NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Obinutuzumab with mycophenolate mofetil for treating lupus nephritis [ID6420]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Obinutuzumab with immunosuppressive therapies for treating lupus nephritis [ID6420]

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 Roche
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2. **Company summary of information for patients (SIP)** from Roche
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4. **Patient group, professional group and NHS organisation submissions** from:
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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

Obinutuzumab for treating lupus nephritis [ID6420]

Company evidence submission

July 2025

File name	Version	Contains confidential information	Date
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Contents

Tables and figures

Abbreviations

Abbreviation	Definition
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ACR	American College of Rheumatology
AD	active disease
AESI	adverse event of special interest
AIC	Akaike information criterion
ALT	alanine aminotransferase
ANA	antinuclear antibody
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
AZA	azathioprine
BAFF	B-cell activating factor
BCFU	B-cell follow-up
BCG	Bacillus Calmette-Guérin
BEL	belimumab
BIC	Bayesian information criterion
BLQ	below the limit of quantitation
BLyS	B-lymphocyte factor
BMI	Body Mass Index
BNF	British National Formulary
BSR	British Society for Rheumatology
BTK	Bruton's tyrosine kinase
C3	complement 3
C4	complement 4
CBA	cost-benefit analysis
CCA	cost-consequence analysis
CCOD	clinical cut-off date
CD19	cluster of differentiation 19
CD20	cluster of differentiation 20
CDSR	Cochrane Database of Systematic Reviews
CE	cost-effectiveness
CEA	cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CFB	change from baseline
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMA	cost-minimisation analysis
CMH	Cochrane-Mantel-Haenszel
CNI	calcineurin inhibitor
COI	cost of illness

Abbreviation	Definition
COVID	Coronavirus disease
CPI	consumer price index
CR	complete response
CRR	complete renal response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CUA	cost-utility analysis
CYC	cyclosporin
D	dialysis
DIC	deviance information criterion
dL	decilitre
DLNS	Dutch Lupus Nephritis Study
DNA	deoxyribonucleic acid
DSU	Decision Support Unit
EAG	External Assessment Group
EAP	Early Access Programme
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
eMIT	electronic Market Information Tool
EPAR	European Public Assessment Report
EPO	erythropoietin
ERA-EDTA	European Renal Association-European Dialysis Transplantation Association
ERG	Evidence Review Group
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
EULAR	European Alliance of Associations for Rheumatology
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
g/g	grams per gram
GBP	Great British Pound
GC	glucocorticoid
GFR	glomerular filtration rate
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCQ	hydroxychloroquine
HCRU	healthcare resource use
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl-CoA
HPF	high-power field
HR	hazard ratio
HRQoL	health-related quality of life

Abbreviation	Definition
HSUV	health state utility value
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
IRR	infusion-related reaction
ISN/RPS	International Society of Nephrology/Renal Pathology Society
ITC	indirect treatment comparison
IU	international units
IV	intravenous
IVC	intravenous cyclophosphamide
JAK	Janus-associated kinase
KDIGO	Kidney Disease: Improving Global Outcomes
KEQ-5D	Korean EuroQol-5 dimension
kg	kilogram
KOL	key opinion leader
kU	kilounits
L	litre
LAT	Latin America
LLN	lower limit of normal
LLOQ	lower limit of quantification
LN	lupus nephritis
LN-TAG	Lupus Nephritis Terminology Advisory Group
LYG	life-years gained
M	metre
MHRA	Medicines and Healthcare products Regulatory Agency
mg	milligram
mL	millilitre
MMF	mycophenolate mofetil
MMR	measles, mumps and rubella
MPA	mycophenolic acid
MPAA	mycophenolic acid analogue
NCI	National Cancer Institute
NHB	net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NMB	net monetary benefit
NSAID	non-steroidal anti-inflammatory drug
OBI	obinutuzumab
OLE	open-label extension
OLT	open-label treatment
ONS	Office for National Statistics
OR	odds ratio
ORR	overall renal response

Abbreviation	Definition
OWSA	one-way sensitivity analysis
PAS	Patient Access Scheme
PGA	physician's global assessment
PICO	population, intervention, comparator, outcome
PML	progressive multifocal leukoencephalopathy
PO	per os (by mouth)
PR	partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	patient-reported outcome
PRR	partial renal response
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q1	first quartile
Q3	third quartile
QALY	Quality-adjusted life-year
RBC	red blood cell
RCT	randomised controlled trial
RNA	ribonucleic acid
RRT	renal replacement therapy
RTX	rituximab
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SE	standard error
SFU	study follow-up
SGA	subject's global assessment
SLE	systemic lupus erythematosus
SLEDAI-2K	Systematic Lupus Erythematosus Disease Activity Index 2000
SLR	systematic literature review
SMC	Scottish Medicines Consortium
SMR	standardised mortality ratio
SOC	standard-of-care
SUCRA	surface under the cumulative ranking curve
TA	technology appraisal
TAC	tacrolimus
TBNK	T-cell, B-cell, NK cell
TEAE	treatment-emergent adverse event
TSD	Technical Support Document
TTD	time-to-treatment discontinuation
UK	United Kingdom
UKKA	UK Kidney Association
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio

Abbreviation	Definition
US	United States
UTI	urinary tract infection
VAS	Visual Analog Scale
VOC	voclosporin
WBC	white blood cell
µL	microlitre

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

1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

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	People with lupus nephritis	People with lupus nephritis	
Intervention	Obinutuzumab with immunosuppressive therapies	Obinutuzumab with immunosuppressive therapies	

Comparator(s)	Established clinical management without OBI including:
	• induction alongside hydroxychloroquine and corticosteroids including:
	  ○ cyclosporin with or without mycophenolate
	  ○ cyclophosphamide
	  ○ mycophenolate
	  ○ rituximab with mycophenolate
	  ○ tacrolimus with or without mycophenolate
	  ○ voclosporin with mycophenolate mofetil
	  ○ belimumab with mycophenolate
	• maintenance treatment with mycophenolate, azathioprine or a calcineurin inhibitor (such as tacrolimus).
		Established clinical management without OBI including:
		• mycophenolate
		• rituximab with mycophenolate
		• voclosporin with mycophenolate mofetil alongside corticosteroids
			Full rationale is provided in Section 3.2.3.

Outcomes	The outcome measures to be considered include: • renal response rate and severity of renal-related events (e.g., flares) • rate and duration of remission • incidence of end-stage renal disease • corticosteroid use • mortality • adverse effects of treatment • health-related quality of life.	The outcome measures to be considered include: • renal response rate and severity of renal-related events (e.g., flares) • rate and duration of remission • incidence of end-stage renal disease • corticosteroid use • mortality • adverse effects of treatment • health-related quality of life.	
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 or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	Incremental cost per quality-adjusted life year. Lifetime time horizon. Costs considered from an NHS and Personal Social Services perspective. Patient access scheme for obinutuzumab considered.	

1.2 Description of the technology being evaluated

The technology being appraised is described in Table 2. See Appendix A for details of the draft summary of product characteristics (SmPC) and European Public Assessment Report (EPAR).

