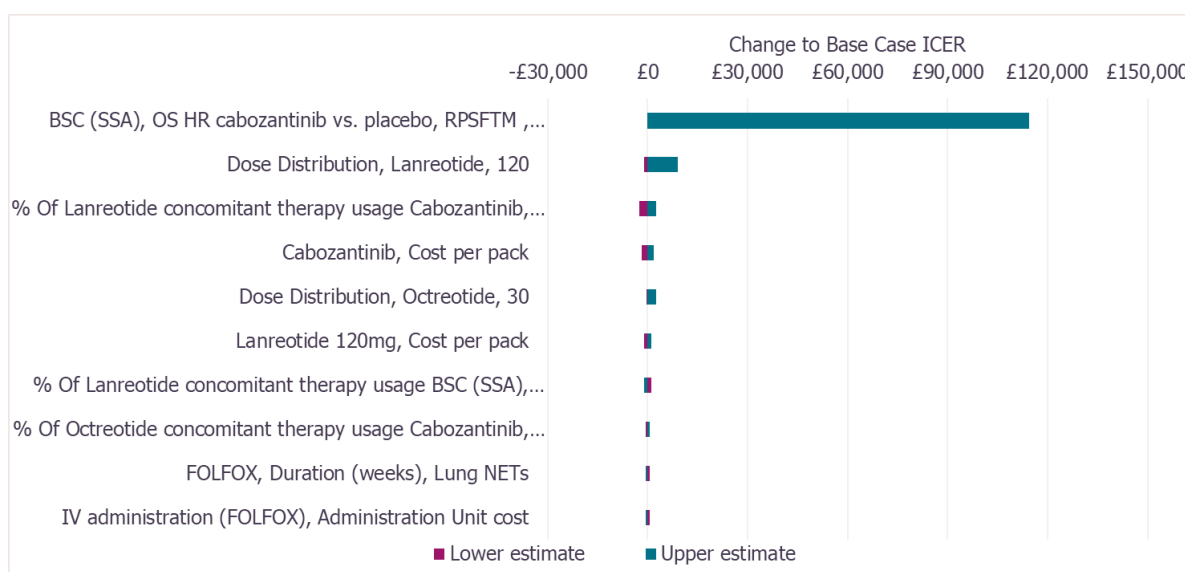
The one-way sensitivity analysis versus BSC in the CABINET population is shown in Figure 56, Figure 57 and Figure 58.

Figure 56. Tornado plot pNETs cabozantinib vs BSC



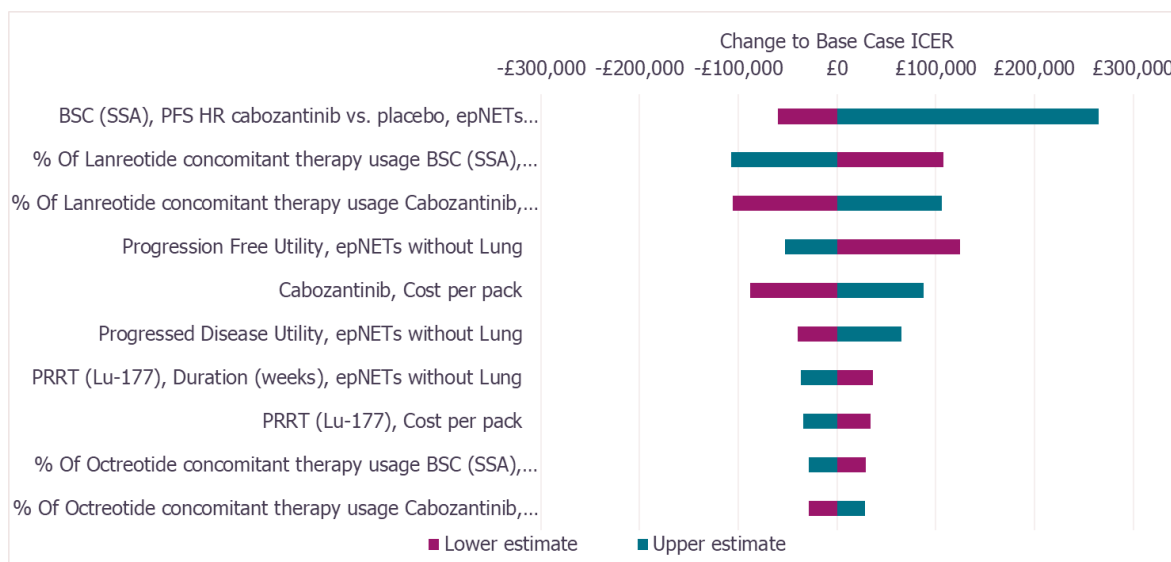
Abbreviations: BSC, best supportive care; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NET, neuroendocrine tumour; OS, overall survival; PFS, progression free survival; pNETs, pancreatic neuroendocrine tumours; QALY, quality-adjusted life year; RPSFTM, Rank preserving structural failure time model; WTP, willingness-to-pay.

Figure 57. Tornado plot lung NETs cabozantinib vs BSC



Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NET, neuroendocrine tumour; OS, overall survival; PFS, progression free survival; QALY, quality-adjusted life year; RPSFTM, Rank preserving structural failure time model; WTP, willingness-to-pay.

Figure 58. Tornado plot epNETs without lung cabozantinib vs BSC



Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression free survival; QALY, quality-adjusted life year; WTP, willingness-to-pay.

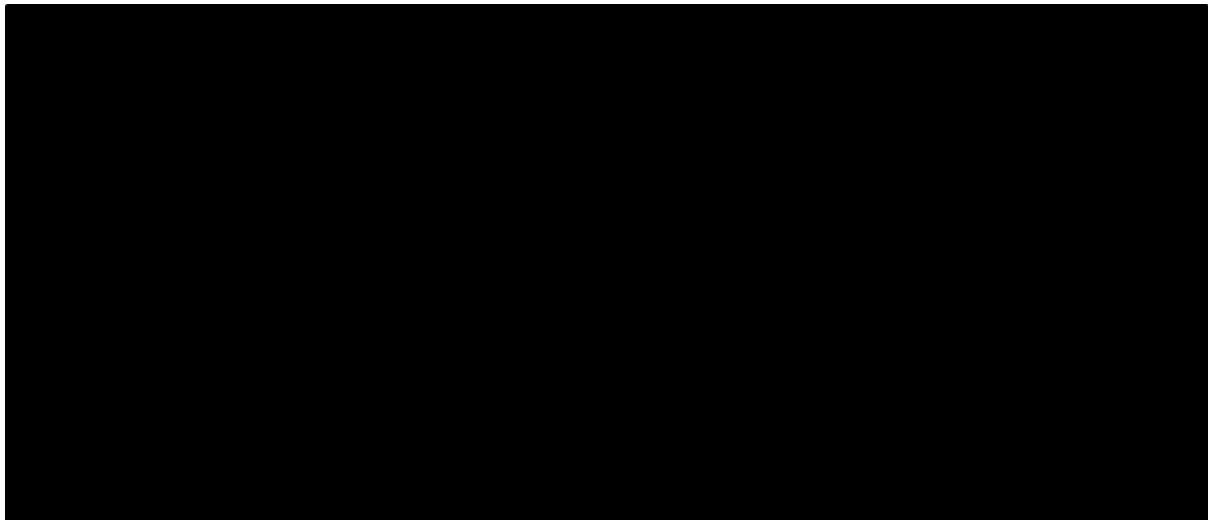
6.4.1.3 PSA EAG base case

Scatterplots illustrating PSA results in the cost-effectiveness plane, and cost-effectiveness acceptability curves (CEACs) are presented for each patient population below. In all cases, the deterministic and mean probabilistic results are closely aligned. Results for both the CABINET and less heavily pretreated populations are presented.

6.4.1.3.1 pNETs population

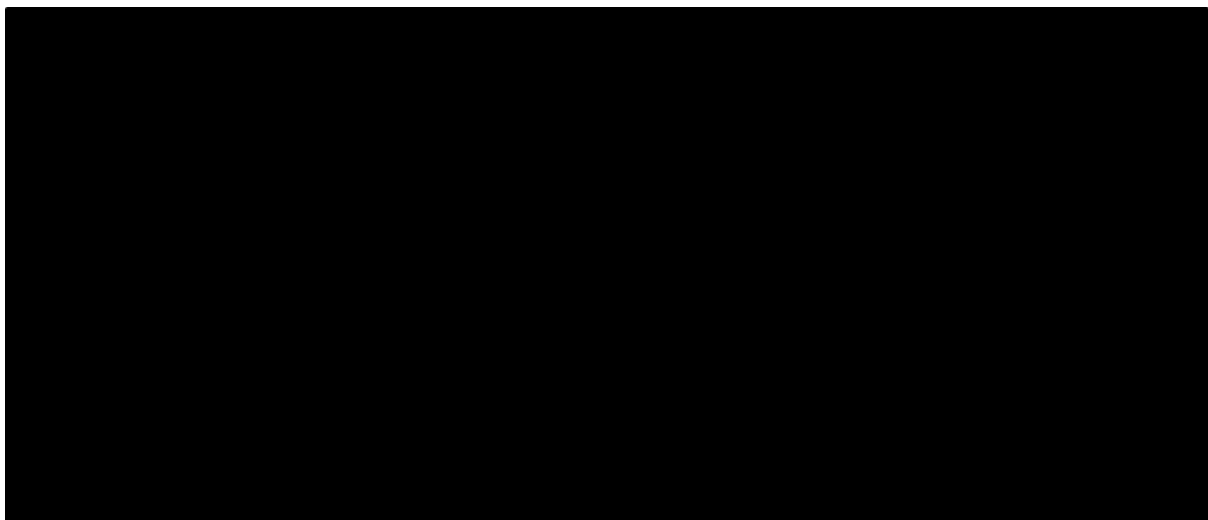
PSA scatterplots for pNET patients in the CABINET population with BSC as a comparator are presented in Figure 59 and a CEAC is presented in Figure 60.

Figure 59. Scatterplot of PSA estimates on a cost-effectiveness plane pNETs (CABINET, cabozantinib vs BSC)



Abbreviations: BSC, best supportive care; pNETs, pancreatic neuroendocrine tumours; QALY, quality-adjusted life year; WTP, willingness-to-pay.

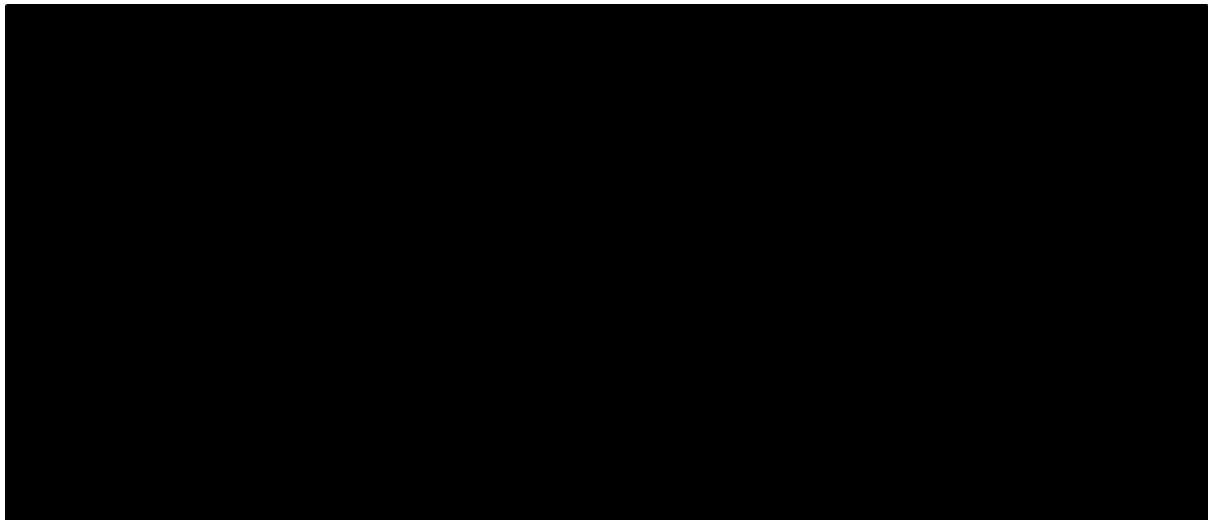
Figure 60. Cost-effectiveness acceptability curve pNETs (CABINET, cabozantinib vs BSC)



Abbreviations: BSC, best supportive care; pNETs, pancreatic neuroendocrine tumours; SSA, somatostatin analogue.

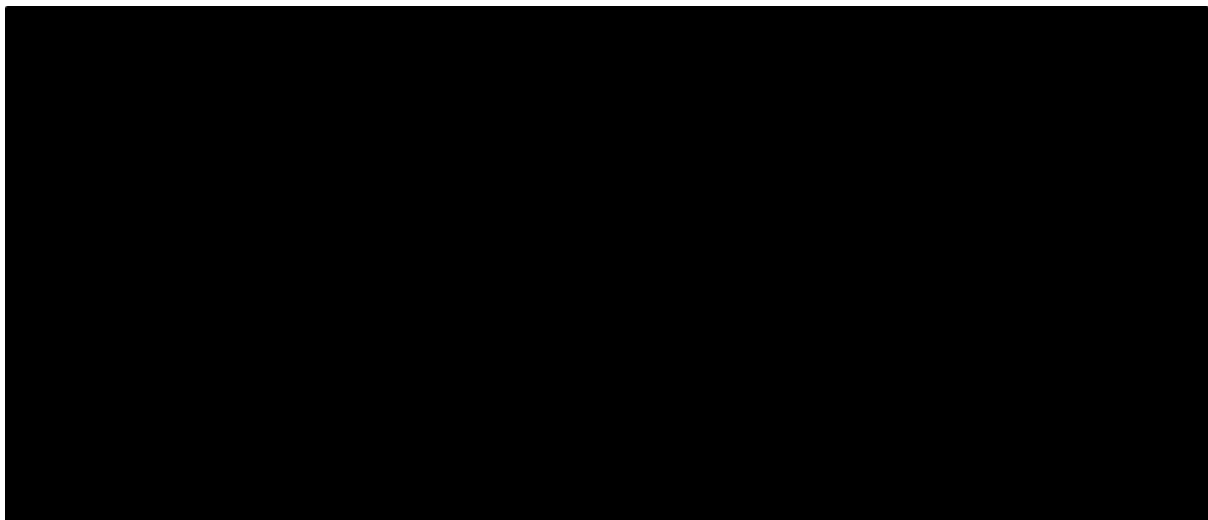
PSA scatterplots in the less heavily pretreated population for pNETs patients are shown in Figure 61 and Figure 62 for sunitinib and everolimus as comparators respectively. A CEAC is presented in Figure 63.

Figure 61. Scatterplot of PSA estimates on a cost-effectiveness plane pNETs (less heavily pretreated population, cabozantinib vs sunitinib)



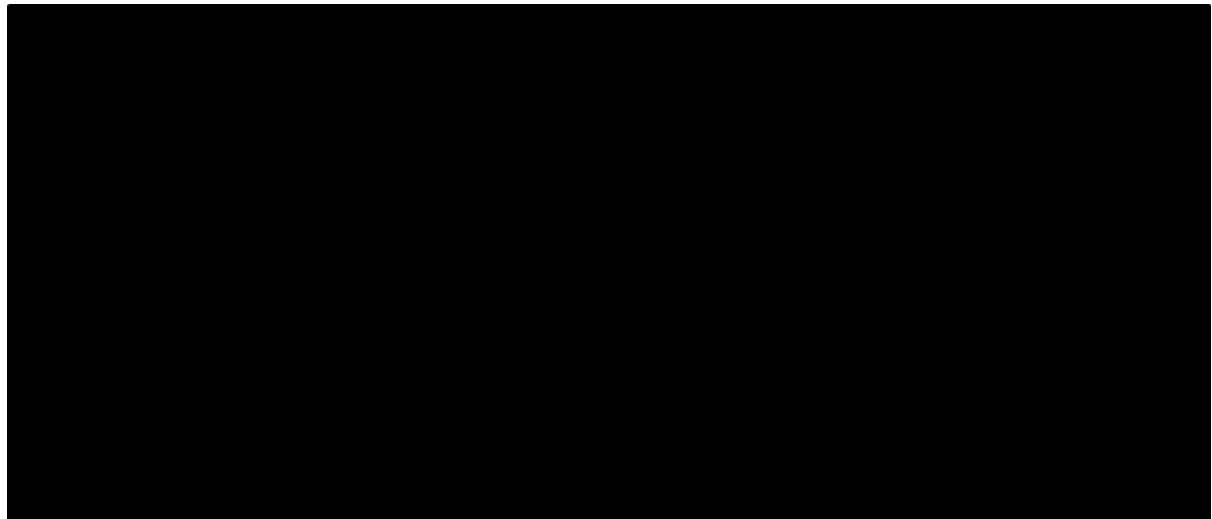
Abbreviations: pNETs, pancreatic neuroendocrine tumours; QALY, quality-adjusted life year; WTP, willingness-to-pay.

Figure 62. Scatterplot of PSA estimates on a cost-effectiveness plane pNETs (less heavily pretreated population, cabozantinib vs everolimus)



Abbreviations: pNETs, pancreatic neuroendocrine tumours; QALY, quality-adjusted life year; WTP, willingness-to-pay.

Figure 63. Cost-effectiveness acceptability curve pNETs (less heavily pretreated population, cabozantinib vs sunitinib and everolimus)

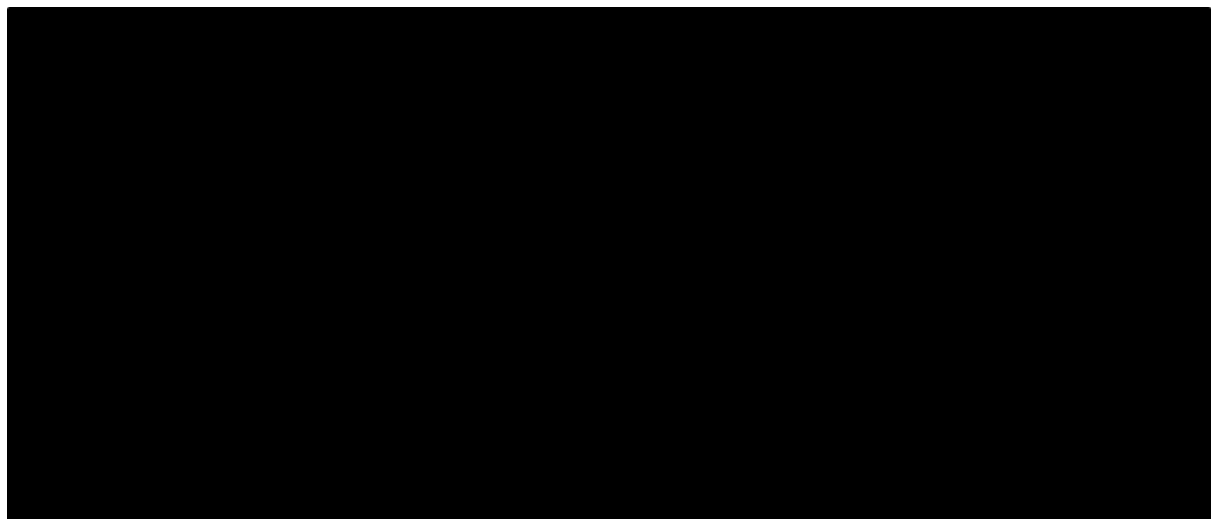


Abbreviations: pNETs, pancreatic neuroendocrine tumours.

6.4.1.3.2 epNETs lung population

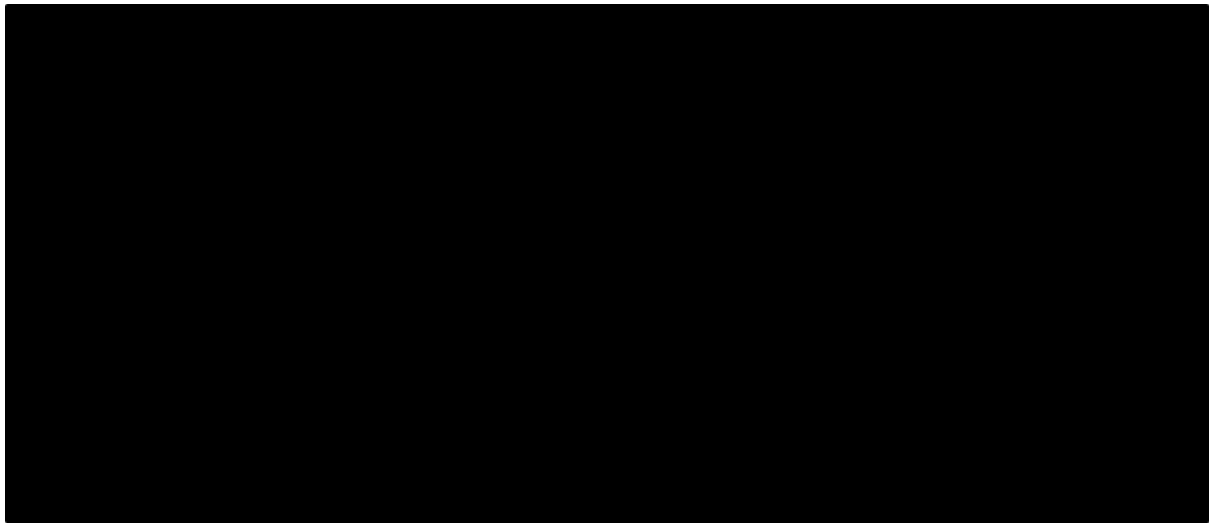
A PSA scatterplot for epNETs lung patients in the CABINET population with BSC as a comparator is presented in Figure 64 and a CEAC is presented in Figure 65.