Table 2: Technology being evaluated

UK approved name and brand name	Obinutuzumab (GAZYVARO®)
Mechanism of action	Obinutuzumab (OBI) is a recombinant, monoclonal, humanised and glycoengineered type II CD20 antibody of the IgG1 isotype that specifically targets the extracellular loop of the CD20 transmembrane antigen that is expressed on the surface of non-malignant and malignant pre-B and mature B lymphocytes but not on hematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissue (1-3). Compared with type I anti-CD20 antibodies, OBI has greater antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis, has more direct B-cell–killing effects, and is less reliant on complement-dependent cytotoxicity (1). Because OBI does not elicit CD20 redistribution to membrane-bound lipid rafts, OBI is also associated with reduced internalisation (4). Glycoengineering of the Fc portion of OBI results in a higher affinity for FcγRIII receptors on immune effector cells such as natural killer (NK) cells and macrophages/monocytes (1).
Marketing authorisation/CE mark status	A license application will be submitted to the MHRA through the International Recognition Procedure, using EMA as the reference regulator in [redacted]. Marketing authorisation is anticipated around [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The European Medicines Agency (EMA) granted approval of Gazyvaro for chronic lymphocytic leukaemia in July 2014 and for follicular lymphoma in July 2017. The proposed additional indication is as follows: [redacted]
Method of administration and dosage	<u>Premedication</u> Patients will receive 80 mg methylprednisolone (IV), 650–1000 mg paracetamol (oral) and 50 mg diphenhydramine (oral or IV) to reduce the risk of an infusion-related reaction (IRR). The administration of all premedications must be completed between 30 and 60 minutes prior to the OBI infusion. Starting from Dose 6, methylprednisolone should only be administered to patients who have experienced an IRR in the prior infusion <u>Obinutuzumab</u> OBI should be administered under the close supervision of an experienced physician and in an environment where full resuscitation facilities are immediately available. The dosing schedule of OBI (IV) is as follows: Dose 1 initial infusion 1,000 mg Dose 2 week 2 1,000 mg Dose 3 week 24 1,000 mg Dose 4 week 26 1,000 mg Dose 5+ every 6 months* 1,000 mg *6 months after Dose 4

	Infusions should be made through a dedicated line and commence at a rate of 50 mg/hr. This may be escalated at a rate of 50 mg/hr every 30 minutes to a maximum of 400 mg/hr. If a planned dose of OBI is missed, it should be administered as soon as possible - do not wait until the next planned dose. The schedule of administration should be adjusted to maintain the appropriate interval between doses.
Additional tests or investigations	Active lupus nephritis is usually confirmed by kidney biopsy.
List price and average cost of a course of treatment	List price: £3,312.00 (1,000 mg vial)
Patient access scheme (if applicable)	[redacted] (simple discount) Net price: £[redacted] per 1,000 mg vial

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

1.3.1 Disease overview

1.3.1.1 Background

Systemic lupus erythematosus (SLE) is a chronic rheumatic disease characterised by widespread tissue damage as a result of autoimmune reactions against common self-antigens (5-9). Symptoms can vary greatly between individuals but commonly include fatigue, joint pain, skin rashes, fever and hair loss (10).

Lupus nephritis (LN), the most common organ-threatening manifestation of SLE (11), is an incurable, debilitating and potentially life-threatening disease that can cause permanent kidney damage (12). It is a form of glomerulonephritis, that is, inflammation of the glomeruli and the surrounding capillaries, which impairs the selective filtering properties of the kidney (11, 13). LN occurs in up to 60% of patients with SLE and is associated with significant morbidity and mortality (11, 12).

Approximately half of all patients with SLE develop LN within five years of diagnosis. The early stages of LN are typically asymptomatic, but as kidney damage progresses, patients often experience fatigue, hypertension, oedema and urinary symptoms. These symptoms can lead to impairments in health-related quality-of-life (HRQoL), with fatigue being particularly burdensome (14, 15).

There is no cure for LN; the primary aim of treatment is to preserve nephrons that would be lost through inflammatory flares (16). This is achieved through an induction phase using high-dose glucocorticoids (GCs) alongside immunosuppressive agents to control inflammation and immune responses. Once remission is achieved in the induction phase, patients continue with a maintenance phase involving lower doses of immunosuppressants to prevent disease relapse and minimise long-term kidney damage. Despite advances in LN treatment, around one-third of patients do not achieve remission with standard induction therapy, and 10-30% progress to end-stage renal disease (ESRD) within 15 years of diagnosis (17). Patients who reach ESRD require invasive procedures such as kidney

transplantation or dialysis and experience higher mortality rates, underscoring the necessity for more effective therapeutic options.

1.3.1.2 Pathophysiology

The development of SLE arises from genetic and environmental factors disrupting self-tolerance and triggering abnormal immune responses (5, 6). A key feature is the production and proliferation of autoantibodies against nuclear and cellular self-antigens (7), which induce systemic autoimmunity and tissue damage through cytokine induction or immune complex deposition (7-9).

In LN, immune complexes deposit in the kidney glomeruli and tubulointerstitium, provoking inflammation and fibrosis (11, 18). These complexes may arise from circulation, form *in situ* due to autoantibody targeting of glomerular antigens, or result from impaired clearance of apoptotic debris (8). Their deposition activates complement, recruits immune cells, and heightens pro-inflammatory cytokines (5), leading to podocyte and capillary damage, with untreated cases risking irreversible kidney failure (18). LN is classified into six histological classes by the 2003 ISN/RPS system (Section 1.3.1.5), with Class III, IV, and V LN posing the highest risk for progression to chronic kidney disease (5).

B-cells are recognised as key mediators of SLE pathogenesis (19), with increased numbers of circulating naïve and mature B-cells commonly observed in active SLE (20). In LN, B-cells infiltrate the kidneys and play a large role in disease pathogenesis through production of immunomodulatory cytokines and pathogenic antibodies, and through antigen presentation to T-cells (21).

1.3.1.3 Epidemiology

In England and Wales, approximately 3,000 people are diagnosed with SLE each year, and the estimated prevalence is 60,000 cases (22). The prevalence is significantly higher among individuals of Chinese, Afro-Caribbean and Indo-Asian descent compared to Caucasians (23). SLE predominantly affects women of childbearing age, with men accounting for around 10% of cases (24).

Data on the incidence and prevalence of LN in the UK are currently sparse. The most recently published UK study is a retrospective analysis conducted in the Northwest of England in 2001, which reported overall incidence and prevalence rates of 0.4 and 4.4 per 100,000 people, respectively (23). In agreement with published studies in other countries (25-30), this study confirmed that the UK prevalence of LN aligns with the racial and ethnic distribution observed in SLE, where the disease was more prevalent in Chinese (65.5 per 100,000), Afro-Caribbean (60.8 per 100,000) and Indo-Asian (12.6 per 100,000) populations, relative to the Caucasian population (3.5 per 100,000) (23). Prevalence was greater among women (female-to-male ratio of 5:1) and the median age at diagnosis was 35 for women and 65 for men (23).

1.3.1.4 Natural history

LN substantially increases the risk of end-stage renal disease (ESRD) and death (31). 2014). It has been shown that 10–30% of patients with LN develop ESRD requiring dialysis or transplant (17). Patients who have a low nephron number at the start of life (i.e. those with

low birth weight) or who have had episodes of previous or ongoing nephron loss typically have a shorter kidney lifespan, and are therefore at increased risk of developing ESRD (5). In a recent study, only 61% of patients with LN were alive and without kidney failure or a kidney transplant after 10 years of follow-up (32).