Figure 64. Scatterplot of PSA estimates on a cost-effectiveness plane lung epNETs (CABINET, cabozantinib vs BSC)



Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; QALY, quality-adjusted life year; WTP, willingness-to-pay.

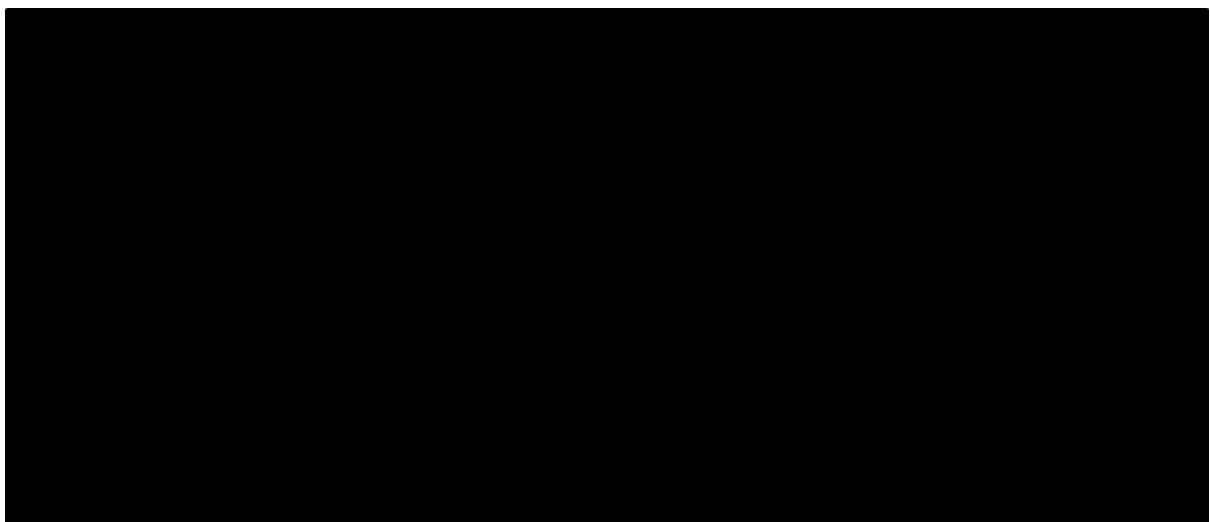
Figure 65. Cost-effectiveness acceptability curve epNETs lung (CABINET)



Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; SSA, somatostatin analogue.

PSA scatterplots for epNETs lung patients in the less heavily pretreated population, with everolimus as a comparator, is shown in Figure 66. A CEAC is not presented, as cabozantinib had a 0% probability of cost-effectiveness at all WTP thresholds tested.

Figure 66. Scatterplot of PSA estimates on a cost-effectiveness plane lung epNETs (less heavily pretreated population, cabozantinib vs everolimus)

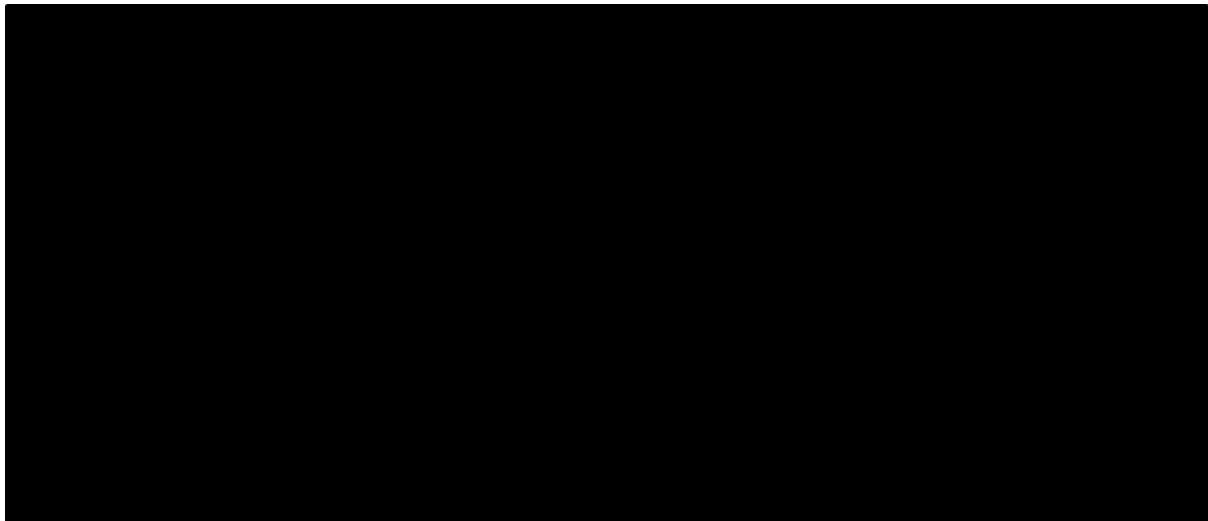


Abbreviations: epNETs, extra-pancreatic neuroendocrine tumours; QALY, quality-adjusted life year; WTP, willingness-to-pay.

6.4.1.3.3 epNETs without lung population

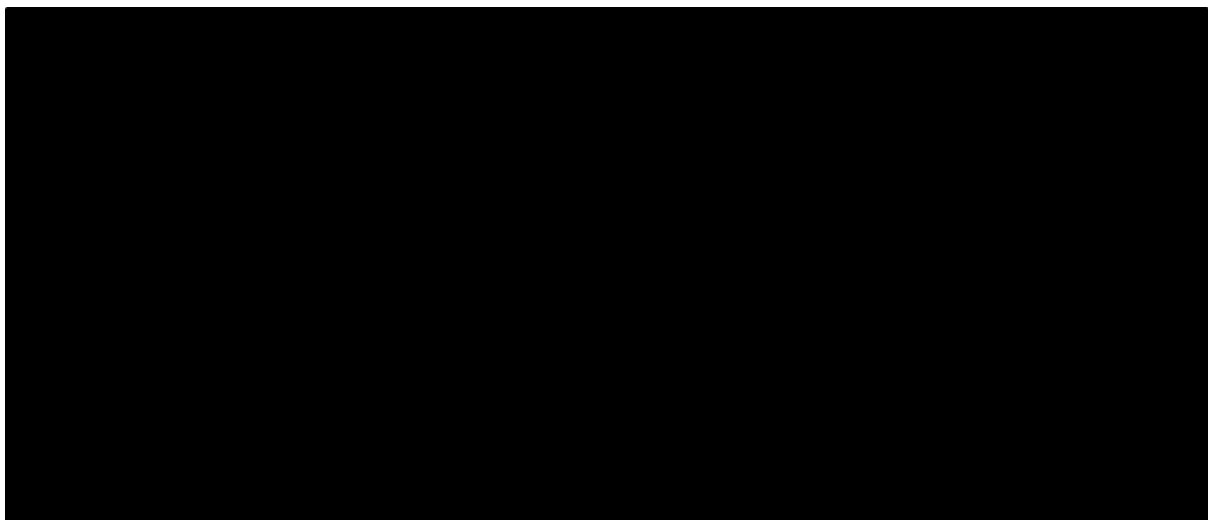
A PSA scatterplot for epNETs without lung patients in the CABINET population with BSC as a comparator is presented in Figure 67, Figure 64 and a CEAC is presented in Figure 65.

Figure 67. Scatterplot of PSA estimates on a cost-effectiveness plane epNETs without lung (CABINET, cabozantinib vs BSC)



Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; QALY, quality-adjusted life year; WTP, willingness-to-pay.

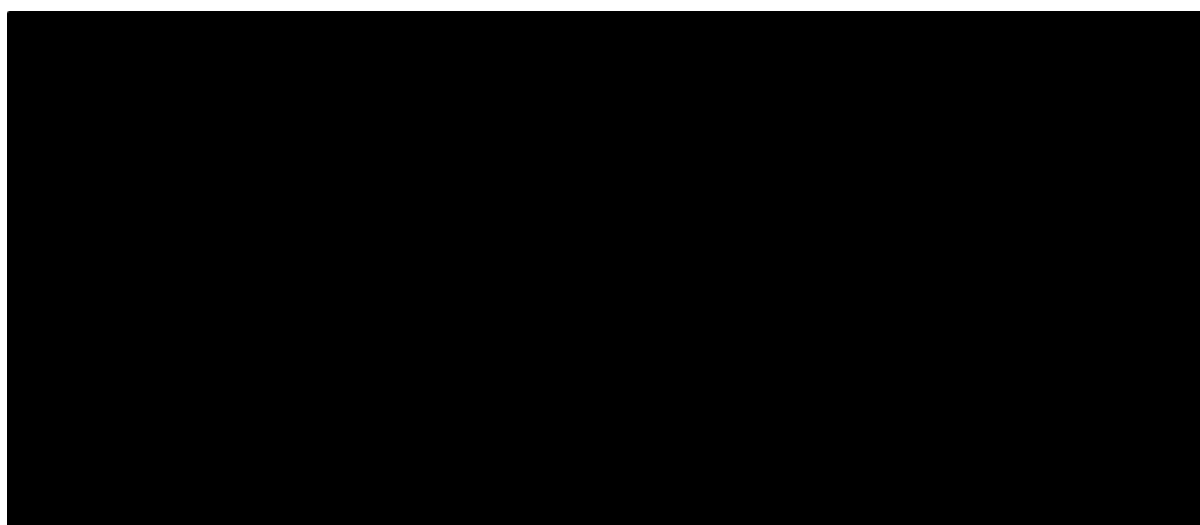
Figure 68. Cost-effectiveness acceptability curve epNETs without lung (CABINET)



Abbreviations: BSC, best supportive care; epNETs, extra-pancreatic neuroendocrine tumours; SSA, somatostatin analogue.

PSA scatterplots for epNETs without lung patients in the less heavily pretreated population, with everolimus as a comparator, is shown in Figure 69. A CEAC is not presented, as cabozantinib had a 0% probability of cost-effectiveness at all WTP thresholds tested.

Figure 69. Scatterplot of PSA estimates on a cost-effectiveness plane epNETs without lung (less heavily pretreated population, cabozantinib vs everolimus)



Abbreviations: epNETs, extra-pancreatic neuroendocrine tumours; QALY, quality-adjusted life year; WTP, willingness-to-pay. 'Cabozantinib FAC updated model epNET without lung MA.xlsm!individual_simulation_incrQALYs_live

6.4.2 Scenarios around the EAG base case

A number of scenarios were conducted around the EAG's base case, listed below:

- Scenario 1: A scenario was conducted using the EAG's base case assumptions on the pooled epNETs subgroup.
- Scenario 2: The EAG ran a scenario where Weibull curves were fitted for both the cabozantinib and the BSC PFS curves.
- Scenario 3: Using the original DCO for OS.
- Scenario 4: The EAGs preferred RPSFTM-adjusted OS HRs are used in the original DCO OS analysis, instead of the IPCW HRs preferred by the company.

- Scenario 5: Alternative utilities scenario using the utility value from CABINET for the PF state PF for both pNETs and epNETs and the Swinburn *et al.* 2012 decrement for PD for pNET patients and the RADIANT-4 decrement for epNETs.
- Scenario 6: alternative concomitant treatment (pNETs, epNETs without lung and epNETs lung): proportion of patients receiving concomitant treatment with SSAs was aligned with the proportion of patients with functional NETs in the CABINET trial, pooled between treatment arms (■■■ in the epNETs population and ■■■ in the pNETs population); lung epNETs and without lung epNETs were not considered separately due to lack of relevant data
- Scenario 7. Using lanreotide as the only SSA in the model.
- Scenario 8. Using octreotide as the only SSA in the model.

Results for the scenarios are reported in Table 84, Table 85 and Table 86 for pNETs, epNETs lung and epNETs without lung.

Table 84. Deterministic results of the EAG's scenario analyses around the EAG base case pNETs

	Incremental		ICER
	Costs	QALYs	
EAG base case			
Sunitinib (less heavily pretreated population)	■■■	■■■	£875,490
Everolimus (less heavily pretreated population)	■■■	■■■	£682,374
BSC (CABINET)	■	■	£137,794
Scenario 1: independently fitted Weibull curves BSC			
Sunitinib (less heavily pretreated population)	■■■	■■■	£875,490
Everolimus (less heavily pretreated population)	■■■	■■■	£682,374
BSC (CABINET)	■	■	£135,040
Scenario 2: Original DCO RPSFTM company OS extrapolations			
Sunitinib (less heavily pretreated population)	■■■	■■■	£1,013,718
Everolimus (less heavily pretreated population)	■■■	■■■	£808,033
BSC (CABINET)	■	■	£59,572
Scenario 3: Original DCO IPCW company OS extrapolations			

Sunitinib (less heavily pretreated population)	■	■	£1,013,718
Everolimus (less heavily pretreated population)	■	■	£808,033
BSC (CABINET)	■	■	£38,768
Scenario 4: HSUV scenario			
Sunitinib (less heavily pretreated population)	■	■	£671,860
Everolimus (less heavily pretreated population)	■	■	£511,576
BSC (CABINET)	■	■	£104,918
Scenario 5: alternative concomitant treatment			
Sunitinib (less heavily pretreated population)	■	■	£693,227
Everolimus (less heavily pretreated population)	■	■	£536,862
BSC (CABINET)	■	■	£138,278
Scenario 6: Only lanreotide			
Sunitinib (less heavily pretreated population)	■	■	£879,810
Everolimus (less heavily pretreated population)	■	■	£685,822
BSC (CABINET)	■	■	£137,789
Scenario 7: Only octreotide			
Sunitinib (less heavily pretreated population)	■	■	£860,175
Everolimus (less heavily pretreated population)	■	■	£670,147
BSC (CABINET)	■	■	£137,810
Abbreviations: BSC, best supportive care; DCO, data cut-off; HSUV, health state utility; ICER, incremental cost-effectiveness ratio; IPCW, inverse probability of censoring weights; QALY, quality adjusted life years; RPSFTM, rank preserving structural failure time model.			

Table 85. Deterministic results of the EAG's scenario analyses around the EAG base case epNETs lung

	Incremental		ICER
	Costs	QALYs	
EAG base case			
Everolimus (less heavily pretreated population)	■	■	£620,201
BSC (CABINET)	■	■	£17,758

Scenario 2: Original DCO RPSFTM			
Everolimus (less heavily pretreated population)	■	■	£618,657
BSC (CABINET)	■	■	£17,713
Scenario 3: Original DCO IPCW			
Everolimus (less heavily pretreated population)	■	■	£618,657
BSC (CABINET)	■	■	£17,278
Scenario 4: HSUV scenario			
Everolimus (less heavily pretreated population)	■	■	£620,201
BSC (CABINET)	■	■	£19,736
Scenario 5: alternative concomitant treatment			
Everolimus (less heavily pretreated population)	■	■	£595,202
BSC (CABINET)	■	■	£17,276
Scenario 6: Only lanreotide			
Everolimus (less heavily pretreated population)	■	■	£623,811
BSC (CABINET)	■	■	£17,840
Scenario 7: Only octreotide			
Everolimus (less heavily pretreated population)	■	■	£607,402
BSC (CABINET)	■	■	£17,467
Abbreviations: BSC, best supportive care; DCO, data cut-off; HSUV, health state utility; ICER, incremental cost-effectiveness ratio; IPCW, inverse probability of censoring weights; QALY, quality adjusted life years; RPSFTM, rank preserving structural failure time model.			

Table 86. Deterministic results of the EAG's scenario analyses around the EAG base case epNETs without lung

	Incremental		ICER
	Costs	QALYs	
Base case			
Everolimus (less heavily pretreated population)	■	■	£3,042,543
BSC (CABINET)	■	■	£197,483
Scenario 2: Original DCO RPSFTM company OS extrapolations			
Everolimus (less heavily pretreated population)	■	■	£3,167,021

BSC (CABINET)	■	■	-£9,498
Scenario 3: Original DCO IPCW company OS extrapolations			
Everolimus (less heavily pretreated population)	■	■	£3,167,021
BSC (CABINET)	■	■	-£85,052
Scenario 4: HSUV scenario			
Everolimus (less heavily pretreated population)	■	■	£2,535,453
BSC (CABINET)	■	■	£164,569
Scenario 5: alternative concomitant treatment			
Everolimus (less heavily pretreated population)	■	■	£2,931,273
BSC (CABINET)	■	■	£206,388
Scenario 6: Only lanreotide			
Everolimus (less heavily pretreated population)	■	■	£3,058,612
BSC (CABINET)	■	■	£197,400
Scenario 7: Octreotide			
Everolimus (less heavily pretreated population)	■	■	£2,985,575
BSC (CABINET)	■	■	£197,777
Abbreviations: BSC, best supportive care; DCO, data cut-off; HSUV, health state utility; ICER, incremental cost-effectiveness ratio; IPCW, inverse probability of censoring weights; QALY, quality adjusted life years; RPSFTM, rank preserving structural failure time model.			

Table 87. epNETs EAG base case scenario

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results (less heavily pretreated population population)							
Cabozantinib	■	2.31	■	-	-	-	-
Everolimus	■	2.31	■	■	■	■	£1,628,114
Deterministic results (CABINET population)							
Cabozantinib	■	2.31	■	-	-	-	-
BSC	■	2.31	■	■	■	■	£120,050
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year							

6.5 Conclusions of the cost effectiveness sections

The company have positioned the treatment in line with their marketing authorisation as a second line systemic treatment. The clinical evidence from CABINET represents patients who are heavily pretreated, but does not reflect the population who are at an earlier stage in the treatment pathway and may have had only one prior systemic treatment (other than an SSA). Patients eligible to receive cabozantinib as a second-line systemic treatment (after SSAs) are eligible for other systemic treatments in the NHS such as PRRT, everolimus or sunitinib. The EAG performed exploratory Bucher ITCs to compare results from the CABINET trial with those from other trials which had been included in previously published NICE TAs for everolimus and sunitinib for patients with pNETs, epNETs, lung NETs or epNETs (without lung). Comparisons with PRRT were not possible.

The company have stated a preference to use data from the original data cut-off point as the updated DCO was derived from an unplanned OS sweep. Overall, the EAG notes a paramount level of uncertainty around the relative effectiveness of cabozantinib vs BSC; everolimus and sunitinib on OS. Results of the CABINET trial showed a PFS advantage for cabozantinib over placebo for in both the pNET and epNET cohorts. In contrast, results for OS were non-significant, and numerically favoured placebo in the updated DCO OS data. However, results of the OS analysis are subject to a number of limitations, including potential data immaturity and small number of patients in the placebo groups, which rendered the results of cross-over adjustment survival highly uncertain. The EAG considered the apparent discrepancy in the direction of the PFS and OS results in the CABINET trial, particularly when the updated DCO OS data are used. The EAG's preference remains to use the more mature OS data, and notes that 12 months of additional OS trial data should not be ignored (as is the company's preference in their base case). The EAG acknowledges that the number of patients in CABINET is considerably small, leading to a small number of patients crossing over and a reduced number of OS events in patients who crossed over. Consequently, OS results with different adjustment methods are uncertain. The EAG concluded that assuming equal survival for cabozantinib and BSC in the economic model was a more plausible approach than using the ITT or the RPSFTM HRs for the updated DCO. The latter imply a survival advantage for placebo against cabozantinib, which lacks clinical validity.