Flares, or relapses, defined as periods of increased disease activity requiring alternative treatment or more intensive therapy (33), are inherent to the relapsing–remitting course of LN (34). Flares are characterised by a combination of increases in proteinuria, haematuria or urine sediment, and/or reduced kidney function. A single LN renal flare can reduce the glomerular filtration rate by approximately 40% and results in irreversible nephron loss that shortens kidney lifespan by decades and, in some cases, can evolve to ESRD (5, 35). A study investigating the impact of repeat flares on the clinical course of LN found that a progressive number of flares is associated with a lower response to therapy and an adverse prognosis for kidney function and patient survival (36). The risk of flares is increased in patients who have genetic variants associated with increased risk of kidney disease or variants causing podocyte abnormalities. The relative duration of a renal flare is also an independent predictor of incident and progressive CKD (5).

Mortality associated with SLE is significantly higher in patients who go on to develop LN, and death directly attributable to kidney disease occurs in 5% to 25% of patients with proliferative LN within 5 years of onset (8). Furthermore, LN increases the risk of death by 3-fold in patients with SLE: the standardised mortality ratio (SMR) is 6–6.8 in those with LN, versus 2.5 in those with SLE (37-41).

1.3.1.5 Diagnosis and classification

The diagnosis of SLE should be based on the characteristic signs and symptoms of the disease (see Section 1.3.1.6) (42). When SLE is diagnosed, approximately 25% to 50% of patients have clinical evidence of LN (5).

An early diagnosis of LN is crucial to preserve kidney function and improve prognosis (42). A kidney biopsy is the gold standard for confirming the diagnosis of LN and for classifying the subtype based on the histology of the biopsy material (42). A biopsy is recommended in patients with SLE and no prior kidney involvement if there is evidence of glomerular haematuria and/or cellular casts, proteinuria is > 0.5 g/24 hours (or spot UPCR > 0.5 g/g), or if there is an unexplained decrease in GFR (43). Patients with SLE should therefore have periodic assessments of serum creatinine, estimated glomerular filtration rate (eGFR) and a urinalysis [urinary albumin/creatinine ratio and/or urinary urine protein-to-creatinine ratio (UPCR), urinary sediment]. These determinations should be more frequent in patients with a higher propensity to develop LN (42). Patients with suspected LN should also be tested for other serum biomarkers, including anti-dsDNA and anti-C1q autoantibodies, and complement levels (C3 and C4) (43). These biomarkers are important in the diagnosis and monitoring of LN due to their direct involvement in the pathogenesis of LN and their correlation with disease activity and severity.

LN is classified into subtypes based on the degree of inflammatory activity and the extent of irreversible tissue damage, as determined by microscopic analysis of renal biopsy material. The findings should be interpreted by an expert nephropathologist for accurate classification

(42). The most widely adopted classification system for LN was established by the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) in 2003 (Table 3). This system is based on the extent and severity of glomerular involvement and was designed to address ambiguities present in earlier classification methods and to standardise the definitions of LN (44). Whereas Classes I and II LN do not cause significant clinical symptoms and typically do not require treatment, Classes III and IV ± V disease are considered proliferative forms requiring immunosuppression, and Class VI disease requires renal replacement therapy (5).

Table 3: The 2003 ISN/RPS classification of LN

Class	Description
I	Minimal mesangial lupus nephritis
II	Mesangial proliferative lupus nephritis
III	Focal lupus nephritis[a] (< 50% of glomeruli) III (A): active lesions III (A/C): active and chronic lesions III (C): chronic lesions
IV	Diffuse lupus nephritis[b] (≥ 50% of glomeruli) Diffuse segmental (IV-S) or global (IV-G) lupus nephritis IV (A): active lesions IV (A/C): active and chronic lesions IV (C): chronic lesions
V	Membranous lupus nephritis[c]
VI	Advanced sclerosing lupus nephritis (≥ 90% globally sclerosed glomeruli without residual activity)

[a]Indicates the proportion of glomeruli with active and with sclerotic lesions. [b]Indicates the proportion of glomeruli with fibrinoid necrosis and cellular crescents. [c]Class V may occur in combination with III or IV, in which case both will be diagnosed.

1.3.1.6 Clinical presentation

SLE can affect nearly every organ system, including the skin, joints, central nervous system and the kidneys. It is characterised by a relapsing–remitting course and a wide spectrum of clinical features (12). Signs and symptoms of SLE vary between individuals and can range from mild to severe. Symptoms can include arthritis, fevers, fatigue, rash, hair loss, sores, swollen glands, swelling in the legs or around the eyes, pain due to inflammation of the lining of the lungs and heart, headaches and abdominal pain. Systemic inflammation can cause damage to organs including the kidney, brain, heart, blood vessels and lungs (10).

LN can be evidenced by urinalysis, where proteinuria is the characteristic feature, present in all patients, and indicative of renal damage (11). Other renal abnormalities may include microscopic haematuria, renal insufficiency, nephrotic syndrome and urinary red blood cell casts (37). Patients may also exhibit extrarenal symptoms including rash, fatigue, muscle and joint pain, fever and hypertension (45). The approximate prevalence of the clinical manifestations of LN are shown in Table 4 (37).

Table 4: Approximate prevalence of clinical manifestations of LN

Clinical manifestation	Approximate prevalence, %
Nephrotic range proteinuria / nephrotic syndrome	50
Microscopic haematuria	80
Macroscopic haematuria	< 5

Clinical manifestation	Approximate prevalence, %
Urinary red blood cell casts	30
Other urinary cellular casts	30
Renal insufficiency	60
Rapid decline in kidney function	15
Hypertension	30
Tubular abnormalities	70

Renal flares are also characteristic of LN. In 2009, the Lupus Nephritis Terminology Advisory Group (LN-TAG) defined renal flares in LN as an increase in proteinuria or serum creatinine levels, an abnormal urinary sediment or a reduction in creatinine clearance due to active disease (46). Renal flares can also be further subdivided into proteinuric flares or nephritic flares.

A flare of LN is equivalent to an episode of acute kidney injury (5). Given the significant loss of nephrons and consequent decrease in GFR that result from flares (Section 1.3.1.4), a single flare can reduce the lifespan of the kidney by decades (5). Therefore, it is crucial to limit flares through prevention and/or prompt, aggressive treatment.

1.3.1.7 Burden of disease

1.3.1.7.1 Health-related quality of life

LN is associated with considerable humanistic burden and reduced HRQoL (14, 47-50). Moreover, this burden increases with progression to ESRD and the requirement for dialysis and kidney transplantation (51). Studies comparing HRQoL between patients with LN and healthy controls have reported poorer scores in all eight domains of the 36-Item Short Form (SF-36) health questionnaire among patients with LN (general health, physical functions, physical limitations, emotional limitations, energy/ fatigue, emotional well-being, pain, social functions and health change) (14, 15, 52). HRQoL is worse in patients with Class III/IV LN compared with Class I/II LN (14) and in patients with active disease compared with patients without active disease (14, 47).

A higher proportion of patients with LN report problems in the EQ-5D-3L domains of self-care ($p < 0.001$), pain ($p < 0.003$), anxiety/depression ($p < 0.009$) and mobility ($p < 0.009$) compared with those with SLE without LN (14). The presence of extrarenal symptoms can also further negatively impact HRQoL. An observational, multi-centre study examined HRQoL in 181 patients with LN using the PROMIS-29 questionnaire; patients with extrarenal disease (n = 75) reported significantly worse pain, physical function, fatigue and ability to participate socially compared with those with isolated renal disease (n = 106) (48). Rash (45%), arthritis (40%) and alopecia (40%) were the most commonly reported extrarenal symptoms and arthritis was the most strongly associated extrarenal symptom with worse scores in pain interference, physical function and fatigue domains (48).

Generally, fatigue is reported to be the most burdensome symptom of LN and is associated with worse HRQoL and increased treatment dissatisfaction (14). The severity of fatigue has been reported to be significantly worse in patients with Class III–V disease compared with Class I–II ($p < 0.001$) (52). Dissatisfaction with treatment has been associated with greater

fatigue severity and greater impact of disease on daily activities (15, 53). Moreover, significant associations between the cognitive and motor aspects of fatigue and reduced HRQoL ($p < 0.01$) have been reported (54).

1.3.1.7.2 Caregiver burden

In a UK-specific burden of illness study recruiting patients with SLE (n=121) and caregivers (n=31), 52% of caregivers in paid employment missed time from work, 55% reported a worsened financial status, and 87% experienced interference with social activities (55). These findings are consistent with a larger US-based survey of 253 caregivers of patients with SLE. Despite mean HRQoL being similar to the mean of the general US population, caregivers who were employed missed an average of 12.8% of paid work time due to caregiving responsibilities and reported a 33.5% reduction in on-the-job effectiveness (56). Nearly half of the caregivers surveyed (49.4%) indicated that their caregiving responsibilities impacted their ability to socialise with friends, and almost all caregivers (97.6%) reported experiencing increased anxiety and stress in relation to their caregiving role (56).

As ESRD develops in a considerable proportion of patients with LN (5–30% of patients within 10 years of diagnosis) and significant caregiver burden is associated with ESRD (57), progression to ESRD further adds to the caregiver burden of LN. A systematic literature review (SLR) identified a positive correlation between the duration and frequency of dialysis with the level of caregiver burden; a greater degree of burden was reported for caregivers of patients with ESRD (all-cause) receiving haemodialysis compared with peritoneal dialysis, renal transplant and those not yet receiving dialysis (58).

1.3.1.7.3 Treatment-related burden

Standard-of-care (SOC) therapy for patients with LN includes glucocorticoids (GCs) in combination with either mycophenolate mofetil (MMF), cyclosporin (CYC) or azathioprine (AZA), which are associated with substantial toxicities that contribute to the morbidity of the disease (49, 50). Chronic GC use also increases the risk of serious adverse events, including organ injury, opportunistic infections and iatrogenic osteoporosis among other complications (59, 60).

Belimumab (BENLYSTA), which is a B-lymphocyte stimulator (BLyS)-specific inhibitor, and voclosporin (LUPKYNIS), which is a second-generation calcineurin inhibitor (CNI) immunosuppressant, were licensed for the treatment of patients with active LN who are receiving SOC therapy (61-64). However, adverse effects of belimumab and voclosporin have been reported (65). Moreover, CNIs as a class are associated with hemodynamic effects (vasoconstriction affecting eGFR and blood pressure) in addition to other risks and toxicities (66).

The frequency of treatment when managing a chronic condition such as LN can also have an impact on the HRQoL of the patient (67). There is considerable burden with the frequency of belimumab treatment for active LN, which is administered either subcutaneously (two 200 mg injections once weekly for 4 doses, followed by one 200 mg injection weekly thereafter) or intravenously (once every 2 weeks for the first 3 doses followed by once every month thereafter) (61, 63). Moreover, voclosporin is administered orally twice daily via multiple

capsules (up to six per day), resulting in a high pill burden, particularly when combined with pill-based MMF (62, 64). At a recent advisory board conducted by Roche – consisting of 11 clinical experts ranging from consultant nephrologists, consultant rheumatologists, clinical nurse specialist and clinical pharmacists – UK clinical experts agreed that lack of patient adherence due to high pill burden is a prominent issue that negatively influences treatment outcomes in patients with LN, and emphasised the need for an effective treatment that can be dosed infrequently (68).

The treatment-related burden associated with progression of LN to ESRD is substantial and includes both renal replacement therapy (dialysis or kidney transplant) and increased use of medications (51, 69).

1.3.2 Current treatment practice in the UK

There is currently no cure for LN, with treatment focused on preserving kidney function, preventing disease progression and flares, and reducing morbidity and mortality (70). The primary aim of treatment is to achieve complete clinical remission, which is strongly associated with better long-term outcomes (70, 71). In a study of 86 patients with Class IV LN, 10-year kidney survival rates were shown to be 94% for patients in complete remission, compared with 45% for those with partial remission and 19% for those without remission (71). Corresponding overall survival rates were 95%, 76% and 46%, respectively (71).

SOC therapy for LN has traditionally included hydroxychloroquine (HCQ) along with conventional immunosuppressive therapies such as MMF, CYC, or azathioprine (AZA), in combination with GCs (70). However, this approach has several limitations, including modest remission rates and prolonged GC exposure (70). To address these limitations, the treatment landscape has evolved in recent years, including through the NICE approval of voclosporin in 2023, as the first drug specifically indicated for LN treatment, and treatment guidelines now recommend upfront triple immunosuppressive therapy to maximise long-term remission in patients with active Class III/IV + V LN (72-75). These regimens add belimumab or a CNI, such as voclosporin or tacrolimus, to the dual combination of GCs and mycophenolic acid analogs (MPAA) or CYC (see Section 1.3.3).

1.3.2.1 Targeted therapies

1.3.2.1.1 Belimumab

Belimumab (BEL) is a humanised monoclonal antibody targeting the B-lymphocyte stimulator (BlyS; also known as B-cell activating factor [BAFF]). It reduces autoreactive B-cell survival and autoantibody production, decreasing inflammation associated with LN (76). BEL is licensed for both intravenous and subcutaneous administration in the US, EU and UK for the treatment of active LN, in combination with standard immunosuppressive therapies (61, 63).

In the phase III BLISS-LN trial (NCT01639339), 448 patients with active LN were randomised to receive either BEL or placebo alongside standard induction therapy (76). Over 104 weeks, the BEL group achieved significantly higher renal response rates compared with placebo (43% vs. 32%; p = 0.03) and had a significantly reduced risk of

kidney-related events or death (hazard ratio, 0.51; 95% CI: 0.34, 0.77; p = 0.001). The safety profile was comparable between BEL and placebo groups (76).

In the 28-week open-label extension of BLISS-LN to assess safety and efficacy of BEL, 255 patients received BEL 10 mg/kg with SOC therapy (77). Adverse events occurred in 62% of placebo-to-BEL and 70% of BEL-to-BEL patients, with serious adverse events in 4% and 8%, respectively. Primary renal response rates increased from 60% to 67% in the placebo-to-BEL group and from 70% to 75% in the BEL-to-BEL group, while complete renal response rates improved from 36% to 48% and 48% to 62%, respectively (77). No new safety signals were identified (77).