In the EAG's exploratory ITC, for PFS and OS, there were no statistically significant differences between cabozantinib and either everolimus or sunitinib for any group, with everolimus showing a numerical PFS advantage against the treatments and a numerical disadvantage for OS. The EAG

caveats its exploratory analysis results by the fact that there were marked differences in trial populations and number of previous treatments received across the different trials included in the ITCs which are impossible to address with Bucher ITCs. Instead, the EAG considers that more advanced methods (such as matching-adjusted indirect comparisons -MAICs) could provide a more robust method of analysis for comparisons between cabozantinib (using the CABINET subgroup of patients who had only received one prior systemic treatment, other than SSAs) and everolimus or sunitinib, taking into account difference in trial populations.

The EAG considered the apparent discrepancy in the direction of the PFS and OS results in its exploratory analysis. Furthermore, the EAG considered external evidence showing that cabozantinib has a statistically significant survival advantage over everolimus in previously treated advanced renal cell carcinoma (METEOR trial) and a numerical but not statistically significant OS benefit against sunitinib (CABOSUN trial). After consideration of the evidence, the EAG concluded that assuming a PFS benefit for cabozantinib (i.e., using the Bucher exploratory HRs) and assuming equal survival for cabozantinib, everolimus and sunitinib in the economic model reflected a more clinically plausible approach, while still reflecting the uncertainty around the survival benefits for cabozantinib.

The EAG acknowledges the uncertainty in using the post-hoc lung NETs and epNETs without lung results in the model, however, notes it is apparent from the observed analysis that benefit for cabozantinib in CABINET in the epNET population is likely being driven by the lung NET population. The EAG also notes that there is a marked difference in baseline characteristics of patients in the cabozantinib and the placebo arms for the lung NET group, which could potentially bias the results in favour of cabozantinib, as they appear to be indicative of a worse prognosis in the placebo group. To illustrate this, if the original DCO were to be used and the IPCW crossover method, cabozantinib is still not cost-effective at a threshold of £30,000, versus BSC, in the EAG base case for either epNET without lung group. When epNET is split into the two groups cabozantinib is not cost-effective at £30,000 in the w/o lung group even with all the company base case assumptions with an ICER of £164,975 vs BSC.

In epNET lung cabozantinib does appear to be cost-effective versus placebo at a WTP of £20,000, given an ICER vs BSC of £12,737. However, in patients with functional NETs who had previously been treated with chemotherapy everolimus would be a relevant comparator. Cabozantinib is not likely to be cost-effective versus everolimus in this group of patients given significantly lower cost and approximately equal efficacy (based on ITC results).

The pNET population is significantly impacted by use of the later DCO, yet, even if the original DCO were used with the company preference of crossover method (IPCW) the treatment would not be cost-effective versus BSC at an ICER of £49,208. As the company submitted ICER was between £20,000 and £30,000 for pNET it is more likely to be raised over a £30,000 WTP threshold by the cumulative impact of the less significant key issues, with cabozantinib only remaining under £30,000 in 9 of the 14 scenario analysis conducted by the EAG individually, using the company base case (see Table 75).

In addition, the pNET population has an additional comparator in the less heavily pretreated population(sunitinib) and in no scenario conducted by the EAG is cabozantinib cost effective versus sunitinib or everolimus. This is also true when comparing cabozantinib to everolimus in the lung NET and epNET without lung population.

7 Severity modifier

The company carried out severity modifier calculations using an automatic function in the economic model. Expected total quality-adjusted life expectancy (QALE) for the general population was estimated using general population mortality data informed by Office for National Statistics life tables (2021-2023) and UK population EQ-5D HRQoL values from Hernández Alava *et al.* 2020.^{76, 77} Separate estimates were calculated for the pNETs and epNETs populations, based on the age at baseline and sex of the relevant population of the CABINET trial. Discounting of 3.5% per year was applied.

QALE for people living with NETs receiving current treatment was also estimated separately for the pNETs and epNETs populations, and aligned with the total QALYs estimated for the BSC arm for the relevant population (with 3.5% per year discounting applied). The EAG notes that QALE for people living with NETs was informed by OS for the BSC population in the model, which was calculated by applying a crossover-adjusted HR to OS for the cabozantinib population; hence, the EAG's concerns around uncertainty in OS also apply to the severity modifier calculations.

The EAG considers that the approach for estimating QALE for the general population was appropriate. However, the EAG's preferred approach for estimating QALE for people with NETs aligns with the EAG's base case as follows:

- The latest DCO was used to inform BSC OS (Sections 4.2.3.1.4.2 and 4.2.3.1.4.3);
- The EAG's preferred choice of OS curve used for cabozantinib was used, with BSC OS calculated by applying RPSFTM adjustment and capping of OS HRs for BSC at 1 (Section 4.2.3.1.4.3);
- EAG-preferred HSUVs were used (Section 4.2.6.1.1);
- Disutilities for AEs were applied during the first cycle, with EAG-preferred disutilities (Sections 4.2.5.1 and 4.2.6.2.1).

The EAG also considered the epNET with and without lung populations separately.

The EAG performed severity modifier calculations separately for the CABINET trial population and for the exploratory analysis in the less heavily pretreated population. The relevant current treatment was considered to be BSC in the CABINET population. For the less heavily pretreated population, the

current treatment was aligned with the comparator with the highest total QALY estimate, i.e. sunitinib for pNETs, and everolimus for epNETs without lung and lung NETs.

Results of the severity modifier calculations and consequent weighting are found in

Table 88. In the company's analysis, the epNET population was found to qualify for a severity modifier of 1.2, and the pNET population was found not to qualify for a severity modifier. In the EAG's analysis, the lung NETs population was found to qualify for a severity modifier of 1.2 in both the less heavily pretreated and CABINET trial populations, but the pNETs and epNETs without lung populations were found not to qualify for a severity modifier.

Table 88. Summary features of QALY shortfall analysis: EAG and company base case

Population	Expected total QALE for the general population	Current treatment	Total QALE that people living with NETs would be expected to have with current treatment	Absolute QALE shortfall	Proportional shortfall	Severity weighting
Company base case						
pNETs	12.61	BSC	2.23	10.39	0.82	1.00
epNETs	11.61	BSC	1.13	10.48	0.90	1.20
EAG base case (CABINET population)						
pNETs	12.61	BSC	2.19	10.42	0.83	1.00
epNET lung	11.61	BSC	0.68	10.93	0.94	1.20
epNET without lung	11.61	BSC	1.89	9.72	0.84	1.00
EAG base case (less heavily pretreated population population)						
pNETs	12.61	Sunitinib	2.28	10.34	0.82	1.00
epNET lung	11.61	Everolimus	1.36	10.25	0.88	1.20
epNET without lung	11.61	Everolimus	1.91	9.71	0.84	1.00
Abbreviations: EAG, External Assessment Group; epNETs, extra-pancreatic neuroendocrine tumours; pNETs, pancreatic neuroendocrine tumours; NETs, neuroendocrine tumours, QALE, quality-adjusted life expectancy.						

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9 Appendices

9.1 Price sources for treatments included in the confidential appendix

Table 89. Source of the confidential prices used in the confidential appendix

Treatment	Source of price/type of commercial arrangement
Lutetium (177Lu) oxodotreotide (solution for infusion)	Simple PAS
Lanreotide (Injection vial)	commercial access agreement procured through MPSC
Octreotide (Injection vial)	commercial access agreement procured through MPSC

Abbreviations: PAS, patient access scheme; MPSC, medicines procurement supply chain.

9.2 EAG critique for OS data cut

The EAG considers that the latest data cut-off: 4 September 2024, should be used to inform the analysis. That being said, the EAG has prepared a critique of the company base case data cut-off 24 August 2023.

As discussed in section 3.4.2.2, the EAG preference is for RFSFTM (Rank Preserving Structural Failure Time Model). Progressed is a relative statement in the context of this trial, as there are patients who are progressed into a disease condition equivalent to some of the progression-free patients' disease status at baseline. This also means there is variability in the number of lines of therapy received by patients at baseline. Also, sensitivity analysis around the common treatment effect assumption, provided at clarification, grant credence to the key assumption of RPSFTM of a common treatment effect having limited impact on the HR. This was shown in table 19 of the company clarification response, which illustrated that assuming a common treatment effect vs assuming a [REDACTED] acceleration factor (reduction in OS had patients not switched to cabozantinib) resulted in only a [REDACTED] change in the HR for pNET and epNET. However, for lung NETs no RPSFTM adjusted HR has been provided so the EAG base case uses IPCW, though RPSFTM would appear more appropriate.

The EAG disagrees with the company's use of a HR, although it is acknowledged that a proportional hazards assumption would be reasonable. An independently fitted curve provides a more flexible extrapolation, producing more plausible results. Since the purpose of the economic evaluation is to compare the two treatments, use of a HR represents a restrictive assumption that could lead to not accurately measuring the difference between treatments.

Ideally the EAG would test independent extrapolations on the company's base case, but at clarification the company confirmed that they could not produce reliable KM curves for IPCW adjusted data.

As with PFS, the company only provided KM data for the cabozantinib arm for the epNET lung and without lung subgroup, for the BSC arm they applied the HR derived from the total epNET population. This is inappropriate for the same reason described in Section 4.2.3.1.3. Following a post-clarification request the company was able to provide the HRs for the specific subgroups (epNET [lung] and epNET [without lung]), though only IPCW crossover and ITT HRs were provided for lung NETs.

Table 90. EAG and company preferred OS curves summary

Subgroup	Company base case		EAG base case	
	Cabozantinib	BSC	Cabozantinib	BSC
pNET	Exponential	HR [REDACTED]	Exponential	Exponential
epNET	LogLogistic	HR [REDACTED]	Weibull	Weibull
epNET (lung)	Weibull	HR IPCW (epNET) [REDACTED]	Weibull	HR IPCW (epNET lung) [REDACTED]
epNET (w/o lung)	LogLogistic	HR IPCW (epNET) [REDACTED]	LogLogistic	HR IPCW (epNET w/o lung) [REDACTED]

Abbreviations: BSC, best supportive care; EAG, external assessment group; HR, hazard ratio; w/o, without.

9.2.1 Population reflecting the less heavily pretreated population – everolimus and sunitinib as comparators

The OS curves derived from the HR ITC are shown in Figure 70, Figure 71, Figure 72 and Figure 73 for pNET, epNET, lung NET and epNET without lung respectively. Compared to cabozantinib, there is a none statistically significant OS benefit for both sunitinib and everolimus in pNET, this is also the case vs everolimus in epNET. Only RPSFTM crossover was available to produce the HRs for the curves.

Figure 70. OS extrapolations, additional comparators RPSFTM (pNET)

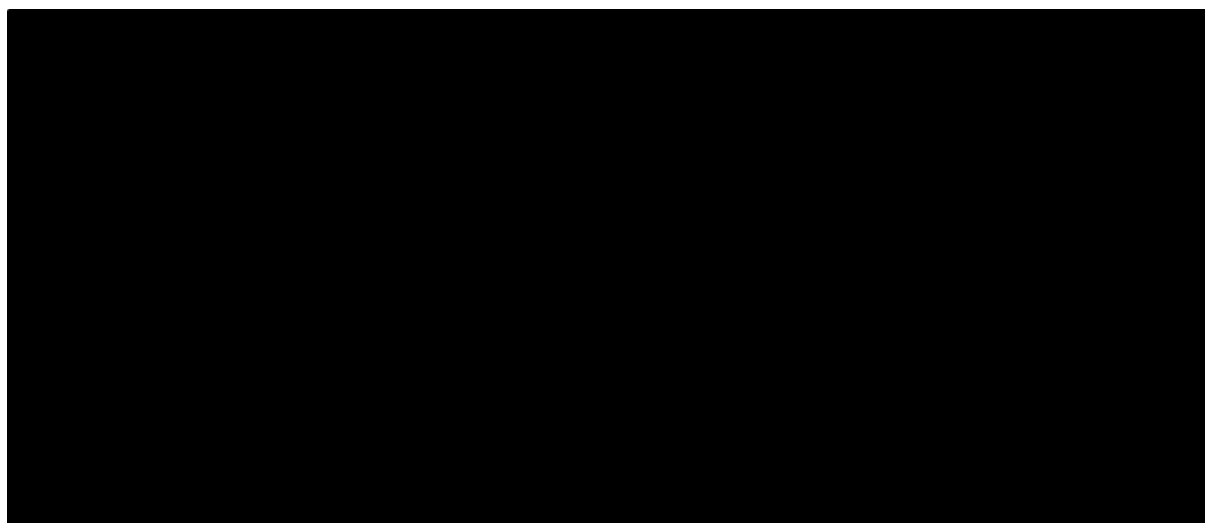


Figure 71. OS extrapolations, additional comparators (epNET)

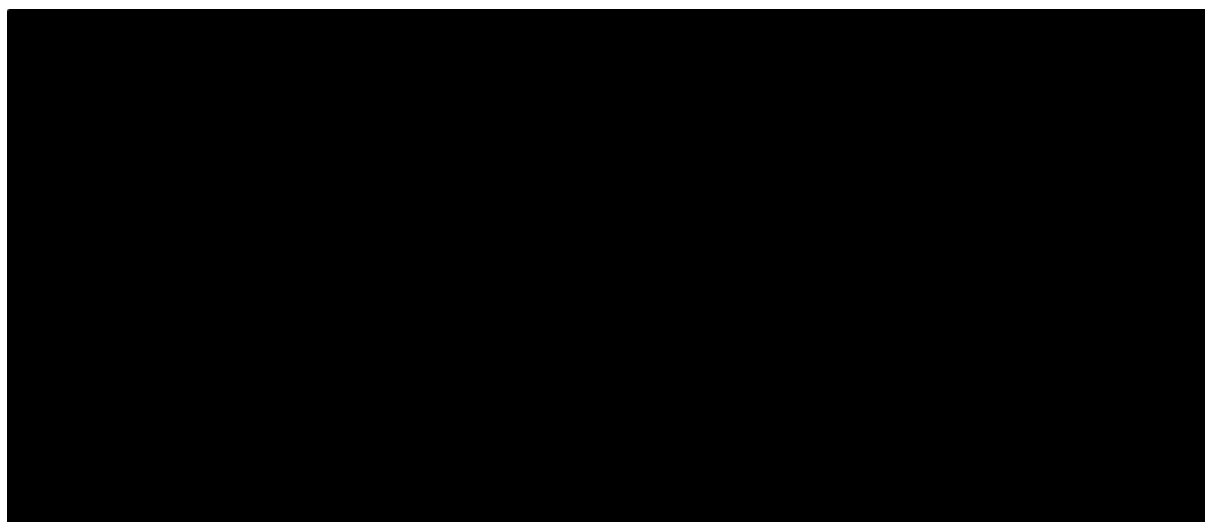


Figure 72. OS extrapolations, additional comparators (lung NETs)

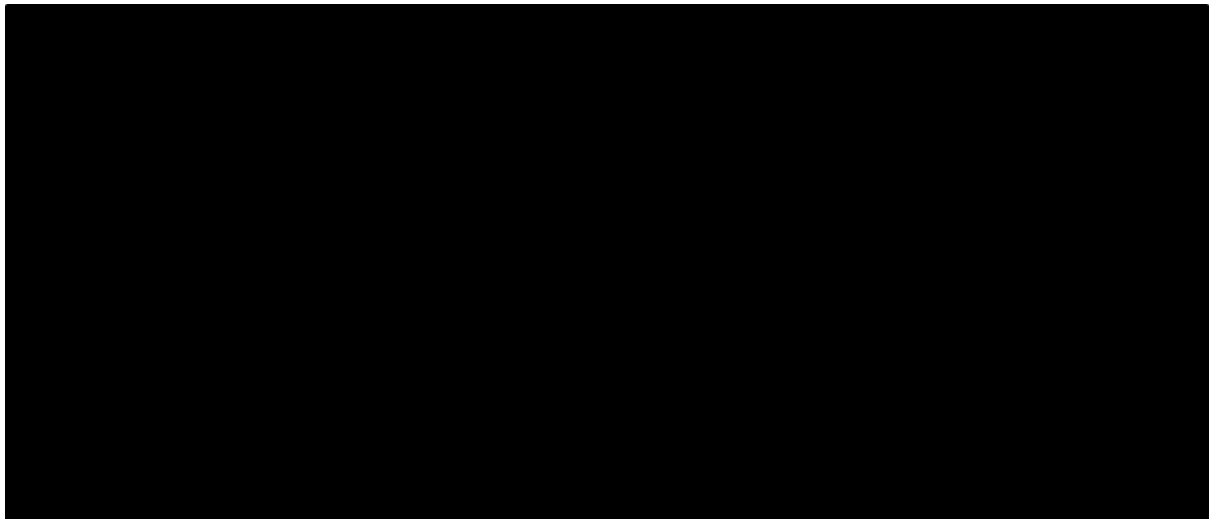
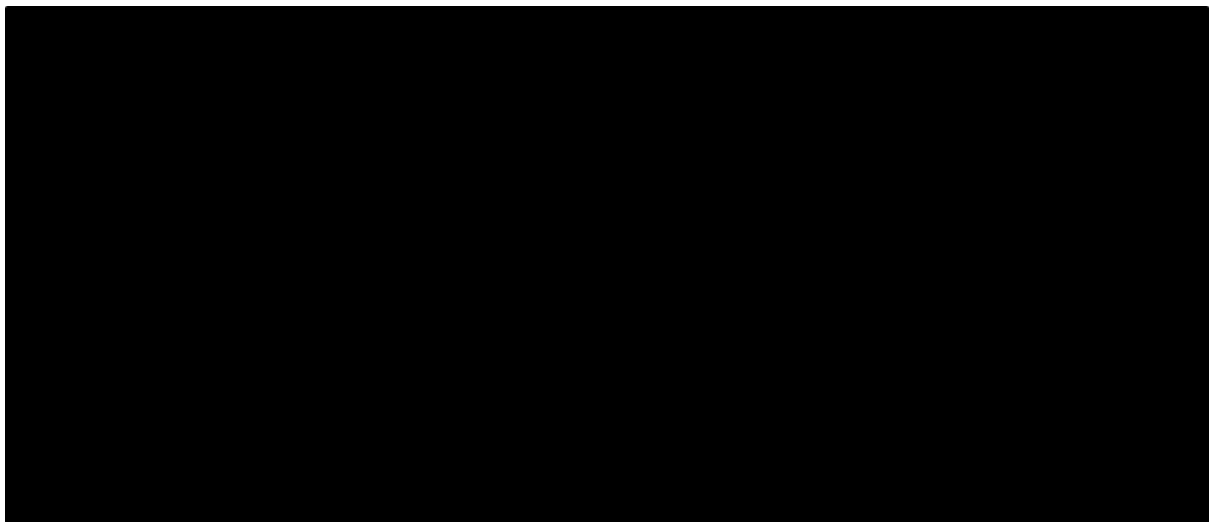


Figure 73. OS extrapolations, additional comparators (epNET without lung)



As with the ITC ran against the second DCO, after consideration of the evidence, the EAG concluded that assuming equal survival for cabozantinib, everolimus and sunitinib in the economic model was a more plausible approach than using the exploratory ITC results showing a PFS advantage for cabozantinib and an OS disadvantage for the treatment against everolimus and sunitinib. Results of the EAG's exploratory analysis are reported in Section 6. Additional details on the reasoning for this can be found in section 4.2.3.3.

Single Technology Appraisal

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 23 July 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as **“confidential”** should be highlighted in turquoise and all information submitted as **“depersonalised data”** in pink.

Issue 1 Identified Factual Issues

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 25, Section 1.3, Table 2 states: <i>“the CABINET population does not fully reflect the population in the company’s marketing authorization”</i> <i>“The second population reflects the anticipated marketing authorisation and the company’s intended positioning for cabozantinib in the treatment pathway, which is as a second (or further) line systemic treatment option. These patients are earlier in the treatment pathway than those in the CABINET trial, having had one (or more) prior</i>	All instances where the EAG have referred to a misalignment of the CABINET population and the marketing authorisation should be amended to ensure it is not implied that these populations are mutually exclusive. The company acknowledge that the CABINET eligibility criteria and the marketing authorisation are broad, and thus it is possible that the population eligible for treatment with cabozantinib in clinical practice under the marketing authorisation may differ from the CABINET population, which enrolled a substantial proportion of patients with multiple treatment failures. Any text representing the “marketing authorisation population” and the “CABINET population” as mutually exclusive populations that make up the “overall population eligible to receive cabozantinib” should be removed or amended. The “marketing authorisation population” could instead be termed an “earlier	The marketing authorisation wording for cabozantinib was informed by the eligibility criteria for the CABINET trial, and thus it is misleading to suggest that these populations are misaligned or mutually exclusive. The company acknowledge that both the CABINET eligibility criteria and the marketing authorisation wording are broad in nature, and therefore in principle could encompass a broad range of potentially eligible patients. The company acknowledge that the CABINET trial population enrolled a large proportion of heavily pre-treated patients, but in line with the eligibility criteria (which is reflected in the wording of the marketing authorisation), CABINET	For clarity, the EAG has changed the title of the exploratory ITC population to the <i>“less heavily pretreated population”</i>. The EAG also acknowledged the subgroup of patients from CABINET who have received only one previous systemic treatment in their report. Additionally, the EAG has added a request for the company to use this subgroup in any future ITCs for comparator treatments.

<i>systemic treatments (excluding SSAs)."</i> Page 47, Section 2.3: <i>"The EAG notes that the population in CABINET was heavily pretreated"... "Therefore, patients were at a late stage in the treatment pathway, where the only remaining option for most patients in the NHS would be BSC. In contrast, the marketing authorisation positions cabozantinib as a second (or further) systemic treatment line (other than previous treatment with an SSA), at which stage other systemic therapies are treatment options in the NHS."</i>	line population" where other systemic treatments may be relevant alternative treatment options. However, both an earlier line population and the CABINET population could in principle be captured within the broad marketing authorisation, but it cannot be implied that the marketing authorisation and CABINET are mutually exclusive. All statements where the EAG have suggested the CABINET trial reflects cabozantinib positioning to a specific later line of therapy such as third-line or fourth-line and so on should be amended, given these statements are explicitly misaligned with the CABINET trial eligibility criteria, and thus the population enrolled in the CABINET trial, which included a significant minority of patients who had received only one prior systemic treatment other than an SSA.	also includes a significant proportion of patients that have only had one prior systemic treatment other than an SSA. In epNETs 44% and 48% in the cabozantinib and placebo arm, respectively had received only one prior line of therapy. For pNETs 27% and 32% of patients had only prior line of therapy in the cabozantinib and placebo arms, respectively. Suggesting the positioning of cabozantinib in line with the CABINET population reflects third or fourth lines, as specified throughout the EAG report, excludes patients who would be eligible to receive cabozantinib after one prior systemic treatment and where BSC would be their only option. This includes the vast majority of patients with lung NETs (where the only other available systemic	

Page 48, Section 2.3 and page 55, Section 2.3.1: <i>“The CABINET population, who are heavily pretreated, and reflect NHS patients who may receive cabozantinib as a fourth (or further) line of systemic treatment for pNETs (excluding prior SSAs)”</i> Page 54, Section 2.3.1: <i>"In contrast to the CABINET trial, the marketing authorisation positions cabozantinib as a second (or further) systemic treatment line (other than previous treatment with an SSA)."</i> Page 55, Section 2.3.1: <i>“The CABINET population, who are</i>		treatment other than chemotherapy is everolimus) or functional GI NETs, who are currently captured within the CABINET trial population, and for which there is the highest unmet need for new treatment options. The suggestion that the CABINET trial population reflects a third or fourth-line positioning is a misrepresentation and oversimplification of the treatment pathway. The company are positioning cabozantinib in line with the population enrolled in the CABINET trial, but maintain that this population is in line with the population of patients who would be treated in clinical practice under the marketing authorisation (despite the broad nature of the marketing authorisation wording). This is supported by feedback from the EAG's	

<i>heavily pretreated, and reflect NHS patients who may receive cabozantinib as a fourth (or further) line of systemic treatment for pNETs (excluding prior SSAs); or epNET patients who may receive cabozantinib as a third (or further) line of systemic treatment, excluding prior SSAs. BSC is an appropriate comparator for this group”</i> Page 59, Section 2.3.1: <i>“The EAG’s clinical experts also added that, currently, they would not want to prescribe cabozantinib as an earlier treatment line than that reflected in the CABINET trial, as no evidence is available for treatment effectiveness in that setting.”</i>		own clinical experts, who added that, currently, they would not want to prescribe cabozantinib as an earlier treatment line than that reflected in the CABINET trial, as no evidence is available for treatment effectiveness in that setting. Clinical experts confirmed that BSC was the most relevant comparator for this patient population.	

Page 73, Section 3.2: <i>“where cabozantinib is given as a fourth (or further) line of systemic treatment for pNET patients (excluding previous SSAs); and as a third (or further) line of systemic treatment for epNET patients, excluding previous SSAs.”</i> Page 197, Section 6.2 <i>“The EAG also notes that even though the analyses for the CABINET and the marketing authorisation populations have been considered separately in the EAG report, it is the combined CABINET and marketing authorisation populations that constitute the overall population eligible to receive cabozantinib”</i>			

Page 222, Section 6.5: <i>“The company have positioned the treatment in line with their marketing authorisation as a second line systemic treatment”</i> <i>“The clinical evidence from CABINET only represents patients who are heavily pre-treated, and does not fully reflect the population in the company’s marketing authorisation who may have had only one prior systemic treatment (other than an SSA).”</i>			
Page 25, Section 1.3, Table 2 states: <i>“The EAG caveats the results of its exploratory ITC by the fact that there were marked differences</i>	The second statement should be corrected to: <i>“the company did not deem a robust ITC to be feasible for a comparison with the other comparators outlined in the NICE final scope, as part of their feasibility assessment”</i>	The company conducted a comprehensive feasibility assessment for an ITC versus other systemic therapies which indicated a robust ITC was not feasible, and this feasibility assessment is presented in	The EAG thanks the company for highlighting this omission. Changes have been made to Sections 1.3 and 3.4 to acknowledge the company’s feasibility assessment.

<i>in trial populations and in the number of previous treatments received across the different trials included in the ITCs, which the EAG was unable to address with the available data (but which the company could attempt to resolve“</i> Page 103, Section 3.4: <i>“the company did not consider it necessary to perform any indirect treatment comparisons (ITCs) for the other comparators in the NICE final scope”</i>	All instances where the EAG refer to ITCs should acknowledge that the company completed an in-depth ITC feasibility assessment, outline the methodology of this assessment and acknowledge the conclusions drawn, before stating the EAG’s conclusion around the robustness of an exploratory ITC. All information regarding the ITC feasibility assessment was provided to the EAG in Appendix A of the company’s responses to the EAG CQs.	full in Appendix A of the responses to the EAG CQs. To the company’s knowledge, there is no reference to the company’s ITC feasibility assessment throughout the EAG report. This assessment evaluated the feasibility of an ITC at length, providing multiple limitations that precludes a robust ITC versus other systemic treatments. These included, but were not limited to small sample sizes in CABINET, widespread differences in many relevant treatment effect modifiers (TEMs), incomplete reporting on TEMs in comparator trials, non-eligibility of certain patient groups in CABINET and non-stratification of epNET subgroups. It is factually inaccurate to suggest that the company	

		did not consider conducting these analyses, and the company's considerations and conclusions around the feasibility of a robust ITC should be clearly acknowledged by the EAG in their report.	
Page 26, Section 1.3, Table 2 and Page 110, Section 3.4.2.3 states: <i>“MAICs could provide a more robust method of analysis for comparisons between cabozantinib and everolimus or sunitinib, taking into account differences in trial populations. MAICs would enable the CABINET population to be adjusted to more closely align with the populations from other trials, focusing on those patients who had fewer prior systemic treatments”</i>	The EAG's suggestion that MAICs could provide a more robust method of analysis are speculative, and should be caveated with the limitations of such analyses, including but not limited to: MAICs can only adjust based on the CABINET data, and thus there are limits to the extent to which populations can be matched. Importantly, all patients in CABINET had received at least one prior systemic treatment (other than SSAs), whereas many patients in comparator trials were systemic treatment-naïve, and/or had no prior treatment with everolimus, sunitinib and PRRT. It is therefore not	The EAG should acknowledge these potential limitations, which informed the company's conclusion that no robust ITC was feasible on the basis of available evidence (as per the ITC feasibility assessment reported in Appendix A of the CQ response).	This is not a factual inaccuracy; no change is required.

Page 112, Section 3.4.2.3: <i>“The EAG considers that the recommended analyses would reduce most of the uncertainties associated with the EAG’s exploratory ITCs, thereby providing a more robust assessment with which to compare the effects of cabozantinib and other systemic treatments for patients who have had at least one prior systemic treatment (other than an SSA)”</i>	possible to match the CABINET trial data to comparator trial populations for this characteristic. • MAICs rely on reweighting, which reduces effective sample size, and sample sizes from CABINET are already limited. MAICs are therefore likely to be subject to substantial uncertainty. • Reweighting in the context of an anchored MAIC breaks randomisation, which can introduce further bias and uncertainty. Based on the above limitations, it cannot be said with confidence that a MAIC would permit a robust ITC between cabozantinib and other systemic treatments; the company’s conclusion following the ITC feasibility assessment was that no robust ITCs were feasible.		
Page 26, Section 1.3, Table 2 states:	This statement should be omitted on the basis of factual inaccuracy of updated to the following:	It is a factual inaccuracy to suggest that MAIC methods can be used to estimate a	The EAG thanks the company for highlighting this factual inaccuracy. The

<i>“These [MAICs] could provide a more robust assessment with which to compare the effects of cabozantinib and other systemic treatments for patients who are included in the company’s marketing authorisation and who are not represented in the CABINET trial.”</i>	“These could provide a more robust assessment with which to compare the effects of cabozantinib and other systemic treatments for patients included in the company’s marketing authorisation”	treatment effect for patients not reflected in the CABINET trial. A MAIC can only match populations by reweighting outcomes for patients already captured in the CABINET trial.	suggested amendment has been made to the report.
Page 27, Section 1.3, Table 3 states: <i>“The company highlighted concerns about the limitations of the lung NET analysis, particularly in relation to the small number of lung NET patients in the trial, and the fact that the lung NET subgroup was not prespecified in the trial.”</i>	Please could the highlighted statement be updated to specify that these considerations apply to both epNET without lung and lung NET subgroups. Furthermore, it should be noted that the differences in baseline characteristics of patients in the cabozantinib and the placebo arms for the epNET without lung subgroup could potentially bias the results in favour of BSC.	It should be noted that small patient numbers were present in both the lung NET and epNET (without lung) subgroups. These subgroups were also not prespecified, and (conversely to the lung subgroup) differences between treatment arms could potentially bias the results in favour of BSC.	The EAG has acknowledged the company’s concerns about the epNET (without lung) subgroup.

<i>“The EAG acknowledges the uncertainty in these post-hoc analyses and the fact that there is a marked difference in baseline characteristics of patients in the cabozantinib and the placebo arms for the lung NET subgroup. These differences could potentially bias the results in favour of cabozantinib”</i>			
Page 28, Section 1.3, Table 4 states: <i>“The company preferred the data from the first DCO due to concerns around the updated DCO having more marked imbalances in prognostic factors”</i> <i>“The EAG does not consider that the imbalances in prognostic factors are an issue</i>	This first statement should be amended to highlight that there were concerns around the imbalances in prognostic factors for both DCOs, but that the impact of the imbalances on outcomes are more marked in the updated DCO. The company did not suggest that imbalances in prognostic factors differ between DCOs. This second statement should be removed accordingly.	The imbalances in prognostic factors apply to both DCOs, but the impact of this imbalance appears to be more pronounced in the updated DCO due to longer follow-up. This may be because data are more mature, which contributes to a greater discrepancy in the stratified HRs (as shown in the addendum to the response to EAG CQs). This was very clearly stated in the	The EAG thanks the company for highlighting this discrepancy. Both sentences in the table have been updated to clarify that it is the impact of the imbalances in prognostic factors that is the company’s key concern about the updated DCO.

<i>related to using a more mature OS data cut.”</i>		addendum to the company’s response to the EAG CQs: <i>“There are observed imbalances in prognostic factors across treatment arms within the largest stratum for the pNETs cohort, and the impact of these imbalances is more pronounced in the updated DCO.”</i> The second statement is a misrepresentation on the basis of the text above. Imbalances in prognostic factors are not expected to differ at a more mature DCO, but unevenly distributed prognostic factors at baseline can lead to more pronounced differences over longer follow-up periods. This is not to say that imbalances do not affect the earlier DCO, but it should be acknowledged that earlier DCOs, especially where pre-	

		specified, are likely to be less impacted by bias.	
Page 28, Section 1.3, Table 4 states: <i>“12 months of additional OS trial data should not be ignored (as is the company’s preference in their base case).”</i>	The statement should be corrected as follows: <i>“12 months of additional OS trial data was considered by the company, even if not used in their base case”</i>	Whilst the company acknowledge that the updated DCO was not considered in their base case, a scenario was included in the model where the longer OS data was incorporated but where HRs from the primary DCO were applied given adjustment for crossover may be more robust. These data were not ignored, they were not considered as robust as the primary DCO for the purposes of the base case analysis.	This is not a factual inaccuracy; no change is required.
Page 29, Section 1.3, Table 5 states: “(given the uncertainty around OS estimates)”	This statement should be clarified as to whether it is referring to OS or PFS.	This section discussed PFS estimates and then provides a comment on the uncertainty of OS. Please could the EAG clarify which data they are referring to?	The EAG thanks the company for highlighting this factual inaccuracy. The EAG has now corrected “OS” to “PFS” in the text

Page 30, Section 1.3, Table 6 states: <i>“The latter are not compatible with using fixed hazard ratios as loglogistic curves imply time varying hazards”</i> Page 144, Section 4.2.3.2.1.3 <i>“The EAG has some concerns with the company’s selected loglogistic curves for the OS updated DCO. The latter are not compatible with using fixed hazard ratios as loglogistic curves imply time varying hazards”</i>	The EAG should acknowledge that the company proactively considered the acceptability of the use of fixed HRs in combination with models that imply time-varying hazards. This is commonplace in oncology modelling, on the assumption that resulting curves are clinically plausible. Similarly, application of external assumptions around changes in hazard (such as equalisation of hazards following a treatment stopping rule) are commonplace and result in curves that don’t strictly follow the form of the selected parametric distributions. For transparency, the EAG should report the company rationale in line with the wording provided in Section 3.3.3 of the company submission, and consider the implications for their conclusion: "It is noted that choice of parametric extrapolation for the cabozantinib treatment arm (to which relevant HRs would be applied) was not limited to proportional hazards models, but also	The EAG’s argument does not acknowledge that the company proactively provided a justification for the selected curves and instead does not include the wording outlined in the company submission.	This is not a factual inaccuracy; no change is required.

	considered functions such as accelerated failure time (AFT) models. The purpose of this was to maximise choice from a range of potentially clinical valid extrapolations. Whilst the combining of HRs with survival probabilities estimated from an AFT model is technically mixing assumptions on how treatment effects would (theoretically) be applied in the survival model (acting on the time scale for an AFT model) and how they are modelled in the comparative analysis (acting on the hazard scale). However, there is no reason to artificially constrain the comparator curves to the same form. If the estimated curves for the comparators are clinically valid, the conflating of technical assumptions is immaterial." It is also not quite true to say that fixed hazard ratios are not "compatible" with "time varying hazards" as standard proportional hazard models allow for time-varying hazards (albeit typically less flexibly for PH models than for some AFT models). Fixed hazard ratios merely		

	assume proportional hazards; however, the underlying baseline hazards need not be constant but can and do vary over time.		

Page 33, Section 1.3, Table 9 states: <i>“Due to the relatively high costs of SSAs, the approach to modelling discontinuation of SSAs has a major effect on the cost-effectiveness of cabozantinib”</i>	This statement should be amended to: <i>“...the approach to modelling discontinuation of SSAs has a moderate effect on the cost-effectiveness of cabozantinib”</i>	Suggesting that the discontinuation has a major impact on results, given the ICERs provided by the EAG (showing a maximum change of <£4000), is an exaggeration of the change in results.	This is not a factual inaccuracy. The change in ICER in the lung NET and epNET without lung subgroups was approximately £8,000 (vs BSC). In addition, the impact on the ICER for cabozantinib vs. sunitinib and vs. everolimus in the pNET population is over £200,000.

Page 33, Section 1.3, Table 9 states: <i>“In particular, patients receiving concomitant treatment with SSAs would be expected to continue receiving treatment indefinitely, as SSAs would be used to manage symptoms of functional NETs, regardless of which (if any) systemic treatment was being used.”</i>	These two statements directly contradict each other and show be clarified to resolve the discrepancy.	The approach in the EAG model is such that patients receive concomitant SSA from baseline until death, but clinical feedback to the EAG also suggests that SSAs would be discontinued on initiation of a subsequent systemic treatment. Given subsequent treatments are modelled, which the EAG considers, the approach to modelling concomitant SSAs appears to contradict the clinical feedback provided by both the company’s and EAG’s clinical advisors.	The EAG is unclear on what contradiction the company is referring to. The EAG assumes the company means that the statement quoted contradicts the statement in the same table: <i>“The EAG’s clinical experts stated that, in UK clinical practice, the majority of patients receiving systemic treatment with SSAs would discontinue treatment upon starting another systemic treatment.”</i> This is not a contradiction since the first sentence refers to treatment with concomitant SSAs (for patients remaining on other systemic treatments); and the second sentence refers to SSAs as systemic treatments .

Page 43, Section 2.2.1 states: <i>“Upon progression, the patient would be eligible to receive any of the alternative treatments, including cabozantinib.”</i> <i>“For example, a patient who initially received PRRT and progressed while on treatment, would then be eligible to receive either sunitinib, everolimus or cabozantinib.”</i>	These statements should be amended to the following: <i>“Upon progression, the patient would be eligible to receive alternative treatments (subject to their specific disease characteristics), including cabozantinib”</i> <i>“For example, a patient who initially received PRRT and progressed while on treatment, may then be eligible to receive either sunitinib, everolimus or cabozantinib if their disease characteristics permit the use of these alternative therapies”</i>	The treatment pathway for NETs is incredibly heterogenous and highly dependent on specific disease characteristics. Reimbursement of currently available systemics are restricted based on these and certain tumour locations. Therefore, it is a misrepresentation to suggest that all patients would be eligible for any alternative treatments without clearly specifying these restrictions. In contrast, these restrictions do not apply to cabozantinib.	The EAG thanks the company for highlighting this factual inaccuracy. The proposed amendment has been added to the report.
Page 26, Section 1.3, Table 2 states: <i>“lung NET patients, with comparisons against everolimus”</i>	In each case where everolimus is highlighted as a relevant comparator, this should specify that this is not appropriate for the lung subgroup and is only appropriate for non-functional GI NETs. Additionally, each time the EAG refers to either the GI or lung NET subgroups, whether they are referring	Due to the highly heterogenous nature of NETs, treatments are optimised to specific populations on the basis of disease characteristics. The EAG note that off-label chemotherapy does not represent a relevant	The EAG thanks the company for highlighting this factual inaccuracy. The relevant sections have been updated to highlight that everolimus is only a relevant comparator in these subgroups for GI NET patients who have non-

Page 43, Section 2.2.1 states: <i>“For instance, patients with lung NETs who have chemotherapy will then be eligible for either cabozantinib or everolimus”</i> Page 44, Section 2.21: <i>“As such, while the EAG acknowledges that there are some populations where cabozantinib may be considered an alternative to BSC (such as for patients with functional GI NETs), it notes that PRRT, everolimus and sunitinib are also relevant comparators to cabozantinib.”</i>	to functional or non-functional populations should be specified. This applies through the report as it is currently inconsistent.	comparator for cabozantinib, because it is generally reserved for a very specific subset of patients with "higher grade disease" or "aggressive tumours". This applies across all tumours subtypes, including lung NETs. The EAG note that chemotherapy use may be higher in patients with lung NETs, particularly those with functional lung NETs where there are no other treatment options. For non-functional lung NETs where everolimus is reimbursed, it is anticipated that everolimus would be prescribed first-line in the vast majority of cases (except for higher grade NETs, as above). Therefore, whilst the company acknowledges that everolimus and chemotherapy could both be used as a first-line treatment	functional tumours, and lung NET patients who have non-functional tumours and have had prior chemotherapy.

Page 149, Section 4.2.3.3: <i>“As previously noted, everolimus is a relevant comparator not only for pNETs but also in non-functional epNET lung patients”</i>		for lung NETs, they are likely to be used in very different patient populations. Whilst everolimus could be positioned after chemotherapy in theory, this could only be in the case of first-line chemotherapy use in non-functional lower grade NETs; this scenario may not be clinically relevant, or at least apply only to a very small population of patients and would likely therefore not be appropriate for decision making". Consequently, BSC is likely to be the comparator in the majority of non-functional NET patients. If the EAG continue to make these comparisons, this is important context for the committee, which is not currently reflected consistently throughout the document. In all cases where cabozantinib is compared	

		with everolimus in lung NETs, it should be clearly specified that this is specifically for patient who received first-line chemotherapy and have non-functional lung NETs.	
Page 49, Section 2.3, Table 14: <i>“the EAG is concerned that the company’s rationale for excluding RCTs where less than 70% of patients...”</i> Page 65, Section 3.1: <i>“Any study where $\geq 70\%$ of patients had experienced disease progression following treatment with a systemic therapy was included in the review.”</i>	These statements should be amended to reflect the company’s full criteria for inclusion/exclusion of studies. The second statement should be corrected to: <i>“Any study where results were not stratified by prior line of therapy (i.e. a mixed population), a $\geq 70\%$ threshold for patients who had experienced disease progression following treatment with a systemic therapy were included. In all cases where results were stratified by a prior line of treatment, studies were included and the 70% threshold did not apply”</i>	The company acknowledges that this justification was not provided as part of the company submission. However, the company’s SLR used a 70% threshold for any studies which did not present results that were stratified by patients having received at least one prior systemic therapy. In other words, where outcomes were presented for a mixed population (including first-line patients), the 70% threshold was applied to ensure the outcomes were sufficiently generalisable for a pre-treated population. In all cases where stratified results would have been presented, the 70% threshold would not	The EAG thanks the company for providing this additional information. The relevant sections have been updated to acknowledge the full criteria for the inclusion/exclusion of studies.