A post-hoc analysis of BLISS-LN reported that BEL reduced the risk of an LN flare by 55% relative to placebo (hazard ratio, 0.45; 95% CI: 0.28, 0.72; nominal p = 0.0008), with 14.4% of patients on the BEL arm and 26.0% of patients on the MMF arm experiencing an event during the last 18 months of the study (78).

BEL received a positive NICE recommendation in December 2021 (TA752) as an add-on treatment in patients with active autoantibody-positive SLE with high disease activity despite standard treatment (79). However, BEL is not NICE-approved as a treatment for LN specifically because the relevant NICE appraisal (TA806) was terminated by the manufacturer (80). At a recent advisory board led by Roche, UK clinical experts confirmed that uptake of BEL for LN in England is currently low due to the complexity of local guidelines governing its use and lack of national reimbursement (68).

1.3.2.1.2 Voclosporin

Voclosporin (VOC) is an orally administered CNI that reduces T-cell activation, indirectly modulates B-cell activity, and subsequently suppresses the inflammatory and autoimmune responses associated with LN (81). VOC has been approved in the US, EU and UK for the treatment of active LN in adults, in combination with standard immunosuppressive therapies (62, 64). VOC in combination with MMF was approved by NICE for the treatment of active Class III/IV ± Class V LN in May 2023 (82).

The phase 3 AURORA 1 trial (NCT03021449) enrolled 357 patients with active LN, who were randomised to receive either VOC or placebo on a background of MMF and rapidly tapered low-dose oral GCs for 52 weeks, followed by a 24-week follow-up period to evaluate long-term outcomes (81). VOC was more effective than placebo in achieving renal remission, with 41% of patients achieving complete renal response compared with 23% in the placebo group (odds ratio 2.65; 95% CI: 1.64, 4.27; p < 0.0001); VOC reduced proteinuria and improved kidney function, although it was associated with adverse events including hypertension, gastrointestinal disturbances, and an increased risk of infections (81).

The AURORA 2 trial (NCT03597464) extended treatment for an additional two years in 216 patients who continued their assigned treatment (VOC or placebo) (83). Persistent reductions in proteinuria over three years resulted in more frequent complete renal responses in the VOC group than in the placebo group (50.9% vs. 39.0%; odds ratio 1.74; 95% CI 1.00, 3.03; p = 0.051) (83). Adverse events such as hypertension (8.6% vs. 7.0%)

and decreases in glomerular filtration rate (GFR; 10.3% vs. 5.0%) were also reported more frequently in the VOC group than in the placebo group (83).

Over the three-year treatment period, a laboratory-confirmed ≥30% decrease in corrected eGFR from pre-treatment baseline was reported in 12.1% of patients in the VOC group and 10% of patients in the control group. There was no statistically significant improvement in rates of renal flares and non-renal flares in the VOC group compared with the placebo group (23.8% vs. 26.0%, respectively, and 18.1% vs. 14%, respectively) (83). Changes in systemic markers of lupus activity (anti-dsDNA, and C4) were similar between the two groups over the three-year treatment period (81, 83).

UK clinical experts consulted by Roche commented that VOC does not address the underlying pathology of LN or SLE and exerts its main effects through a reduction in proteinuria (68). They estimated only 5-10% of LN patients in the UK are currently treated with VOC, and these patients often have highly nephrotic disease (68). The experts also informed Roche that the majority of their patients receiving VOC require a dose reduction due to worsening eGFR or serum creatinine (68, 84). Moreover, since the underlying disease can potentially worsen whilst on treatment, withdrawal of VOC carries a high risk of flares (85).

Other CNIs, such as CYC and tacrolimus (TAC), have been studied as part of multi-target therapy for LN, in combination with MMF and GCs (86).

1.3.2.2 Unapproved treatment options

Rituximab (RTX) is a CD20-directed monoclonal antibody that promotes B-cell depletion. The phase III LUNAR trial evaluated RTX combined with standard induction therapy (MMF and GCs) in patients with Class III or IV LN. After one year, there was no statistically significant improvement in overall renal response rates in patients receiving RTX compared with those receiving placebo (45.8% vs. 56.9%; p = 0.18), alongside SOC therapy (87). However, a post hoc analysis of the LUNAR trial demonstrated that patients with complete peripheral B-cell depletion were significantly more likely to achieve a complete response (unadjusted OR, 5.8; 95% CI, 1.2–28; p = 0.03) (88). An SLR of 26 studies on RTX treatment in refractory LN found that RTX effectively induced remission in patients who have not responded to standard therapies (89).

RTX has been used as an off-label treatment in the UK to treat refractory SLE since the mid-2000s (90). Current treatment guidelines for LN recommend considering off-label treatment with RTX in patients with persistent disease activity or inadequate response to initial SOC therapy (72-74).

1.3.3 Treatment guidelines

National and international guidelines for the management of LN are incorporated into broader guidelines for SLE. The most recent SLE guidelines were published in 2023 by the European Alliance of Associations for Rheumatology / European Renal Association - European Dialysis and Transplantation Association (EULAR/ERA-EDTA) (73), in 2024 by the Kidney Disease: Improving Global Outcomes (KDIGO) group, and in 2025 by the American College of Rheumatology (ACR) (72, 74). The British Society for Rheumatology

(BSR) published SLE guidelines in 2018. An update to these guidelines was presented in draft form at the BSR Annual Conference 2025 and the final guidelines will be published later in 2025 (75). In addition, the updated EULAR guidelines for SLE with kidney involvement were presented in draft form at the EULAR 2025 Congress and will also be published later in 2025 (91). At a recent advisory board conducted by Roche, UK clinical experts confirmed that local LN guidelines in England and Wales are based on those published by BSR, EULAR/ERA-EDTA and KDIGO (68).

All guidelines on management of LN:

- Emphasise the importance of early biopsy-based classification to guide treatment and a patient-centered approach to care (72-75, 91). Treatment is tailored according to the class of LN and individual patient factors.
- Introduce triple immunosuppressive regimens as a key approach for managing active Class III/IV LN. These regimens consist of GCs combined with either CNIs, such as VOC or TAC, plus MPAAs, or BEL or OBI with either CYC or MPAA (72-75, 91). UK clinical experts consulted by Roche emphasised that upfront triple therapy is crucial for driving long-term disease remission (68).
- Encourage minimisation of GC exposure, with a target dose of ≤ 5 mg/day of prednisone (72-75, 91).
- Recommend maintaining immunosuppressive therapy for at least 3–5 years post-remission (72-75, 91).
- Underscore the need for adjunctive care, including cardiovascular and renal protection, shared decision-making, and regular monitoring, to optimise treatment outcomes and ensure long-term safety (17, 72-75).

The recommended approaches for the induction and maintenance treatment of active Class III/IV ± V LN, as outlined in the BSR, EULAR and KDIGO guidelines (73-75, 91), are summarised in Table 5.