<i>“the company’s decision to exclude studies where fewer than 70% of patients had a prior relevant systemic therapy”</i>	This applies in all cases where the EAG have included commentary on the 70% threshold in the SLRs.	have been required. This approach aimed to ensure all trials presenting outcomes for a comparable population to CABINET (either for the full trial population or a subgroup) were captured in the SLR.	
Page 56, Section 2.3.1 states: <i>“the EAG notes that no justification was provided for the company’s use of a site-agnostic approach for the epNET population”</i>	This statement is factually incorrect, as per the company submission, and should be amended.	The company submission provided a comprehensive rationale for the site-agnostic approach (please see Table 1 of the company submission, an extract of which is provided below): <i>‘subgroup analysis of the epNETs cohort by specific tumour location (i.e. lung, GI tract or other) was not pre-specified. Post-hoc subgroup analysis for PFS and OS by specific tumour location have been presented for completeness but are subject to high risk of bias due to small patient numbers and breaking of randomisation, and results</i>	For clarity, the EAG has amended the sentence to <i>“The EAG notes that no sufficient justification (according to Murphy et al. 2021) was provided for the company’s use of a site-agnostic approach for the epNET population”</i>.

		<i>are inconsistent with the stratified subgroup analysis by primary tumour site (midgut GI/unknown versus non-midgut GI/lung/other). Therefore, these subgroup analyses are not sufficiently robust for decision-making and are not included in the economic model.</i>	
Page 62, Section 2.3.3 states: <i>“only assessing the cost-effectiveness of cabozantinib in cases where patients have received multiple prior treatments”</i>	This statement should be removed or amended as it is factually incorrect.	The EAG acknowledge that BSC is the most relevant comparator for the population reflected in the CABINET trial. The CABINET trial does not restrict to patients who have received multiple prior treatments. The company acknowledge that the CABINET trial population enrolled a large proportion of heavily pre-treated patients, but in line with the eligibility criteria, CABINET also includes a significant proportion of patients that have only had one prior systemic treatment other	The EAG thanks the company for highlighting this factual inaccuracy. This has been amended in the report.

		than an SSA. In epNETs 44% and 48% in the cabozantinib and placebo arm, respectively had received only one prior line of therapy. For pNETs 27% and 32% of patients had only prior line of therapy in the cabozantinib and placebo arms, respectively. The model therefore assessed the cost-effectiveness of patients with one (or more) prior lines of therapy systemic therapy, in line with the CABINET trial. This statement is therefore factually inaccurate.	
Page 78, Section 3.2.2.1 states: <i>“The covariates included in the IPCW OS model for probability of crossover were as follows: prior SSA use; age; primary tumour site; tumour</i>	The statement should be updated as follows: <i>“The covariates included in the IPCW OS model for probability of crossover were as follows: number of prior therapies, prior SSA use; age; primary tumour site; tumour grade; and functional status.”</i>	The EAG has omitted a key covariate for the IPCW OS model (number of prior therapies).	The EAG thanks the company for highlighting this factual inaccuracy. The proposed amendment has been added to the report.

grade; and functional status.”			
Page 79, Section 3.2.2.1 states: <i>“Furthermore, the small number of patients crossing over means that it is likely that the IPCW weights will be unstable and highly uncertain.”</i>	This statement should be corrected as follows: <i>“Although the small number of patients crossing over could result in unstable IPCW weights, this was not the case as per the weighted histograms provided in the appendices of the company submission”</i>	TSD 24 states that IPCW often does not perform well in small sample sizes due to the generation of extreme weights, however these were not generated as part of the analyses (please see the weighted histograms in Figures 36 and 37 of the company submission appendices). This context should be reported for transparency.	Thank you for highlighting this omission. Information about the weighting in the company’s analysis has been added to the report.
Page 79, Section 3.2.2.1 states: <i>“The EAG also does not agree with the company’s argument for rejecting the RPSFTM methodology”</i>	This statement should be corrected to the following: <i>“The EAG also does not agree with the company’s argument for considering the RPSFTM methodology less robust than an IPCW adjustment”</i>	The company did not reject the RPSFTM method but instead considered it less robust than the IPCW methodology.	The EAG thanks the company for highlighting this factual inaccuracy. The proposed amendment has been added to the report.
Page 79, Section 3.2.2.1 states:	It should be clearly acknowledged that the authors describe presented RPSFTM-adjusted results as “close to	Whilst the company acknowledge that there is limited evidence of how well	This is not a factual inaccuracy; no change is required.

<i>“while Latimer et al. 2024 does suggest that RPSFTM may perform poorly when the ITT OS HR is “close to 1”, this is on the basis of a case study of a single RCT; it is unclear to what extent this conclusion is generalisable to other trials (for example, how “close to 1” the ITT HR must be for the RPSFTM-derived HR to be unreliable).”</i>	1”, some of which are very similar to the ITT HRs from the CABINET trial, as shown below: <i>“The RPSFTM analyses provided point estimates of the treatment effect that were close to 1 for both estimands (Estimand 1 HR 0.91, 95% CI: 0.49–1.68; Estimand 2 HR 0.87, 95% CI: 0.02–35.88 for RPSFTM 1, Table 3) across all analyses”</i>	RPSFTM adjusts for ITT HRs similar to those reported from the CABINET trial, the study authors at least had a similar notion of “close to 1” as the company.	
Page 81, Section 3.2.2.1 states: <i>“A high proportion of patients in the updated DCO who received subsequent treatments.”</i> Page 82, Section 3.2.2.1 states:	This statement should be corrected to the following, and the conclusions from the EAG should be amended in light of this change: <i>“A high proportion of patients in the updated DCOs who received subsequent treatments, specifically crossover cabozantinib”</i>	The updated DCO CQ response from the company specifically stated: <i>“There was higher proportion of patients receiving subsequent treatment and crossover cabozantinib in the updated DCO which may lead to poorer performance of crossover adjustment methods.”</i>	The EAG thanks the company for highlighting this factual inaccuracy. The discussion of the company’s concerns about subsequent treatments and crossover cabozantinib has been amended.

<i>“The EAG also has few concerns about the higher proportion of patients who have subsequent treatments in the updated DCO. Although this should be acknowledged when interpreting the results, particularly as placebo patients had a higher percentage of subsequent treatments than those in the cabozantinib arm, this is likely to reflect clinical practice.”</i>		The company’s concerns were specifically related to a higher proportion of subsequent crossover to cabozantinib, which may increase uncertainty in analyses explored to adjust for crossover. This omission from the EAG report does not fully reflect the argument presented by the company and should therefore be amended.	
Page 107, Section 3.4.2.1 states: <i>“the EAG notes that the company has conducted subgroup analysis by number of prior systemic treatments, which reports similar results for the relative benefit observed with cabozantinib for PFS and OS whether patients</i>	An addendum to this statement should be added to highlight the limitation of these analysis as follows: <i>“However, these analyses only consider the impact of prior treatment on the treatment effect of cabozantinib; there is no evidence that treatment effect of everolimus and sunitinib would also be consistent at later lines in the treatment pathway, and thus it is unclear whether prior</i>	The EAG should acknowledge here that this subgroup analysis only considers the impact of prior treatment on cabozantinib treatment effect and there is no evidence to suggest that the treatment effect of everolimus and sunitinib would be consistent in later treatment lines. This is a	Thank you for highlighting this omission. This section has been updated to acknowledge that while the subgroup analysis only relates to the effects of prior treatments on cabozantinib, there is some evidence that prior systemic treatments also have a limited impact on the effects of everolimus.

<i>had 1, 2 or ≥ 3 prior systemic treatments (Figures 16 and 17 of CS). Therefore, while the difference in the number of prior systemic treatments between studies must be acknowledged, the EAG does not consider it a sufficient limitation to prevent consideration of the exploratory analysis”</i>	<i>treatment might represent a treatment effect modifier”</i>	significant limitation that requires acknowledgement.	
Page 129, Section 4.2.3.1.2 states: <i>“EAG raised its concerns around the assumption that PH holds for the pNET and epNET PFS data. Whilst the p-value for both Schoenfield residual curves was not sufficient to reject the null hypothesis at 95% CI, this is insufficient justification for accepting the null hypothesis. Inspecting the</i>	Please could the EAG provide additional context here, including the number at risk, particularly when they are referring to downward trends at later timepoints in these plots. A suggested amendment could include: <i>“EAG raised its concerns around the assumption that PH holds for the pNET and epNET PFS data. Whilst the p-value for both Schoenfield residual curves was not sufficient to reject the null hypothesis at 95% CI, this is insufficient justification for accepting the null hypothesis.</i>	The EAG’s conclusions are largely based on trends in the Schoenfield residual curves and hazard plots at later timepoints which are limited by small patient numbers and are at risk of overinterpretation. The small numbers of patients at risk at later timepoints must be acknowledged.	For transparency, the requested change has been incorporated.

<i>plots reveals a downwards trend</i>	<i>Inspecting the plots reveals a downwards trend (albeit based on 11 patients at risk at month 11)</i>		
Page 129, Section 4.2.3.1.2 states: <i>“cabozantinib seems more effective early on, with the relative benefit narrowing later”</i> Page 131, Section 4.2.3.1.2: <i>“trend of a decrease of the relative treatment effect of cabozantinib vs placebo in CABINET”</i> <i>“Cabozantinib seems more effective early on compared with placebo but the advantage narrows later”</i>	These statements should be corrected as follows: <i>“cabozantinib seems less effective early on, with the relative benefit increasing later”</i> AND <i>“trend of an increase in the relative treatment effect of cabozantinib vs placebo in CABINET”</i> AND <i>“Cabozantinib seems less effective early on compared with placebo but the advantage later”</i>	If the hazard ratio decreases, this would mean that the benefit of cabozantinib over placebo increases over time. The EAG have currently misinterpreted this in the opposite direction. The direction of effect change (if any) is evident from the following: - the log cumulative hazards widen, so the gap between the two treatments also widens - smoothed hazard plots show a greater increase in hazard over time for placebo than for cabozantinib again suggesting the	The EAG thanks the company for highlighting this factual inaccuracy. The proposed corrections have been added.

		gap widens between treatments the downward trend the EAG claims suggests in the Schoenfeld plots would suggest a decreasing HR for cabozantinib versus placebo from <1 (lower hazard for cabozantinib vs placebo) to an even lower hazard for cabozantinib relative to placebo	
Page 131, Section 4.2.3.1.2 states: <i>“with a slight rise and fall implying time-varying effects”</i>	This statement should be amended as follows: <i>“with a slight rise and fall which could either imply time-varying effects or random noise”</i>	Random noise is equally plausible in this case, particularly since there is no consistent trend and given the wide confidence intervals, and this should be acknowledged.	For additional context, the EAG has added the subsequent sentence: <i>“The EAG notes that the wide confidence intervals add uncertainty to the interpretation of the assessment of PH.”</i>
Page 131, Section 4.2.3.1.2 states:	This statement should be correct to the following:	Both 95% CIs include the respective other hazard trend line consistency across	This is not a factual inaccuracy; no change is required.

<i>“Finally, the smoothed hazard plots for placebo and cabozantinib in Figure 25 show considerably different hazard trends”</i>	<i>“Finally, the smoothed hazard plots for placebo and cabozantinib in Figure 25 ~~considerably different~~ hazard trends (albeit overlapping 95% CI suggest no significant difference)”</i>	timepoints, so there are no significant differences in hazard trends. This is therefore a factual inaccuracy presented by the EAG.	
Page 131, Section 4.2.3.1.2 states: <i>“the most appropriate and robust approach to compare cabozantinib with BSC is to independently fit survival curves to CABINET data and to not rely on the PHs assumption.”</i> Page 232, Section 9.2: <i>“An independently fitted curve provides a more flexible extrapolation, producing more plausible results. Since the purpose of the economic</i>	The following statement should be included for transparency: <i>“However, there is inherent uncertainty in independently modelling, particularly for BSC, given these are based on such small sample numbers. It should also be noted that HRs produced extrapolation consistent with clinical expert predictions”</i>	There is inherent uncertainty in independently modelling, particularly for such limited patient numbers. Independent modelling can also be subject to greater uncertainty, given that HRs are based on data across both trial arms, whereas independent extrapolations for BSC are only based on data for the placebo arm. HRs also produced extrapolations consistent with clinical expert predictions. Therefore, the EAG should acknowledge this as part of their commentary.	This is not a factual inaccuracy; no change is required.

evaluation is to compare the two treatments, use of a HR represents a restrictive assumption that could lead to not accurately measuring the difference between treatments”			
Page 137, Section 4.2.3.2 states: <i>“This is inappropriate as the key purpose of subgroup analysis is to observe how (and if) effectiveness differs in these two groups”</i>	This statement is factually incorrect and should be amended to reflect that whilst the company approach may not model how effectiveness differs in these two groups, it does capture differences in prognosis, which was the main limitation highlighted by clinical experts.	The purpose of the subgroup analysis was to primarily determine the impact of differences in prognosis, given the clinical experts raised differences in prognosis and availability of treatment options in the lung NET subgroup. This was outlined as part of the EAGs clarification questions. The company approach aimed to reflect these prognostic differences whilst utilising the most robust estimate of comparative treatment effect in the epNETs population.	For clarity, the EAG has altered the statement to: <i>“This is inappropriate as one of the key purposes of subgroup analysis is to observe how (and if) effectiveness differs in these two groups.”</i>
Page 144, Section 4.2.3.2.1.3 states:	The company have several major concerns with the EAG’s description of the company’s structured expert	The company conducted a robust elicitation exercise to obtain predictions of long	Thank you for highlighting this factual inaccuracy. The

<i>“In addition, selecting a survival curve to fit the cabozantinib KM observed data based on 5, 10 and 15-year clinical expert opinion does not seem appropriate as it is unclear what experience could inform these estimates, given cabozantinib is a novel treatment in this area. On this topic, NICE TSD 26 states that the number of patients treated by clinical experts with the novelty drug should be considered and reported. The company has not provided this information and, given cabozantinib has not been available for 15 years, it is also not possible for experts to be able to provide an estimate for this time period. Instead, the company should have</i>	elicitation exercise to obtain landmark survival estimates, which subsequently heavily informed base case curve selection: • TSD26 was not published at the point that the exercise was conducted, and thus misalignment is not unexpected. The experience of the clinical experts with the novelty drug was not requested by the EAG. Both of these points should be acknowledged. • Despite this, many of the recommendations in TSD26 were followed by the company, which have not been acknowledged by the EAG. The approaches taken here were also consistent with all appraisals identified in TSD26 using structured expert elicitation to validate long term survival estimates. Alignment with these highly relevant guidelines and prior appraisals should also be acknowledged	term survival for cabozantinib and BSC, which were subsequently used to inform base case curve selections in line with TSD14 and TSD26. The EAG have not provided an accurate, comprehensive or fair assessment of this exercise with respect to the recommendations within TSD26 (acknowledging that this was not published at the point the exercise was conducted). This section of the EAG report should be updated in full.	relevant paragraph has been removed.

<i>validated the resulting BSC curves, which clinicians would have had experience with.”</i>	for transparency. These include: ○ Recruiting five experts with varying expertise (TSD26 recommends no fewer than three experts), with no restriction to exclude those with knowledge of the trial data ○ Provision of the relevant clinical evidence to inform clinician’s estimates as per the recommendations for the “evidence dossier”, including the baseline characteristics of the CABINET trial, as well as available landmark survival data within the trial follow-up ○ Eliciting upper and lower plausible limits (akin to 95% CIs) to characterise uncertainty around the value of the survivor function for a		

	given time point, rather than just a single value ○ The predictions from the survival models (fitted to CABINET data) were not shared with the clinical experts. ● As per TSD26, experience with the novelty technology is not a prerequisite to provide informed estimates of survival; all recruited experts had extensive disease area expertise and were provided with the relevant clinical evidence as context for their estimates. In fact, TSD26 highlights potential technical advantages to excluding experts with prior experience (if using Bayesian methods to synthesis the available data and expert judgement), and provides recommendations to manage risks of their inclusion: <i>'such experts will need to be included to give the expert panel credibility, but risks of motivational bias will need to</i>		

	<i>be managed. Such experts may have enthusiasm about the intervention, and conflicts of interest if affiliated with the company or involvement in the pivotal trial(s) design/conduct. Including experts who are more distant from the new intervention is also desirable.</i>“ Suggesting that “<i>it is unclear what experience could inform these estimates, given cabozantinib is a novel treatment in this area</i>” is factually inaccurate and fundamentally misrepresents the recommended methods for expert elicitation. • The following statement fundamentally misrepresents the purpose and outputs of structured expert elicitation: “<i>given cabozantinib has not been available for 15 years, it is also not possible for experts to be able to provide an estimate for this time period</i>”. TSD26 provides specific guidance for the exact		

	circumstance where expert judgements are needed to inform long-term survival modelling in the absence of long-term data for a novel therapy. Experts can provide predictions of survival (including information on the level of uncertainty around predictions), on the basis of their extensive disease area expertise, there expectations regarding the change in hazard over time, and considering the clinical data provided prior to the elicitation expertise. This is the most robust method to assess the external validity of survival extrapolations in the absence of long term data. This statement is factually inaccurate. • The EAG note that “<i>the company should have validated the resulting BSC curves, which clinicians would have had experience with</i>”. Experts also provided estimates for BSC curves as		

	part of the elicitation exercise; survival curves were selected considering estimates for cabozantinib and BSC at 5, 10 and 15 years simultaneously. This statement is factually inaccurate.		
Page 144, Section 4.2.3.2.1.3 states: <i>“Given the minimal difference in AIC and BIC values, the EAG has selected the best fitting survival curves which are compatible with using a HR in the model. This is the exponential in the pNET population and the Weibull in the epNET population. As the company stated, the difference in AIC and BIC is minimal, with the Weibull AIC and BIC scores in pNET and epNET being less than 1</i>	In all cases throughout this section, the EAG should transparently report any misalignment between their preferred extrapolations and clinical predictions, in line with guidance from relevant TSDs.	The EAG’s decision to select curves on the basis of statistical and visual fit alone is inappropriate when efforts have been made by the company to elicit long-term predictions from clinicians through structured methods. This is also misaligned with recommendations for curve selection from TSD14 and TSD21, which advise that it is important to take external validity into account when selecting models. The clinical predictions sought by the company are the most robust evidence available to assess the long-term external validity of extrapolations, and should	This is not a factual inaccuracy; no change is required.

different to the best fitting curve.”		be taken into account in the EAG’s conclusions.	
Page 145, Section 4.2.3.2.1.3 states: <i>“and company base case, using the updated DCO”</i> AND Page 146, Section 4.2.3.2.1.3, Table 44 caption: <i>“Table 44: EAG and company preferred OS curves summary updated DCO”</i>	These statements are incorrect and should be amended. The results in Table 44 do not reflect the company base case, given the company base case did not use the updated DCO. Results in Table 44 should be updated to present the company base case (primary DCO), or the text and caption amended for complete clarity.	The company base case did not use the updated DCO. Thus, this is factually incorrect and should be amended.	The EAG thanks the company for highlighting this factual inaccuracy. The text has been altered to refer to the <i>“The EAG base case and company preferences , using the updated DCO,”</i>
Page 168, Section 4.2.6.1.1 states: <i>“The approach of reducing costs by a fixed proportion per cycle is simplistic, and not reflective of how dose</i>	The EAG have not provided justification for their conclusions around dose holds. Additional rationale should be incorporated.	The EAG have suggested that the assumptions surrounding dose holds are “clinically implausible” without justification. Whilst simplistic, these assumptions should reflect expected reduction in costs associated with dose holds on the	This is not a factual inaccuracy. However, for further clarification we have added the sentence: <i>“86% of pNET cabozantinib dose holds and 80% of epNET cabozantinib dose holds were the result of AEs, with these lasting between 2</i>

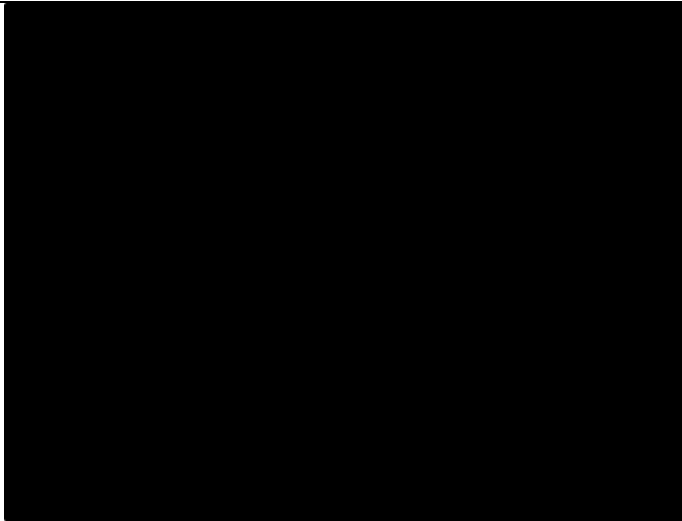
<i>holds work in clinical practice”</i> <i>“assuming a consistent percentage of time per cycle in which treatment is not received is clinically implausible, and is likely to result in inaccuracies in discounting”</i>		cohort level across extended time periods. The EAG have not explained how, or in which direction, the company’s approach to modelling dose holds is likely to bias model results, compared with a more complex approach better reflecting clinical reality for individual patients.	<i>and 52 days (according to company base case inputs). Since AEs occur mostly at the start of treatment, it is not valid to apply a consistent per cycle value for dose hold.”</i>
Page 168, Section 4.2.6.1.1 states: <i>“especially since the economic model does not account for the effect of wastage”</i> <i>“that this approach may be more in line with clinical practice if wastage is taken into account”</i> <i>“The EAG does not consider that the imbalances in prognostic factors are an issue</i>	Statements referring to the inclusion of drug wastage for oral treatments should be removed.	Wastage is not commonly considered for oral treatments given whole doses are either administered or skipped. The latter has been accounted for through adjusting costs based on dose holds.	This is not a factual inaccuracy; no change is required.

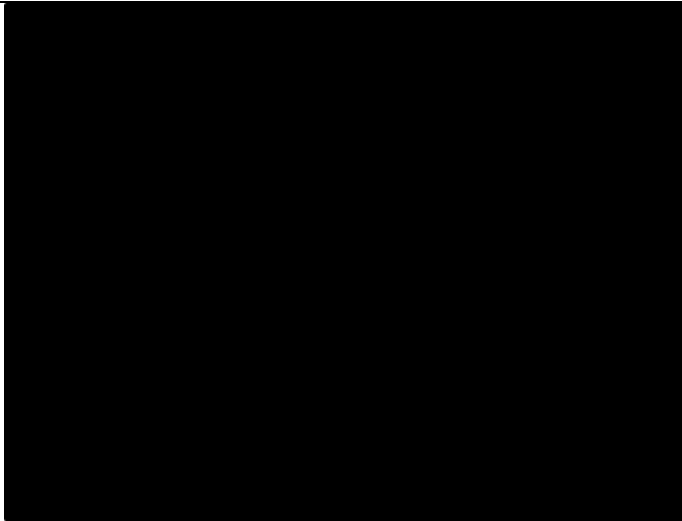
<i>related to using a more mature OS data cut.”</i>			
Page 173, Section 4.2.6.2, states: <i>“the proportion of patients receiving lanreotide or octreotide, as well as the proportion of patients receiving each dosage of these treatments, are based on assumptions, with no rationale given for the values used”</i>	This statement should be amended to incorporate company rationale.	The company acknowledges that it was not clear exactly what data from the CABINET trial informed the proportion of patients receiving concomitant SSAs, was from. These data were informed by CABINET IPD data as opposed to the CSR. The company also acknowledges that no rationale was given for the proportion of patients receiving each dosage of these treatments. These were based on internal market share data from the company (who are also the primary manufacturer of lanreotide).	The company rationale has been incorporated into the relevant section through the sentence: <i>“The company have since clarified that these were based on internal market share data from the company (who are also the primary manufacturer of lanreotide).”</i>
Page 232, Section 9.2 states:	Please could the EAG clarify what they meant here or correct this statement to refer to OS.	N/A.	The EAG thanks the company for highlighting this factual inaccuracy. The text has been amended to refer to “OS”.

<i>“reduction in PFS had patients not switched to cabozantinib”</i>			

Issue 2 Minor Data and Typographical Errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Due to technical errors in the EAGs base case (see Issue 4 EAG Modelling Inaccuracies), multiple values in the following tables are incorrect: Tables 82, 83, 84, 85, 86, 87, 88. These incorrect values will also apply to all values presented in the summary boxes	If the EAG agree with the technical errors detailed in Issue 4 EAG Modelling Inaccuracies, please update these tables and figures, using the correct input values in the model. Please also update the corresponding values in the summary boxes and conclusions. The company have generated an example of the correct cost-effectiveness results below for: The CABINET population	Technical errors in the EAG’s base case render the EAG’s base case results and scenario analyses incorrect throughout the report.	The EAG has updated all relevant tables and figures impacted by errors accepted by the EAG from the company’s Issue 4.

which are not highlighted here. The following figures are also incorrect: Figures 56, 57, 58, 59, 60, 64, 65, 67, 68, 69.	 And the MA population		

			
Page 25, Section 1.3, Table 2 states: <i>“Patients in CABINET had a mean number of 3 prior systemic treatments (excluding SSAs) in the cabozantinib and placebo arms (2.7 and 2.6,</i>	Please amend to: <i>“Patients in the pNET cohort had a mean of 2.7 and 2.6 prior systemic treatments (excluding SSAs) in the cabozantinib and placebo arms, respectively, while patients in the epNET cohort had received a of 1.9 and 1.8, respectively.”</i>	It is factually inaccurate to say that all patients in the CABINET trial had a mean of 3 prior systemic treatments. If the EAG wish to provide a mean value, this should be done per population (given differences in treatment pathways) between arms for each population, these should be reported to one decimal place as otherwise	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.

<i>respectively), while patients in the epNET cohort had received a mean number of two systemic treatments, excluding SSAs (1.9 and 1.8, respectively)."</i>		this can be misleading, particularly for pNETs.	
Page 28, Section 1.3, Table 3 states: <i>"The EAG's preferred ICERs for the lung NETs subgroup were £12,737 vs BSC..."</i>	Please clarify the inputs used to obtain these values.	This result can only be replicated without changing the subsequent treatment duration, which does not align with the EAG-preferred inputs outlined in the report.	This result has now been updated due to corrections as part of issue 4.

Page 30, Section 1.3, Table 7 states: <i>“This was particularly evident in the pNET cohort, where only half of the target number of patients were recruited (95 of the target 185), in comparison to 200 of the target 210 epNET patients.”</i> Page 72, Section 3.2, Table 18 states: <i>“Following the early stop, 200 of the target 210 epNET patients and 95 of the target 185 pNET</i>	Please amend to: <i>“This was particularly evident in the pNET cohort, where only half of the target number of patients were recruited (95 of the target 185), in comparison to 203 of the target 210 epNET patients.”</i> Please amend to: <i>“Following the early stop, 203 of the target 210 epNET patients and 95 of the target 185 pNET patients had been enrolled”</i>	Per the August 2023 DCO, 203 patients were enrolled in the epNET cohort. The clinical cut-off refers to 200 patients but this is separate to the DCO.	The EAG thanks the company for highlighting this factual inaccuracy. The proposed amendment has been added to the report.

patients had been enrolled.”			
Page 31, Section 1.3, Table 7 states: <i>“The follow-up period across all the NET trials (including CABINET) was not dissimilar (approximately 23 months in CABINET, compared to 17 and 34 months for the comparator trials)...”</i>	Please amend to: <i>“The follow-up period across all the NET trials (including CABINET) was not dissimilar (approximately 23 months in CABINET, compared to 17 and 21 months for the comparator trials)...”</i>	This is the correct follow-up period in RADIANT-4 as reported in TA449.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.

Page 34, Section 1.3, Table 9, states: <i>“The impact of using the EAG preferred concomitant treatment assumption (linked to OS) changed the company’s base case ICER from £24,815 to £28,982 in pNET patients, £20,904 to £22,196 in lung NET and £13,718 to £11,825 in epNET without lung patients.”</i>	Please amend to: <i>“The impact of using the EAG preferred concomitant treatment assumption (linked to OS) changed the company’s base case ICER from £24,815 to £28,982 in pNET patients, £20,904 to £28, 015 in lung NET and £13,718 to £22,196 in epNET without lung patients.”</i>	These are the correct outputs using the EAG-preferred inputs in the model.	The EAG thanks the company for highlighting the factual inaccuracies. The proposed amendments have been made to the report.

Page 35, Section 1.3, Table 10 states: <i>“The impact of using the EAG preferred subsequent treatments for the CABINET population changed the company’s base case ICER vs BSC from <u>£24,815</u> to <u>£38,691</u> in pNET patients, <u>£20,904</u> to <u>£4,555</u> in lung NET and <u>£13,718</u> to <u>£22,234</u> in epNET without lung patients.”</i> Page 201, Section 6.3, Table 76 states: Using scenario 14: EAG preferred	Due to technical errors in the EAG’s approach to modelling scenarios using the company’s base case for subsequent treatments, these values are incorrect. The company identified additional settings that were required to replicate the results presented by the EAG. Please could the EAG revisit their critique in key issue 9.	The only way to replicate these results is by changing the subsequent treatment duration to “EAG Scenario (Mujica-Mota et al. 2018, RADIANT-3) and administration cost for PRRT to “Administration cost for PRRT (nuclear medicine only)”. Therefore, the approach taken for this scenario does not align with the suggested changes in key issue 9.	The EAG thanks the company for highlighting the factual inaccuracies. The proposed amendments have been made to the report.

subsequent treatment (CABINET population) for BSC in pNETs incremental costs are ■ and the ICER is £38,691. Page 203, Section 6.3, Table 77 states: Using scenario 14: EAG preferred subsequent treatment (CABINET population) for BSC in lung NETs incremental costs are ■ and the ICER is £4,555. Page 204, Section 6.3, Table 78 states:			

Using scenario 14: EAG preferred subsequent treatment (CABINET population) for BSC in epNETs without lung incremental costs are ■ incremental QALYs are ■ and ICER is £22,234.			
Page 35, Section 1.3, Table 10 states: <i>“In the epNET without lung population the ICER vs everolimus</i>	Please amend to: <i>“In the epNET without lung population the ICER vs everolimus changed from £201,237 to £206,186. The impact of using the EAG preferred assumed no subsequent treatment in the MA population changed the ICER vs everolimus and sunitinib from £148,095 and £261,066 to £158,311 and £269,395 in the pNET population. In the lung NET population the ICER vs everolimus changed from £92,200 to £96,469. In the</i>	These are the correct outputs using the EAG-preferred inputs in the model.	The EAG thanks the company for highlighting the factual inaccuracies. The proposed amendments have been made to the report.

changed from £13,718 to £22,234. The impact of using the EAG preferred assumed no subsequent treatment in the MA population changed the ICER vs everolimus and sunitinib from £148,095 and £261,066 to £158,311 and £269,395 in the pNET population. In the lung NET population the ICER vs everolimus changed from £92,200 to £96,469. In the epNET without lung population the ICER vs everolimus changed from	epNET without lung population the ICER vs everolimus changed from £201,237 to £206,186."		

£13,718 to £22,234.”			
Page 36, Section 1.5, Table 11 states: Using the EAG’s preferred model assumptions for pNET (deterministic results), for the latest DCO, the cumulative ICER vs sunitinib is £451,483, the cumulative ICER vs everolimus is £265,820 and the cumulative ICER vs BSC is £144,574. Page 204, Section 6.3, Table 79 states:	Please amend to: cumulative ICER vs sunitinib “£448,719”, cumulative ICER vs everolimus “£263,021” and cumulative ICER vs BSC “£-93,277”.	These are the correct outputs using the EAG-preferred inputs in the model.	The EAG thanks the company for highlighting the factual inaccuracies. The proposed amendments have been made to the report.

Using the EAG's preferred model assumptions for pNET (deterministic results), for the latest DCO, the cumulative ICER vs sunitinib is £451,483, the cumulative ICER vs everolimus is £265,820 and the cumulative ICER vs BSC is £144,574.			
Page 34, Section 1.3, Table 9 states: <i>“The EAG scenario for patients receiving treatment up to progression changed the EAG base case ICER from £197,577 to</i>	Due to technical errors in the EAG's approach to modelling scenarios using the company's base case for subsequent treatments, these values are incorrect. The company identified additional settings that were required to replicate the results presented by the EAG. Please could the EAG revisit their critique in key issue 9.	This scenario utilised incorrect input values and required more setting changes than the EAG specified. Specifically, the only way to replicate the ICER of £197,577 is by also changing the subsequent treatment duration to “EAG Scenario (Mujica-Mota et al.	The EAG thanks the company for highlighting the factual inaccuracies. The proposed amendments have been made to the report.

<i>£198,062 in pNET patients, £12,737 to £12,255 in lung NET and £575,164 to £584,070 in epNET without lung patients.”</i> Page 37, Section 1.5, Table 11 states: Using the EAG’s preferred model assumptions for pNETs (deterministic results), the cumulative ICER vs BSC is £197,577. Page 205, Section 6.3, Table 79 states:		2018, RADIANT-3) and administration cost for PRRT to “Administration cost for PRRT (nuclear medicine only)”. Therefore, the approach taken for this scenario does not align with the suggested changes in key issue 9.	

Using the EAG's preferred subsequent treatment assumptions for pNETs (deterministic results), the cumulative ICER vs BSC is £197,577. Page 206, Section 6.3, Table 80 states: Using the EAG's preferred subsequent treatment assumptions for lung NETs (deterministic results), the cumulative ICER vs BSC is £12,737.			

Page 37, Section 1.5, Table 11 states: The EAG alternate disease management costs are '<i>Secondary issue 4</i>'.	Please amend to: '<i>Secondary issue 6</i>'	This is the correct secondary issue the EAG-preferred assumption relates to, in order to avoid confusion.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.
Page 37, Section 1.4, Table 12, using the EAG's preferred model assumptions for lung NETs cumulative ICERs	If the EAG agree with the technical errors detailed in Issue 4 EAG Modelling Inaccuracies, please update these tables, using the correct HR values in the model. This applies to all values highlighted or where incorrect HRs have been applied.	Technical errors in the EAG's use of HRs in BSC render these scenario analyses incorrect throughout the report.	The EAG thanks the company for highlighting the factual inaccuracies. The proposed amendments have been made to the report.

vs BSC (all values). Page 203, Section 6.3, Table 77, using the EAG's Independent BSC HRs for lung NETs the incremental costs are ■ the incremental QALYs are ■ and the ICER is £241,485. Page 207, Section 6.3, Table 80, using the EAG's preferred model assumptions for lung NETs cumulative ICERs vs BSC (all values).		In most cases, the first scenario using the incorrect HRs has caused all other scenario results to be incorrect as cumulative ICERs are reported.	
	If the EAG agree with the technical errors detailed in Issue 4 EAG Modelling	Technical errors in the EAG's use of HRs in	The EAG thanks the company for highlighting the

Page 38, Section 1.4, Table 13, using the EAG's preferred model assumptions for epNETs without lung cumulative ICERs vs Everolimus (all values). Page 204, Section 6.3, Table 78, using the EAG's Independent BSC HRs for epNETs without lung the incremental costs are ■ the incremental QALYs are ■ and the ICER is £241,485. Page 207, Section 6.3, Table 81, using the EAG's preferred model	Inaccuracies, please update these tables, using the correct HR values in the model. This applies to all values highlighted or where incorrect HRs have been applied.	everolimus render these scenario analyses incorrect throughout the report. In most cases, the first scenario using the incorrect HRs has caused all other scenario results to be incorrect as cumulative ICERs are reported.	factual inaccuracies. The proposed amendments have been made to the report.

assumptions for lung NETs cumulative ICERs vs everolimus (all values).			
Page 42, Section 2.2 states: <i>“NETs can also have a major impact on health-related quality of life (HRQoL), with the greatest effects seen in patients who have either functional disease (approximately 30% of pNET patients and 70% of epNET patients) or progressive disease.”</i>	Please amend to: <i>“NETs can also have a major impact on health-related quality of life (HRQoL), with the greatest effects seen in patients who have either functional disease (approximately 30–40% of pNET patients and 70% of epNET patients) or progressive disease.”</i>	This is the correct proportion of patients who have functional disease reported in the company submission.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.
Page 68, Section 3.2 states:	Please amend to: <i>“At the point of trial termination... 38.2% of the planned PFS events in the pNET cohort and 67.8% of the planned PFS event in the epNET cohort had occurred.”</i>	The CSR states that the sample sizes of the CABINET population permitted 149 PFS events in the pNET cohort and 164 in	The EAG thanks the company for highlighting the factual inaccuracies. The proposed amendments have been made to the report.

<i>“At the point of trial termination... 30.9% of the planned PFS events in the pNET cohort and 67.1% of the planned PFS event in the epNET cohort had occurred.”</i> Page 72, Section 3.2, Table 18 states: <i>30.8% of the planned PFS events in the pNET cohort and 53.7% of the planned PFS event in the epNET cohort had occurred.”</i>	<i>Please amend to: “38.2% of the planned PFS events in the pNET cohort and 67.8% of the planned PFS event in the epNET cohort had occurred.”</i>	the epNET cohort. At the August 2023 DCO, 57 (38.2%) and 111 (67.7%) of pNET and epNET patients had experienced a PFS event. Therefore, the planned event percentages do not align.	

Page 70, Section 3.2, Table 18 states: <i>“...with high use of previous everolimus (approximately 70% to 80%) and PPRT (approximately 60%).”</i>	Please amend to: <i>“...with high use of previous everolimus (approximately 60% to 80%) and PPRT (approximately 60%).”</i>	The lower limit of the range of patients with previous use of everolimus is 64%, so a more appropriate approximation is 60%.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.
Page 79, Section 3.3.2 states: <i>“epNET cohort: █ patients crossed over, amounting to █ of the patients who were eligible for treatment switching (i.e., █ patients who survived to progression in the placebo arm).”</i>	Please amend to: <i>“epNET cohort: 20 patients crossed over, amounting to 53% of the patients who were eligible for treatment switching (i.e., 38 patients who survived to progression in the placebo arm).”</i>	The number of patients who survived to progression in the placebo arm as reported in Figure 7 of the company submission was 38, therefore the percentage of patients eligible for treatment switching was 53%.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.

Page 84, Section 3.3.2 states: <i>“RPSFTM HR of ■ for the epNET population.”</i>	Please amend to: <i>“RPSFTM HR of ■ for the epNET population.”</i>	This is the correct value reported in the company post-submission clarification questions response.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.
Page 86, Section 3.3.2, Table 25 states: The ORR 95% CI for the placebo arm in pNETs is 0 and for the placebo arm in epNETs is 0.	Please amend to: “(0.0%, 11.2%)” for pNETs and “(0.0%, 5.2%)” for epNETs.	The EAG report did not present any 95% CIs but these are available. These amended values are the correct 95% CIs reported in the company submission.	Thank you for highlighting this omission. The proposed amendment has been added to the report.

Page 115, Section 4, Table 35 states: The company's base case deterministic total costs of cabozantinib in pNETs is £48,627. Page 188, Section 5.1, Table 72 states: The company's base case deterministic total costs of cabozantinib in pNETs is £48,627.	Please amend to: "£47,827".	This is the correct value reported in the company submission.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.
Page 127, Section 4.2.3, Table 40 states: The KM data for PFS % (95% CI) for cabozantinib at year 5 for pNETs is "13.0%* (NR, NR)".	Please amend to: "NR (NR, NR)".	KM data for year 5 was not reported in the CABINET CSR. This was reported correctly in the company's clarification questions response.	These are not a factual inaccuracies. In order for the table to provide all available information the latest DCO was used.

Page 127, Section 4.2.3, Table 40 states: The KM data for PFS % (95% CI) for BSC at year 1 for pNETs is “12.0% (NE, NE)”.	Please amend to: “0% (NE, NE)”.	The correct value was reported in the company clarification questions response.	
Page 127, Section 4.2.3, Table 41 states: The KM data for PFS % (95% CI) for cabozantinib at year 5 for epNETs is “6.9% (NR, NR)”.	Please amend to: “NR (NR, NR)”.	The correct value was reported in the company clarification questions response.	
Page 127, Section 4.2.3, Table 41 states: The KM data for PFS % (95% CI) for BSC at year 1 for epNETs is “10.3% (NE, NE)”.	Please amend to: “NE (NE, NE)”.	This was not estimable, as is stated in the company clarification questions response, as per the CSR.	