Table 5: Treatment of active Class III / IV ± V LN according to BSR, EULAR/ERA-EDTA and KDIGO guidelines

Stage of therapy	Treatment		
	BSR 2025 (75)	**EULAR 2025 (91)**	**KDIGO 2024 (74)**
Induction (all patients receive oral GC taper)	<u>Preferred</u> OBI* + MPAA, or BEL* + MPAA, or VOC/TAC** + MPAA <u>Alternatives</u> EuroLupus + BEL RTX + MPAA MPAA alone EuroLupus alone	Recommends hydroxychloroquine and GCs (taper to ≤ 5 mg/day by 4-6 months and withdraw when possible) with immunosuppressive (MMF or low-dose CYC) and CNI (VOC or TAC) or biologic (BEL or OBI)	MPAA alone, or Low-dose CYC, or MPAA/low-dose CYC + BEL, or MPAA + CNI#
Maintenance	<u>Refractory</u> Different induction treatment and re-start induction GC	<u>If response achieved</u> Continue MMF in combination with BEL or VOC or OBI (for at least 3	Reduce prednisone to <5 mg/day and: <u>Preferred</u>

Stage of therapy	Treatment		
	BSR 2025 (75)	EULAR 2025 (91)	KDIGO 2024 (74)
	Meeting targets (at 3, 6, and 12 months): Combination without GCs: OBI + MPAA, or BEL + MPAA, or CNI + MPAA, or RTX + MPAA (after 3 years, can consider longer maintenance) Partial response New induction or different maintenance treatment Patients may receive AZA if intolerant to MPAA or on pregnancy plan	years, with gradual withdrawal considered after this time in those with sustained remission) Low-dose CYC to be replaced with MMF or AZA (+/- BEL if used initially)	MPAA Alternatives Continue triple immunosuppression in patients who received it as induction therapy (total duration of initial initial, plus maintenance therapy should be ≥36 months) AZA for patients without access to MPAA CNI or mizoribine or leflunomide if MPAA not tolerated or unavailable

Key: AZA, azathioprine; BEL, belimumab; CNI, calcineurin inhibitor; CYC, cyclophosphamide; GC, glucocorticoid; MMF; mycophenolate mofetil; MPAA, mycophenolic acid analogue; OBI, obinutuzumab; RTX, rituximab; TAC, tacrolimus; VOC, voclosporin. *especially poor adherence or extra-renal disease. **especially if nephrotic. §belimumab should always be given in combination with MMF or low-dose CYC. ^CNIs should be given in combination with MMF. †In relapsing/refractory disease, especially after failure to CYC-based regimens. #When kidney function is not severely impaired (i.e., eGFR ≤ml/min/1.73m^2).

1.3.4 Unmet need

Renal flares in uncontrolled LN lead to progressive, irreversible loss of nephrons, causing a worsening of proteinuria and a decline in GFR (5). When added to age-related nephron loss and kidney injuries that occur over the course of a life, renal flares accelerate the time to ESRD and shorten the lifespan of the kidneys by decades (92). As few as two renal flares in the lifetime of a patient with LN can result in kidney failure. In addition to irreversible nephron loss, renal flares significantly impair treatment responses during future flares (93). Therefore, timely diagnosis of LN followed by prompt, aggressive treatment is critical to prevent further loss of nephrons and worsening of renal prognosis.

While SOC immunosuppressive therapy, typically comprising a traditional immunosuppressant (MMF, CYC or AZA) plus GCs, improves clinical outcomes compared to placebo, a significant proportion of patients do not achieve optimal disease control. Where, up to 70% of patients do not achieve complete renal remission (94, 95), leaving these patients at a higher risk for flares and progression to ESRD. An SLR evaluating the comparative effectiveness of immunosuppressive treatments and GCs in LN concluded that most standard therapies resulted in complete remission rates of less than 50% (96). Furthermore, prolonged exposure to high doses of GCs, frequently required with SOC therapy, is associated with a substantial burden of toxicity. This manifests as infections, osteoporosis, diabetes, cardiovascular abnormalities and avascular necrosis among other serious complications (97).

Subsequent addition of the CNIs such as tacrolimus and cyclosporin to the traditional immunosuppressive regimen of MMF/CYC and GCs in LN has led to improved rates of renal remission, particularly in patients with significant proteinuria (98-100). This additive efficacy also permits a reduction in GC dosage, thereby decreasing cumulative exposure and associated systemic toxicities (5, 99). However, these benefits are balanced against the narrow therapeutic index of CNIs, requiring close blood monitoring, and a well-established adverse event profile of older CNIs. This profile commonly includes nephrotoxicity (acute and chronic kidney damage), hypertension, electrolyte disturbances, increased susceptibility to infections and neurotoxic effects, necessitating careful monitoring and management to mitigate these risks (99, 100).

RTX is not licensed for the treatment of LN. This is based on results from the phase 3 LUNAR study, where RTX did not demonstrate a statistically significant overall renal response benefit versus placebo when combined with standard therapy of MMF and GCs after one year in patients with Class III/IV LN (87). Despite this, the overall renal response rate was numerically higher in the RTX arm. UK clinical experts consulted by Roche confirmed that RTX is routinely used off-label in the management of LN in England. However, B-cells tend to repopulate relatively quickly after RTX administration, limiting the duration of depletion (68).

A significant challenge contributing to the unmet need in LN is the substantial pill and administrative burden experienced by patients. This burden directly impacts patient adherence, which in turn is strongly linked to clinical outcomes, as confirmed by published studies and UK clinical experts (68, 101). For many patients, SOC treatments necessitate daily oral medication. These typically include:

- HCQ: a daily oral pill. Adherence data for HCQ in SLE patients indicates that a significant proportion (25% in one published study) may not take their pills as prescribed at any given time (102, 103). Sub-therapeutic levels of HCQ are associated with an increased likelihood of LN flares (101).
- MMF: requires patients to take approximately 4 pills per day. High rates of MMF non-adherence have been reported among patients with LN (103-105).
- GCs: pills prescribed daily, especially during induction phases, and often at low doses for maintenance over several years.

The introduction of newer oral treatments, while offering therapeutic benefits, can further exacerbate this existing pill burden. For example, VOC requires patients to take up to 6 pills per day. When added to the existing regimen of 4 MMF pills daily and additional pills to control blood pressure and comorbidities, a patient may be required to take 10 or more pills per day (68). Similarly, the monthly dosing requirement of BEL adds to the treatment burden for patients with LN (68). These burdens are especially significant given that most patients are of working and childbearing age, where the complexity of managing medications can impact daily functioning, adherence and quality-of-life to a greater extent.

Whilst advances in LN management guidelines, the definition of treatment goals associated with improved outcomes, and the approval of newer treatments described above have improved care (106-108), patients with LN are still burdened with increased morbidity and mortality (32, 34, 43). In addition, rates of lupus-associated ESRD are stable and have not kept pace with these advances (109, 110).

In summary, despite the recent approval of several new immunosuppressive therapies in LN, there is a need for effective drugs that can offer durable remission whilst not placing pill or administrative burden on patients.