Page 156, Section 4.2.4, Table 47 states: The follow-up period % AE in the cabozantinib epNET population is 12.90% for fatigue, 10.60% for diarrhoea and 20.50% for hypertension.	Please amend to: “12.88%” for fatigue, “10.61%” for diarrhoea and “20.45%” for hypertension.	These values should be reported to two decimal places as in the company model.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.																							
Page 157, Section 4.2.4, Table 48 states: The incorrect values for adverse event rates and follow-up in a “copy of table 41 in company submission”.	Please amend to: <table border="1"> <thead> <tr> <th rowspan="2">Adverse Event</th><th colspan="2">pNETs</th><th>epNET</th></tr> <tr> <th>Cabozantinib (n=63) A618111 12</th><th>BSC (n=83) RADIANT -4</th><th>Cabozantinib (n=63) RADIANT-4</th></tr> </thead> <tbody> <tr> <td>Mean follow-up (months)</td><td>25.7</td><td>27.6</td><td>24.4</td></tr> <tr> <td>Fatigue</td><td>11.1%</td><td>3.2%</td><td>12.9%</td></tr> <tr> <td>Diarrhoea</td><td>6.4%</td><td>0.0%</td><td>10.6%</td></tr> <tr> <td>Hypertension</td><td>19.1%</td><td>9.7%</td><td>20.5%</td></tr> </tbody> </table>	Adverse Event	pNETs		epNET	Cabozantinib (n=63) A618111 12	BSC (n=83) RADIANT -4	Cabozantinib (n=63) RADIANT-4	Mean follow-up (months)	25.7	27.6	24.4	Fatigue	11.1%	3.2%	12.9%	Diarrhoea	6.4%	0.0%	10.6%	Hypertension	19.1%	9.7%	20.5%	These are the correct data reported in Table 41 of the company submission. It should be noted that none of the data values have been altered here but the headings correctly updated.	Thank you for highlighting this factual inaccuracy. The table has been removed with text updated to reference table 46: <i>“AEs for everolimus and sunitinib were assumed equivalent to the rates for cabozantinib in the CABINET trial, shown in Table 46.”</i>
Adverse Event	pNETs		epNET																							
	Cabozantinib (n=63) A618111 12	BSC (n=83) RADIANT -4	Cabozantinib (n=63) RADIANT-4																							
Mean follow-up (months)	25.7	27.6	24.4																							
Fatigue	11.1%	3.2%	12.9%																							
Diarrhoea	6.4%	0.0%	10.6%																							
Hypertension	19.1%	9.7%	20.5%																							

Page 164, Section 4.2.5, Table 51 states: The EAG's preferred utility value input for the scenario: CABINET (PF) + Swinburn <i>et al.</i> 2012 decrement (pNETs PD) / RADIANT-4 decrement (epNETs PD) for epNETs is ■ Page 165, Section 4.2.5, Table 53 states: The EAG's preferred AE disutility input value for hypertension is - 0.153.	N/A	The company were unable to confirm if these values are correct as they are in paywalled papers that the EAG have not provided.	This is not a factual inaccuracy.
Page 169, Section 4.2.6, Table 56 states:	Please amend to: "8.28 months".	This is the correct value reported in the CSR.	Thank you for highlighting this factual inaccuracy. The

The median duration of treatment for cabozantinib in pNETs is 6.37 months.			proposed amendment has been made to the report.						
Page 173, Section 4.2.6 states: “Therefore, the EAG adjusted the administration cost to align with the approach described in Thorn et al. 2020, and used PSSRU 2024 costs, which gave a cost per administration of £27.60 compared to the £55.95 used in the company’s base case.”	Please amend to: “Therefore, the EAG adjusted the administration cost to align with the approach described in Thorn et al. 2020, and used PSSRU 2024 costs, which gave a cost per administration of £28.60 compared to the £55.95 used in the company’s base case.”	This is the correct value calculated from the EAG-preferred 27 minutes of Band 7 nurse time using PSSRU 2024 costs plus 5 miles reimbursed at 59p per mile.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been made to the report.						
Page 180, Section 4.2.6, Table 66 states:	Please amend to: <table><tr><td>Subsequent treatment</td><td>pNETs</td><td>epNETs, epNETs w/o lur</td></tr><tr><td></td><td>BSC</td><td>BSC</td></tr></table>	Subsequent treatment	pNETs	epNETs, epNETs w/o lur		BSC	BSC	These are incorrectly reported data.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been made to the report.
Subsequent treatment	pNETs	epNETs, epNETs w/o lur							
	BSC	BSC							

Incorrect values for the EAG analysis proportion of patients receiving individual subsequent treatments for BSC in pNETs, epNETs, epNETs without lung and lung NETs and for everolimus in lung NETs	Sunitinib	15.4%	0%	0%	0%	The EAG has also accepted the company’s suggestion in Issue 4 to not include PRRT in lung NET.
	Everolimus	0%	15.0%	24.4%	0%	
	PRRT (177Lu dotatate)	23.1%	25.0%	0%	0%	
	CAPTEM	7.7%	5.0%	8.1%	32.9%	
	FOLFOX	7.7%	20.0%	32.5%	16.4%	
	Please note that the updated values are those in bold .					
Costs taken from NHS cost collection were unable to be checked in: Page 181, Section 4.2.6, Table 67. Page 182, Section 4.2.6, Table 68. Page 185 and 186, Section 4.2.6, Table 70.	N/A			The NHS cost collection website is currently inaccessible and so these values were unable to be verified.		This is not a factual inaccuracy.

Page 185, Section 4.2.6, Table 70 states: Resource use per 28 days for hospitalisation in epNETs pre-progression for the EAG base case is 0.0714.	Please amend to: “0.0357”.	These are incorrectly reported data.	These are not factual inaccuracies. Hospitalisation is calculated combining general admission and emergency admission categories. Oncologist, palliative care and dietitian are taken from the BSC progressive disease column.
Page 185, Section 4.2.6, Table 70 states: Resource use per 28 days for hospitalisation in epNETs post-progression for the EAG base case is 0.0400.	Please amend to: “0.0051”.		
Page 185, Section 4.2.6, Table 70 states: Resource use per 28 days for medical oncologist	Please amend to: “0.3977”.		

in epNETs post-progression for the EAG base case is 0.3958.			
Page 185, Section 4.2.6, Table 70 states: Resource use per 28 days for palliative care in epNETs post-progression for the EAG base case is 0.1041.	Please amend to: “0.1022” .		
Page 185, Section 4.2.6, Table 70 states: Resource use per 28 days for dietitian in epNETs post-progression for the EAG base case is 0.0129.	Please amend to: “0.0127” .		
Page 185, Section 4.2.6, Table 70 states:	Please amend to: “Chest, abdominal, and pelvic CT scan (conventional)” .	This is the correct category wording for the corresponding resource use values.	This is not a factual inaccuracy. All CT scan categories were combined for this value.

Resource use per 28 days for “CT scan”.			
Page 185, Section 4.2.6, Table 70 states: Resource use per 28 days for CT scan in epNETs post-progression for the EAG base case is 0.2200.	Please amend to: “0.0453” .	This is incorrectly reported data.	These are not factual inaccuracies. CT scan categories were combined. Octreoscan/SRS, MRI and blood test are taken from the BSC progressive disease column.
Page 185, Section 4.2.6, Table 70 states: Resource use per 28 days for octreoscan/SRS in epNETs post-progression for the EAG base case is 0.0372.	Please amend to: “0.0375” .		
Page 186, Section 4.2.6, Table 70 states:	Please amend to: “0.0902” .		

Resource use per 28 days for MRI in epNETs post-progression for the EAG base case is 0.0894.			
Page 186, Section 4.2.6, Table 70 states: Resource use per 28 days for blood test in epNETs post-progression for the EAG base case is 3.9699.	Please amend to: “3.9962” .		
Page 187, Section 4.2.6, Table 71 states: Disease management cost per cycle for PF in pNETs for the EAG base case is £62.75.	Please amend to: “£62.64” .	These are the correct values based on the model.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been made to the report.
Page 187, Section 4.2.6, Table 71 states:	Please amend to: “£270.25” .		

Disease management cost per cycle for PF in epNETs for the EAG base case is £270.69.			
Page 187, Section 4.2.6, Table 71 states: Disease management cost per cycle for PD in pNETs for the EAG base case is £354.04.	Please amend to: “£353.95” .		
Page 187, Section 4.2.6, Table 71 states: Disease management cost per cycle for PD in epNETs for the EAG base case is £236.52.	Please amend to: “£236.12” .		

Page 188, Section 5.1 states: <i>“Lower incremental costs in the epNET population of █ compared to █ in pNET patients, results in a lower ICER in the epNET population.”</i>	Please amend to: <i>“Lower incremental costs in the epNET population of █ compared to █ in pNET patients, results in a lower ICER in the epNET population.”</i>	The value the EAG reported was the ICER not the incremental costs.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been made to the report.																				
Page 193, Section 5.2.1, Figure 54: Presents an incorrect tornado plot for pNETs.	Please update the figure to present the correct tornado plot for pNET.	This figure does not align with the tornado plot generated when the DSA is run in the model.																					
Page 195 and 196, Section 5.2.2, Table 75 states: Incorrect values for the company deterministic scenario analyses in epNET.	Please amend to: <table><tr><th>No.</th><th>Scenario</th><th>Incremental costs (£)</th><th>Incremental QALYs</th><th>ICER</th></tr><tr><td>0</td><td>Company base case</td><td>█</td><td>█</td><td>£12,849</td></tr><tr><td>1</td><td>Discount rate for costs and benefits: 6.0%</td><td>█</td><td>█</td><td>£13,783</td></tr><tr><td>2</td><td>Discount rate for costs and benefits: 1.5%</td><td>█</td><td>█</td><td>£12,067</td></tr></table>	No.	Scenario	Incremental costs (£)	Incremental QALYs	ICER	0	Company base case	█	█	£12,849	1	Discount rate for costs and benefits: 6.0%	█	█	£13,783	2	Discount rate for costs and benefits: 1.5%	█	█	£12,067	These are the correct values reported in Table 75 of the company submission.	The EAG thanks the company for highlighting the factual inaccuracies. The proposed amendments have been made to the report.
No.	Scenario	Incremental costs (£)	Incremental QALYs	ICER																			
0	Company base case	█	█	£12,849																			
1	Discount rate for costs and benefits: 6.0%	█	█	£13,783																			
2	Discount rate for costs and benefits: 1.5%	█	█	£12,067																			

	3	CABINET trial (PF) and Swinburn Vignettes (PD)	■	■	£12,578		
	4	CABINET trial (PF) and ERASMUS relative decrement (PD)	■	■	£12,016		
	5	CABINET trial (PF) and ERASMUS (PD)	■	■	£11,590		
	6	AE disutilities: exclude	■	■	£12,841		
	7	Alternative PFS/TTD curve selection for cabozantinib: PFS: Gompertz, TTD: Weibull	■	■	£13,809		
	8	Alternative OS curve selection for cabozantinib (based on clinical validation): loglogistic	■	■	£12,956		
	9	PFS/TTD: Direct extrapolation: PFS: Lognormal, TTD: Weibull	■	■	£13,273		
	10	Administration costs for orally administered drugs: £0	■	■	£12,711		
	11	Subsequent treatment distribution source: Ipsen Data on File, CABINET CSR	■	■	£10,507		

	1 2 CCT in PD distribution source: Ipsen Data on File, CABINET CSR (pooled SSA use alongside subsequent treatment) £13,522 1 3 Resource use source: Casciano et al. 2013 (adjusted frequency) £15,431 Abbreviations: AE, adverse events; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; KM, Kaplan-Meier; OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; QALY, quality-adjusted life-year; RWE, real-world evidence; TTD, time-to-treatment discontinuation.																		
Page 196, Section 5.2.2, Table 75 states: Incorrect values for the EAG requested scenario analyses in epNET.	Please amend to: <table> <tr> <th colspan="4">EAG requested scenarios</th></tr> <tr> <td>epNET subgroups lung nets</td><td></td><td></td><td>£23,525</td></tr> <tr> <td>epNET subgroups without lung nets</td><td></td><td></td><td>£13,718</td></tr> <tr> <td>Fitting a survival curve to OS BSC instead of using a HR</td><td></td><td></td><td>£12,102</td></tr> </table>	EAG requested scenarios				epNET subgroups lung nets			£23,525	epNET subgroups without lung nets			£13,718	Fitting a survival curve to OS BSC instead of using a HR			£12,102	These are the correct values from the company clarification question response model.	The EAG thanks the company for highlighting the factual inaccuracies. The proposed amendments have been made to the report. However, the EAG is not able to replicate the company's epNET subgroup lung nets from the model submitted 20/06/25 nor in the model sent 30/05/2025 or from the EAG updated model. All of these produce an ICER of £20,904 when
EAG requested scenarios																			
epNET subgroups lung nets			£23,525																
epNET subgroups without lung nets			£13,718																
Fitting a survival curve to OS BSC instead of using a HR			£12,102																

	Adjustment for crossover RPSFTM	■	■	£20,588		the population is set to epNET lung.
	Adjustment for crossover ITT	■	■	£13,606		
	Cabozantini b TTD Method	■	■	£12,384		
	Utilities sources: PF from Mujica-Mota base case PD from relative decrement Swinburn	■	■	£11,638		
	Utilities sources: PF from Mujica-Mota base case PD from relative decrement ERASMUS	■	■	£10,884		
	Utilities sources: PF from Mujica-Mota base	■	■	£11,847		

	case PD from absolute value Swinburn						
	Utilities sources: PF from Mujica- Mota base case PD from absolute value ERASMUS	■	■	£10,967			
	Utilities sources: PF from Mujica- Mota alternative values PD from relative decrement Swinburn	■	■	£12,057			
	Utilities sources: PF from Mujica- Mota alternative values PD from relative decrement ERASMUS	■	■	£11,276			

	Utilities sources: PF from Mujica-Mota alternative values PD from absolute value Swinburn	■	■	£12,106		
	Utilities sources: PF from Mujica-Mota alternative values PD from absolute value ERASMUS	■	■	£11,188		
	Disutility (hypertension, embolism)	■	■	£12,853		
	Concomitant treatment duration scenario using pfs	■	■	£15,753		
	Concomitant treatment	■	■	£21,553		

	duration scenario using OS						
	Subsequent treatment duration Mujica-Mota <i>et al.</i> 2018 for sunitinib and PRRT and RADIANT-3 trial for everolimus.	■	■	£12,850			
	Update costs based on PSSRU 2024 report	■	■	£12,828			
	Administrati on cost approach for SSAs	■	■	£13,417			
	Administrati on cost for PRRT excluding diagnostic services	■	■	£12,848			

Page 201, Section 6.3, Table 76 states: The deterministic ICER vs sunitinib for the EAG's scenario 11: PSSRU 2024 + correction to costing in pNETs is £259,732.	Please amend to: "£259,735".	This is incorrectly reported data.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been made to the report.
Page 201, Section 6.3, Table 76 states: The deterministic ICER vs everolimus for the EAG's scenario 11: PSSRU 2024 + correction to costing in pNETs is £147,917.	Please amend to: "£147,920".		Thank you for highlighting this factual inaccuracy. The proposed amendment has been made to the report.
Page 208, Section 6.4.1.1 states: <i>'Table 84. Company's base</i>	Please amend to: '<i>Table 84. EAG's base case results (epNETs without lung)</i>'.	The results presented in Table 84 are the EAG's base case results; the mislabelled title may be misleading.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been made to the report.

case results (epNETs without lung)'. Page 210, Section 6.4.1.3 states: “PSA scatterplots for pNET patients in the CABINET population with BSC as a comparator are presented in Figure 50 and a CEAC is presented in Figure 51.” Page 216, Section 6.4.1.3 states: “A PSA scatterplot for epNETs without lung patients in the CABINET population with BSC as a comparator is presented in Figure 67 and Figure 64 and a			
	Please amend to: “PSA scatterplots for pNET patients in the CABINET population with BSC as a comparator are presented in Figure 59 and a CEAC is presented in Figure 60.” Please amend to: “A PSA scatterplot for epNETs without lung patients in the CABINET population with BSC as a comparator is presented in Figure 67 and a CEAC is presented in Figure 68.”	The cross-references to the figures for the PSA scatterplots are incorrect.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been made to the report.

<i>CEAC is presented in Figure 65.”</i>			
Page 214, Section 6.4.1.3, Figure 64: Does not align with the results presented in Table 83 of the EAG report.	Please replace Figure 64: Scatterplot of PSA estimates on a cost-effectiveness plane lung epNETs (CABINET, cabozantinib vs BSC) to align with the results presented in Table 83.	The figure does not align with the results presented in Table 83, which presents the mean deterministic incremental QALYs as ■ and the mean probabilistic incremental QALYs as ■.	

Page 220, Section 6.4.2, Table 86 states: For BSC (CABINET) for scenario 4: HSUV scenario, the incremental QALYs are ■ and the ICER is £12,737.	Please amend to: incremental QALYs ■ ICER “£14,155”.	These are the correct values when “EAG report: CABINET (PF) and RADIANT-4 (PD decrement)” utility source is selected in the EAG model.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been made to the report.
Page 222, Section 6.4.2, Table 87 states: For everolimus (MA) for scenario 4: HSUV scenario the ICER is £2,064,567.	Please amend to: “£1,720,472.74”.		Thank you for highlighting this factual inaccuracy. The proposed amendment has been made to the report, though the result is different due to changes from.

Issue 3 Confidentiality Highlighting Errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
CIC highlighting of whole	Please could the EAG confirm why whole sentences and paragraphs have been CIC	In the interests of limiting the CIC highlighting, the company would suggest	Thank you for highlighting this incorrect marking. The

sentences and paragraphs throughout. For example, Page 77 states: “ [REDACTED] and “ [REDACTED] [REDACTED]	highlighted throughout the report, as opposed to just the confidential values.	only highlighting the confidential values.	proposed amendment has been added to the report.
Page 28, Section 1.3, Table 4: Median OS for cabozantinib and placebo in the pNET cohort. Page 80, Section 3.3.2: Median OS for cabozantinib and placebo	Please amend to: “(median OS: [REDACTED] months for cabozantinib and [REDACTED] months for placebo...”	Confidentiality highlighting is required to ensure confidential information is not shared publicly.	Thank you for highlighting this incorrect marking. The proposed amendment has been added to the report.

in the pNET cohort.			
Page 30, section 1.3, Table 6: Number and percentage of patients crossing over in CABINET in both cohorts.	Please amend to: “([REDACTED] of patients in the pNET cohort [n= [REDACTED]] and [REDACTED] in the epNET cohort [n= [REDACTED]])”		

Page 31, Section 1.3, Table 7: Percentage of patients experiencing an OS event during the first DCO. Page 80, Section 3.3.2: Percentage of patients experiencing an OS event during the first DCO.	Please amend to: “with ■ of patients experiencing an OS event during the first DCO...”		Thank you for highlighting this incorrect marking. The proposed amendment has been added to the report.			
Page 78, Section 3.3.1, Table 21:	Please amend to: <table><tr><td>PFS</td><td>Lung NETs</td><td>epNETs (excluding lung)</td></tr></table>	PFS	Lung NETs	epNETs (excluding lung)		Thank you for highlighting this incorrect marking. The proposed amendment has been added to the report.
PFS	Lung NETs	epNETs (excluding lung)				

Number of events, n(%) and Median PFS (months) for cabozantinib and placebo arms in lung NETs and epNETs excluding lung.	<table><tr><th></th><th>Cabozantinib (n=33)</th><th>Placebo (n=16)</th><th>Cabozantinib (n=101)</th><th>Placebo (n=53)</th></tr><tr><td>Number of events, n (%)</td><td>■</td><td>■</td><td>■</td><td>■</td></tr><tr><td>Median PFS (months)</td><td>■</td><td>■</td><td>■</td><td>■</td></tr></table>		Cabozantinib (n=33)	Placebo (n=16)	Cabozantinib (n=101)	Placebo (n=53)	Number of events, n (%)	■	■	■	■	Median PFS (months)	■	■	■	■		
	Cabozantinib (n=33)	Placebo (n=16)	Cabozantinib (n=101)	Placebo (n=53)														
Number of events, n (%)	■	■	■	■														
Median PFS (months)	■	■	■	■														
Page 84, Section 3.3.2: Pooled epNET OS HRs for the updated DCO for the ITT population and RPSFRM HR for the	Please amend to: “The EAG draws attention to the pooled epNET OS HRs presented in the previous section for the updated DCO ■ for the ITT population and RPSFTM HR of ■ for the epNET population.”			No changes made as these appear to already be appropriately highlighted.														

epNET population.			
Page 106, Section 3.4.2: The PFS HR for cabozantinib vs placebo in lung NETs.	Please amend to: “ <i>Cabozantinib (CABINET trial): HR [REDACTED]</i> ”		Thank you for highlighting this incorrect marking. The proposed amendment has been added to the report.
Page 106, Section 3.4.2: The PFS HR for cabozantinib vs placebo in epNETs without lung.	Please amend to: “ <i>Cabozantinib (CABINET trial): HR [REDACTED]</i> ”		Thank you for highlighting this incorrect marking. The proposed amendment has been added to the report.
Page 108, Section 3.4.2:	Please amend to: “ <i>Cabozantinib (CABINET trial): HR [REDACTED]</i> ”		No changes made as this appears to already be appropriately highlighted.