1.3.5 Proposed position of obinutuzumab in the treatment pathway

OBI is expected be used as an option within a first-line triple immunosuppressive regimen for patients with LN. This positioning aligns with draft updates to the BSR and EULAR guidelines on management of SLE (including LN), which recommend use of OBI in combination with GCs and MPAA in the induction and maintenance phases of LN treatment, and is also consistent with feedback that Roche received from UK clinical experts at a recent advisory board (68, 91, 111).

1.4 Equality considerations

In the UK, the prevalence of LN is greater in ethnic minority populations, including Chinese, Afro-Caribbean and Indo-Asian populations, relative to the Caucasian population (Section 1.3.1.3) (23). Health inequalities among ethnic minority populations in the UK are well documented, with several studies reporting poorer health outcomes versus the Caucasian population (112, 113). Therefore, a uniform approach to diagnosing and treating SLE and LN across the UK is essential to mitigate diagnostic and treatment inequities (114).

2 Clinical effectiveness

2.1 Identification and selection of relevant studies

See Appendix B for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

2.2 List of relevant clinical effectiveness evidence

REGENCY serves as the pivotal study in this submission, while NOBILITY primarily plays a supportive role in evaluating primary efficacy. Additionally, NOBILITY provides valuable insights into the B-cell depletive effects of obinutuzumab and helps contextualise the overall and COVID-19 infection rates observed in REGENCY.

Table 6: Clinical effectiveness evidence

Study	REGENCY; NCT04221477	NOBILITY; NCT02550652
Study design	A phase III, randomised, double-blind, placebo controlled, multi-centre	A phase II randomised, double-blind, placebo controlled, multi-centre
Criteria for evaluation	Efficacy, safety, pharmacokinetics, pharmacodynamics and immunogenicity	Efficacy, safety, pharmacokinetics, pharmacodynamics and immunogenicity
Population	Patients with ISN/RPS 2003 Class III or IV ± Class V LN	Patients with ISN/RPS 2003 Class III or IV ± Class V LN
Intervention(s)	OBI plus SOC therapy (MMF and glucocorticoids [GCs])	OBI plus SOC therapy (MMF/mycophenolic acid (MPA) and GCs)
Comparator(s)	Placebo plus SOC therapy	Placebo plus SOC therapy
Indicate if study supports application for marketing authorisation	Yes	Yes
Indicate if study used in the economic model	Yes	Yes
Rationale if study not used in model	N/A	N/A
Reported outcomes specified in the decision problem	• Complete renal response • Complete renal response with steroid taper • Proteinuric response • eGFR • Time to death or renal-related event • Mortality • Safety and adverse events • Health-related quality of life	• Complete renal response
All other reported outcomes	• Overall renal response • Patient-reported outcomes • Renal flares • Serology	• Partial renal response • Renal flares • Pharmacodynamics (B-cell depletion)

	• SLEDAI-2K • Time to complete renal response • Pharmacokinetics • Pharmacodynamics (B-cell depletion)	

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Study design

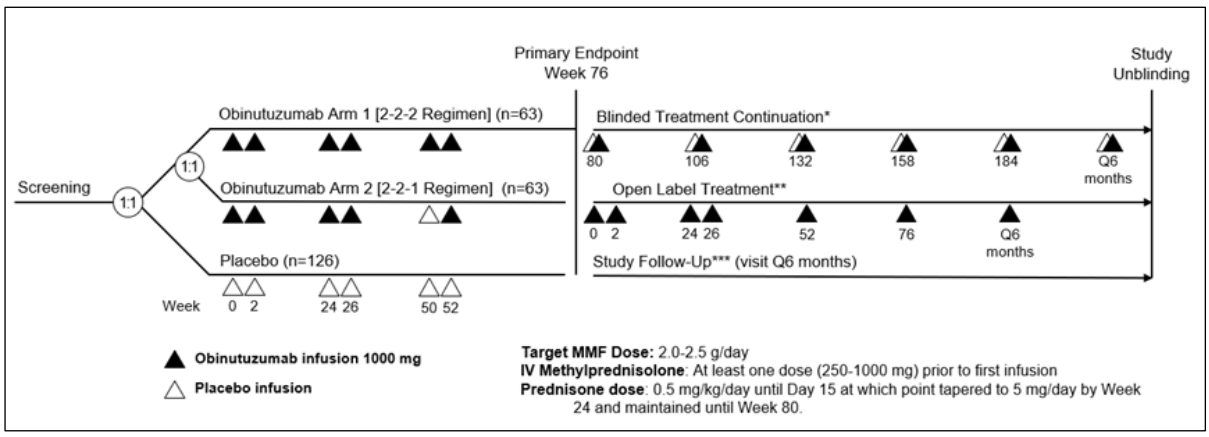
2.3.1.1 REGENCY

REGENCY (NCT04221477) is a phase III, randomised, double-blind, placebo-controlled, multi-centre study evaluating the efficacy and safety of OBI in patients with International Society of Nephrology (ISN)/Renal Pathology Society (RPS) 2003 Class III or IV, with or without concomitant Class V, LN treated with SOC therapy consisting of MMF and GCs. The study has completed enrolment, and the primary analysis has been completed (CCOD: 15 August 2024). The study is ongoing with an estimated completion date in 2028.

The REGENCY study consists of the following study periods: screening, blinded treatment, open-label treatment (OLT) and study follow-up (SFU).

An overview of the study design for REGENCY is presented in Figure 1. Additional details regarding the study design are found in the study protocol.

Figure 1: REGENCY study design



Key: IV, intravenous; MMF, mycophenolate mofetil.
*Patients with an adequate treatment response at Week 76 continue to receive blinded infusions every 6 months starting at Week 80, until study unblinding. **Patients with inadequate treatment response at Week 76 or with loss of response during blinded treatment after Week 80 can enter open-label treatment. ***Patents are followed though Week 76 and for at least 12 months from the last dose of OBI or placebo.

2.3.1.1.1 Blinded treatment up to Week 76

After screening, eligible patients were randomised to receive OBI or placebo in a 1:1 ratio. Randomisation was performed by stratified block design, stratified by region (United States and Canada vs. Latin America and the Caribbean vs. Other) and race (Black vs. Other).

Patients randomised to receive OBI were further randomised in a 1:1 ratio to receive one of the two OBI dosing schedules:

- Arm 1 (2-2-2 regimen): 1000 mg intravenous on Day 1 and Weeks 2, 24, 26, 50 and 52
- Arm 2 (2-2-1 regimen): 1000 mg intravenous on Day 1 and Weeks 2, 24, 26 and 52

In addition to OBI or placebo, all patients received MMF and GCs. MMF was titrated by Week 4 to a target dose of 2.0−2.5 g/day in divided doses. For patients newly initiating MMF, the recommended initial dosage was 1.5 g/day given in divided doses with titration by 500 mg/week to 2.0−2.5 g/day by Week 4. Oral GCs were initiated at a dose of 0.5 mg/kg (maximum 60 mg/day), tapered to a total daily oral maintenance dose of 5 mg at Week 24, and maintained at that dose until Week 76.

The primary efficacy endpoint was assessed at Week 76. The primary analysis was performed when all data were available for all patients who completed the Week 76 visit or discontinued the study prior to Week 76.

2.3.1.1.2 After Week 76

The design of REGENCY post-Week 76 is described in Appendix J.