RPSTFM-adjusted effect estimates for pNETs from CABINET.			
Page 109, Section 3.4.2: ITT population effect estimates for epNETs from CABINET.	Please amend to: “ <i>Cabozantinib (CABINET trial): HR [REDACTED]</i> ”		Thank you for highlighting this incorrect marking. The proposed amendment has been added to the report.
Page 137, Section 4.2.3: The HRs provided in the post-clarification response for	Please amend to: “ <i>Following a post-clarification request the company was able to provide the HRs for the specific subgroups with lung having a HR of [REDACTED] and w/o lung having a HR of [REDACTED]</i> ”		Thank you for highlighting this incorrect marking. The proposed amendment has been added to the report.

lung NETs and epNETs without lung.																																															
Pages 143 and 144, Section 4.2.3, Table 43: OS HRs for cabozantinib vs placebo for updated DCO in CABINET.	Please amend to: <table><thead><tr><th>Population/ Subgroup</th><th>Crossover adjustment</th><th>HR value</th><th>95% CI lower</th><th>95% CI upper</th></tr></thead><tbody><tr><td rowspan="3">pNETs</td><td>IPCW</td><td>■</td><td>■</td><td>■</td></tr><tr><td>RPSFTM</td><td>■</td><td>■</td><td>■</td></tr><tr><td>ITT HR (no adjustment)</td><td>■</td><td>■</td><td>■</td></tr><tr><td rowspan="3">epNETs</td><td>IPCW</td><td>■</td><td>■</td><td>■</td></tr><tr><td>RPSFTM</td><td>■</td><td>■</td><td>■</td></tr><tr><td>ITT HR (no adjustment)</td><td>■</td><td>■</td><td>■</td></tr><tr><td rowspan="3">Lung NETs</td><td>IPCW</td><td>■</td><td>■</td><td>■</td></tr><tr><td>RPSFTM</td><td>■</td><td>■</td><td>■</td></tr><tr><td>ITT HR (no adjustment)</td><td>■</td><td>■</td><td>■</td></tr></tbody></table>	Population/ Subgroup	Crossover adjustment	HR value	95% CI lower	95% CI upper	pNETs	IPCW	■	■	■	RPSFTM	■	■	■	ITT HR (no adjustment)	■	■	■	epNETs	IPCW	■	■	■	RPSFTM	■	■	■	ITT HR (no adjustment)	■	■	■	Lung NETs	IPCW	■	■	■	RPSFTM	■	■	■	ITT HR (no adjustment)	■	■	■		Thank you for highlighting this incorrect marking. The proposed amendment has been added to the report.
Population/ Subgroup	Crossover adjustment	HR value	95% CI lower	95% CI upper																																											
pNETs	IPCW	■	■	■																																											
	RPSFTM	■	■	■																																											
	ITT HR (no adjustment)	■	■	■																																											
epNETs	IPCW	■	■	■																																											
	RPSFTM	■	■	■																																											
	ITT HR (no adjustment)	■	■	■																																											
Lung NETs	IPCW	■	■	■																																											
	RPSFTM	■	■	■																																											
	ITT HR (no adjustment)	■	■	■																																											

	<table><tr><td rowspan="3">epNETs without lung</td><td>IPCW</td><td>■</td><td>■</td><td>■</td></tr><tr><td>RPSFTM</td><td>■</td><td>■</td><td>■</td></tr><tr><td>ITT HR (no adjustment)</td><td>■</td><td>■</td><td>■</td></tr></table> Abbreviations: BSC, best supportive care; CI, confidence interval; EAG, external assessment group; HR, hazard ratio; IPCW, inverse probability coefficient weighting; ITT, intention to treat; RPSFTM, rank preserving structural failure time model	epNETs without lung	IPCW	■	■	■	RPSFTM	■	■	■	ITT HR (no adjustment)	■	■	■		
epNETs without lung	IPCW		■	■	■											
	RPSFTM		■	■	■											
	ITT HR (no adjustment)	■	■	■												
Page 188, Section 5.1: The base case probabilistic analyses incremental QALY gains for cabozantinib in pNET and epNET patients.	Please amend to: “<i>In the base case probabilistic analysis, incremental quality-adjusted life-year (QALY) gains for cabozantinib are similar in pNET and epNET patients with ■ and ■ over BSC respectively.</i>”		Thank you for highlighting this incorrect marking. The proposed amendment has been added to the report.													
Page 188, Section 5.1:	Please amend to: “<i>Lower incremental costs in the epNET population of ■ compared to ■ in pNET patients, results in a lower ICER in the epNET population.</i>”		Thank you for highlighting this incorrect marking. The													

The incremental costs in the epNET and pNET populations.			proposed amendment has been added to the report.										
Page 195, Section 5.2.2, Table 75: Company base case deterministic results.	Please amend to: <table><tr><th>No.</th><th>Scenario</th><th>Incremental costs (£)</th><th>Incremental QAL Ys</th><th>ICER</th></tr><tr><td>0</td><td>Company base case</td><td>■</td><td>■</td><td>£12,849</td></tr></table>	No.	Scenario	Incremental costs (£)	Incremental QAL Ys	ICER	0	Company base case	■	■	£12,849		Thank you for highlighting this incorrect marking. The proposed amendment has been added to the report.
No.	Scenario	Incremental costs (£)	Incremental QAL Ys	ICER									
0	Company base case	■	■	£12,849									
Page 202, Section 6.3, Table 77, row 9: Deterministic results of scenario 2: EAG preferred	Please amend to: <table><tr><td>BSC</td><td>■</td><td>■</td><td>■</td></tr></table>	BSC	■	■	■		Thank you for highlighting this incorrect marking. The proposed amendment has been added to the report.						
BSC	■	■	■										

PFS curves vs BSC.																																																												
Page 219, Section 6.4.2: The proportion of patients with functional NETs in the CABINET trial, pooled between treatment arms.	Please amend to: "...(■ % in the epNETs population and ■ % in the pNETs population)"								Thank you for highlighting this incorrect marking. The proposed amendment has been added to the report.																																																			
Page 222, Section 6.4.2: Table 88, results for the full epNETs population EAG base	<table><tr><th>Intervention s</th><th>Total Costs (£)</th><th>Tota l LY</th><th>Total QALY s</th><th>Increment al costs (£)</th><th>Increment al LYs</th><th>Increment al QALYs</th><th>ICER (£/QALY)</th></tr><tr><td colspan="6">Deterministic results (MA population)</td><td colspan="2"></td></tr><tr><td>Cabozantinib</td><td>■</td><td>2.31</td><td>■</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>Everolimus</td><td>■</td><td>2.31</td><td>■</td><td>■</td><td>0.00</td><td>0.01</td><td>£1,628,114</td></tr><tr><td colspan="6">Deterministic results (CABINET population)</td><td colspan="2"></td></tr><tr><td>Cabozantinib</td><td>■</td><td>2.31</td><td>■</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>BSC</td><td>■</td><td>2.31</td><td>■</td><td>■</td><td>0.00</td><td>0.04</td><td>£399,392</td></tr></table>	Intervention s	Total Costs (£)	Tota l LY	Total QALY s	Increment al costs (£)	Increment al LYs	Increment al QALYs	ICER (£/QALY)	Deterministic results (MA population)								Cabozantinib	■	2.31	■	-	-	-	-	Everolimus	■	2.31	■	■	0.00	0.01	£1,628,114	Deterministic results (CABINET population)								Cabozantinib	■	2.31	■	-	-	-	-	BSC	■	2.31	■	■	0.00	0.04	£399,392			Thank you for highlighting this incorrect marking. The proposed amendment has been added to the report.
Intervention s	Total Costs (£)	Tota l LY	Total QALY s	Increment al costs (£)	Increment al LYs	Increment al QALYs	ICER (£/QALY)																																																					
Deterministic results (MA population)																																																												
Cabozantinib	■	2.31	■	-	-	-	-																																																					
Everolimus	■	2.31	■	■	0.00	0.01	£1,628,114																																																					
Deterministic results (CABINET population)																																																												
Cabozantinib	■	2.31	■	-	-	-	-																																																					
BSC	■	2.31	■	■	0.00	0.04	£399,392																																																					

case scenario.	Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; MA, marketing authorisation; QALY, quality-adjusted life-year		
Page 232, Section 9.2: The assumed acceleration factor, and the results change in HR for pNET and epNET.	Please amend to: “<i>This was shown in table 19 of the company clarification response, which illustrated that assuming a common treatment effect vs assuming a ■ acceleration factor (reduction in PFS had patients not switched to cabozantinib) resulted in only a ■ change in the HR for pNET and epNET.</i>”		Thank you for highlighting this incorrect marking. The proposed amendment has been added to the report.

Issue 4 EAG Modelling Inaccuracies

Location in the model	Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Cells D88:D93 in Settings tab.	As part of the Clarification Questions, the EAG requested the dosage for lanreotide and octreotide be included in the deterministic and probabilistic analyses. In order for this to function	Either the inputs in cells D89:D90 and D92:D93 should be removed, or an additional setting should be added. The additional setting	To correctly vary the inputs in the sensitivity analyses and use EAG added inputs correctly.	Thank you for highlighting this inaccuracy. The proposed correction has been made to the model. The EAG notes that this change has no impact on

	correctly, the distribution of 90mg/60mg and 20mg/10mg for lanreotide and octreotide, respectively, were derived using the inputs for 120mg and 30mg, respectively, from the Sensitivity Analysis filter, assuming that they are evenly distributed with the remaining market share. Therefore, the inputs added in D89:D90 and D92:D93 by the EAG are redundant and not used in the model.	should allow the inputs for lanreotide 90mg/60mg and octreotide 20mg/10mg distributions to be derived either from D89:D90 and D92:D93 in the Settings tab, or from the named cells for lanreotide 120mg and octreotide 30mg, assuming that they are evenly distributed within the remaining market share, as currently modelled. When running sensitivity analyses, the latter setting should be used so the sum of market shares does not exceed 100%. This would affect J17, K17, J20, K20 on Treatment Unit Costs, F46, F47 on Concomitant Therapies, and G82,		any results presented since it is a correction to the probabilistic results of a scenario analysis.

		G83 on Subsequent Treatments.		
Cells M13:M712 in pNETs Extrapolations.	The EAG added a scenario to assume that TTD is equal to PFS for everolimus and sunitinib. The formula has been updated for cycle 0 but not dragged for cycle 1+.	The formula should be applied to all cycles.	To correctly apply to EAG setting to assume TTD equal to PFS for all cycles.	Thank you for highlighting this inaccuracy. The proposed correction has been made to the model. The EAG notes that this change has no impact on the EAG's economic results. However, the TTD median treatment duration values have now been added to the scenario analysis to be varied in the PSA and DSA.
Cells I19:I20 in Base Case Results.	The severity modifier for BSC is applied to incremental QALYs for sunitinib and everolimus.	The severity modifier should be calculated on the Secondary Results tab and applied separately for everolimus and sunitinib.	To ensure that severity modifiers are generated for each comparator and applied separately.	Thank you for highlighting this inaccuracy. The proposed correction has been made to the model. The EAG notes that this change has no impact on any results presented around the QALY shortfall.
Cells G49:G50 in Base Case Results.	Progression free resource use costs have been excluded from the total	The resource use costs calculations should be updated to	To present the correct costs by resource type for sunitinib and everolimus.	Thank you for highlighting this inaccuracy. The

	resource use costs in the Costs Disaggregated by Resource Type table for sunitinib and everolimus.	include progression which is located on cell AS8 on the Sunitinib Trace and Everolimus Trace tabs.		proposed correction has been made to the model. This has no impact on any of the EAG's results presented in the report.
Cells J26:L29 in Patient Characteristics.	Patient characteristics data for the lung epNETs subgroup have been added but not used in the model calculations.	The data should be removed from the table.	To ensure redundant data are not presented in the model.	This is not a factual inaccuracy; no change is required.
Cells M126:P127 in Efficacy.	The EAG has added a scenario for epNET subgroup specific HRs to be applied for OS. However, the inputs added for IPCW adjusted and ITT (no adjustment) HRs, including their respective 95% confidence intervals lower and upper bounds for the lung NETs subgroup, were mistakenly swapped. Specifically, the IPCW HR were presented in the ITT HR input fields, and vice versa.	The ITT HR (no adjustment) should be updated to 0.28 and the IPCW HR should be updated to 0.23 The lower and upper confidence intervals should be updated to 0.12 and 0.62 for the ITT HR, respectively, and to 0.10 and 0.56 for the IPCW HR, respectively.	To correctly present and apply the IPCW and ITT OS HRs for the lung NETs original data cut scenario.	Thank you for highlighting this inaccuracy. The proposed correction has been made to the model. This change did not impact the EAG's base case results since RPSFTM and the new DCO is selected for the EAG base case. This impacts the lung NET results reported in Table 77 and Table 80 that use the original DCO. It also impacts one scenario table 86 and table 77 and 2 in table 80.

				In addition, the EAG has updated the IPCW OS HRs and 95% CIs in the epNET without lung population from truncated to untruncated values to maintain consistency with the rest of the IPCW HRs used (Cells M128:P128 and M141:P141 in Efficacy). This has a very small impact on epNET without lung results contained in Table 78, Table 81 and Table 87 that use the original data cut.
Cell M143 in Efficacy.	The EAG has added a scenario for applying epNET subgroup-specific HRs for OS. However, the updated data cut for epNETs without lung ITT HR (no adjustment) input in this scenario is incorrect, as it uses the HR derived from the RPSFTM analysis	The ITT HR (no adjustment) should be updated to 1.28 when the EAG scenario is used	To correctly present and apply the ITT OS HR for the epNETs without lung updated data cut scenario	Thank you for highlighting this inaccuracy. The proposed correction has been made to the model. The EAG notes that this change has no impact on any results presented in the report. Table 43 was also updated.

Cells D374:D376 in Efficacy.	The median duration of treatment inputs for everolimus (pNETs), everolimus (epNETs), and sunitinib are not included in the Sensitivity Analysis Filter tab.	The median duration of treatment inputs should be added to the Sensitivity Analysis Filter tab.	To allow the inputs to be varied in the deterministic and probabilistic analyses.	Thank you for highlighting this inaccuracy. The proposed correction has been made to the model. The standard error for the median duration of treatment with everolimus and sunitinib was assumed to be equal to cabozantinib and varied by +/- 20% in the DSA.
Cells F19:F20 in Utilities, O31:O36 in Subsequent Treatments.	The EAG has added additional inputs or scenarios but not updated the source calculations in line with this, causing VALUE errors.	The source cell calculation should be updated in line with the additional inputs and scenarios.	To correctly present the data sources.	This is not a factual inaccuracy; no change is required. (Although the VALUE error is in the model, this has no impact on inputs or results)
Cells J61:J62 in Concomitant Therapies, H174:H175, H180:H181, AT94:AT95, AT100:AT101, AT106:AT107, AT112:AT113 in Subsequent Treatments.	The EAG has added concomitant treatment and subsequent treatment distribution inputs for everolimus and sunitinib and used the same inputs as used for cabozantinib. However, the sources have not been updated correctly to reflect this. In some cases, the source indicates that these are placeholders,	The source column for sunitinib and everolimus should be updated to "Assumed equal to cabozantinib".	To correctly present the data sources.	This is not a factual inaccuracy; no change is required.

	while in others, it notes “Assumed equal to BSC”.			
Cells M94:M95 in Subsequent Treatments.	The formula for the lanreotide and octreotide distribution has been dragged for sunitinib and everolimus which has caused a SPILL error for cabozantinib, sunitinib and everolimus for the “Ipsen Data on File, CABINET CSR” scenario. The calculation that was in the model already accounted for the placeholder comparator inputs and therefore did not need to be dragged.	Calculations in the respective cells for everolimus and sunitinib should be deleted.	To correctly present the lanreotide and octreotide distribution in PD and remove SPILL error.	Thank you for highlighting this inaccuracy. The proposed correction has been made to the model. This impacts “Ipsen Data on File, CABINET CSR” scenario (single scenarios in table 74, 75 and 76).
Cells F100:L100, F106:L106, F112:L112, F130:L130 in Subsequent Treatments.	The EAG has added inputs for the subsequent treatment distributions for everolimus and sunitinib. For epNETs, lung NETs, and epNETs without lung, the EAG has added these inputs for sunitinib, assuming equivalence to the cabozantinib distribution. However, since	Data for sunitinib for epNETs, lung NETs, and epNETs without lung populations should be removed.	To appropriately present relevant treatments for each population.	This is not a factual inaccuracy as these inputs are not used in any analyses; no change is required.

	sunitinib is only authorised for pNETs, it should not be presented for the full epNETs or epNETs populations.			
Cells AI110:AO110 in Subsequent Treatments.	For the EAG preferred values scenario, it has been assumed that the distribution of subsequent treatments for the lung NETs subgroup is equal to that for epNETs. However, in the lung NETs BSC arm, the PRRT (Lu-177) subsequent treatment distribution is not assumed to be 0%, in line with the marketing authorisation for PRRT (Lu-177). Therefore, this does not accurately reflect the subsequent treatment options for lung NETs.	The input for cell AL100 should be set to 0%.	To appropriately and correctly present the subsequent treatment distribution inputs for lung NETs.	Thank you for highlighting this inaccuracy. The proposed correction has been made to the model where PRRT was set to 0 and the other treatments proportionally increased based on there rate of uptake in subsequent treatment. This change impacts all lung NET results that use the EAG preferred subsequent treatments (Table 77, Table 80, Table 83 and Table 86).
Cells AY93:AZ94 in Subsequent Treatments.	In the CABINET trial, cross-over was permitted for patients in the placebo arm after progression. As part of the EAG scenario, subsequent treatment	The inputs for BSC patients leaving PF and entering PD should be adjusted for crossover. Therefore, cell AY93 should be	To correctly reflect the subsequent treatment distribution from the CABINET trial where patients in the placebo	Thank you for highlighting this unrealistic assumption. The proposed correction has been made to the model.

	inputs have been added from the CABINET CSR which have not been adjusted for crossover.	updated to (25-12), AY94 should be updated to (21-12), AZ93 should be updated to (40-20) and AZ94 should be updated to (35-20) to reflect the 12 and 20 patients crossing over from placebo to cabozantinib in pNETs and epNETs, respectively.	arm crossed over to cabozantinib.	This impacts all EAG base case results vs BSC by changing the subsequent treatment cost. All tables in section 6 are impacted (table 76 to 88)
Cells F1059:L1059 in Sensitivity Analysis Filter.	As part of the EAG resource use scenario, inputs for the additional costs have been added to the Sensitivity Analysis Filter. For the CT scan costs, the input has been dragged across numerous cells which has overridden other calculations in the row.	The calculations and inputs in cells F1059:L1059 should be in line with the other rows added as part of the EAG scenario.	To ensure that the sensitivity analyses are correctly conducted when the EAG resource use scenario is selected.	Thank you for highlighting this inaccuracy. The proposed correction has been made to the model. This impacts the resource use scenarios on the company's base case (single scenarios in table 74, 75 and 76). Additionally, this change has a small impact on the EAG PSA and DSA results.
Cells D239, F239:G239 in Efficacy.	The EAG has added HRs for sunitinib and everolimus obtained from the ITC that	The PFS HR, lower and upper confidence interval should be	To correctly model PFS for everolimus.	Thank you for highlighting this inaccuracy. The

	they have conducted. The PFS HR for everolimus in the epNETs without lung subgroup presented in the model is 0.79 which is not aligned with the HR included in the EAG report which is 0.86 (Table 45). Similarly, the 95% lower and upper confidence intervals do not align with those presented in the report.	updated to 0.86, 0.46, and 1.59, respectively.		proposed correction has been made to the model. This impacts the EAG base case results in the epNET without lung population.