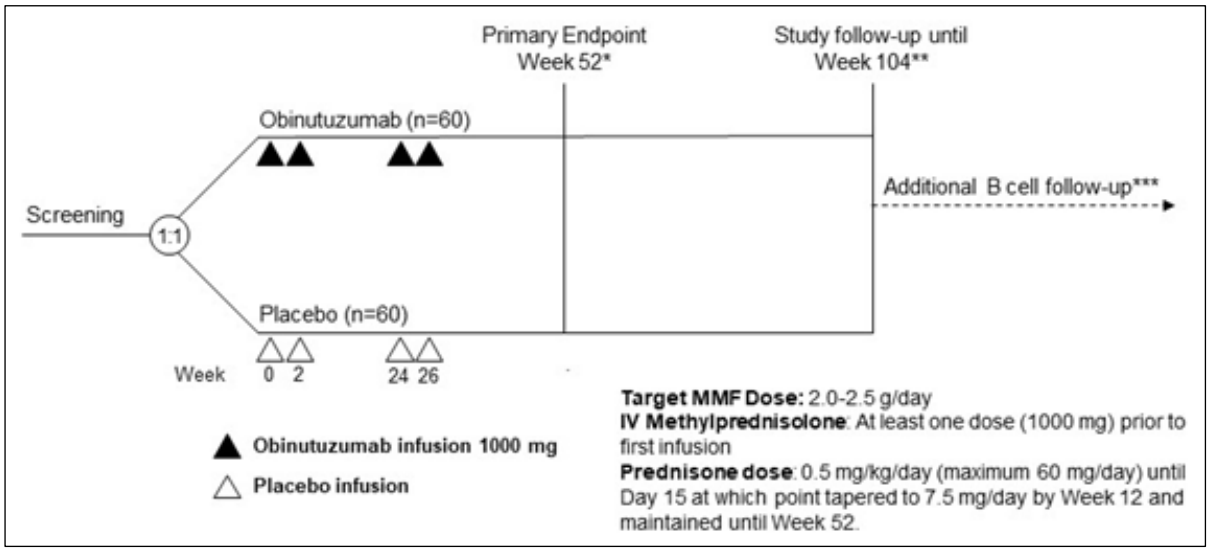
2.3.1.2 NOBILITY

NOBILITY (NCT02550652) is a completed phase II, randomised, double-blind, placebo controlled, parallel-group, multi-centre study that evaluated the safety and efficacy of OBI in patients with SLE and ISN/RPS 2003 Class III or IV, with or without concomitant Class V, LN, treated with SOC therapy consisting of MMF or MPA and GCs.

The study consisted of the following study periods: screening, blinded treatment, and a follow-up period.

An overview of the study design for NOBILITY is presented in Figure 2. Additional details regarding the study design are found in the study protocol.

Figure 2: NOBILITY study design



Key: MMF, mycophenolate mofetil; MPA, mycophenolic acid.
As per protocol, MPA at equivalent doses of 1440–1800 mg/day could be substituted for MMF at investigator discretion. *After Week 52, background immunosuppression was adjusted at the investigator's discretion/best medical judgement. **Patients and investigators remained blinded to the original treatment allocation until week 104.
***Additional B-cell follow-up (BCFU) visits occurred until patients achieved either their baseline CD19+ count or 25 cells/μL (the LLN of CD19+ B cells for this lupus population), whichever occurred first. However, BCFU visits for all patients ended when the last patient completed approximately 18 months of safety follow-up from the last dose of blinded OBI infusion, which marked the end of the study.

2.3.1.2.1 Blinded treatment up to Week 52

After screening, eligible patients were randomised in a 1:1 ratio to receive either OBI 1000 mg (administered by intravenous infusion in weeks 0, 2, 24, and 26) or placebo (infused on the same scheduled days as active treatment).

In addition to OBI or placebo, all patients received at least 1 g of intravenous methylprednisolone prior to randomisation, MMF (or an equivalent dose of MPA) and initiated an oral GC taper of prednisone. The target dose of MMF was 2.0−2.5 g/day; MPA at equivalent doses of 1440–1800 mg/day was substituted as needed. Prednisone was initiated at a dose of 0.5 mg/kg/day (maximum 60 mg/day) tapered to 7.5 mg/day by Day 84 and maintained at that dose until at least Week 52. Background immunosuppression was adjusted at the investigator's discretion.

The randomisation of patients into active treatment or placebo was conducted using a stratified block design, with stratification based on region (United States vs. non-United States) and race (Afro-Caribbean/African American vs. others) to ensure balanced treatment allocation.

No further doses of study treatment were administered after Week 26. The primary efficacy endpoint was assessed at Week 52.

2.3.1.2.2 Study follow-up

After Week 52, patients entered the follow-up period to receive SOC treatment as per the investigator's best medical judgment. During the follow-up period, the randomised treatment assignment was not revealed, and investigators and patients remained blinded until Week 104.

2.3.1.2.3 B-cell follow-up

Patients who did not achieve their baseline CD19-positive B-cell count or LLN of the lupus population entered a BCFU period after Week 104. BCFU visits occurred until patients achieved either their baseline CD19+ count or achieved 25 cells/μL CD19+ count (the LLN of CD19-positive B cells for this lupus population). BCFU visits for all patients ended when the last patient completed approximately 18 months of safety follow-up from the last dose of blinded OBI infusion.

The end of the NOBILITY study was defined as the last patient's last visit at Week 104.

2.3.2 Summary of study methodology

The methodology of the REGENCY and NOBILITIY studies is summarised in Appendices J and K.

2.3.3 Patient demographics and baseline characteristics

2.3.3.1 REGENCY

The OBI arm of the REGENCY study comprised arm 1 (2-2-2 OBI dosing schedule) and arm 2 (2-2-1 OBI dosing schedule) combined (refer to Section 2.3.1.1). The REGENCY patient population was generally well balanced between treatment arms with respect to demographics and baseline characteristics. At a recent advisory board, UK clinical experts agreed that this population is representative of UK clinical practice (Table 7) (68).

Although some difference was observed for the ethnicity category, the two treatment arms were generally well balanced with respect to demographic characteristics (gender, age, and race) in the efficacy-evaluable population (Table 7).

In REGENCY, most patients were female (84.5% OBI; 84.6% placebo) and aged 18−65 years, with a median age of 31.0 years. The median weight was 65.4 kg across both arms. Hispanic or Latino patients comprised 57.6% (62.5% placebo; 52.6% OBI), and 47.6% were White. Stratification by region and race resulted in balanced arms. Patients from Latin America and the Caribbean made up 56.8%, and Black patients were 11.8% overall. EU patients were 19.6%, while 80.4% were from non-EU countries.

Baseline 24-hour UPCR was similar: 3.14 g/g (SD: 2.99) OBI vs. 3.53 g/g (SD: 2.76) placebo. Mean eGFR was 102.8 ml/min/1.73 m² (SD: 29.3) OBI vs. 101.9 ml/min/1.73 m² (SD: 32.2) placebo. Most patients had eGFR ≥ 90 ml/min/1.73 m².

Class IV LN was present in 60.5% of patients, Class III in 39.5%, and Class V in 31.4%. Most had a prior LN history (57.9%), with a median duration of 36.5 months. For those without prior history, median LN duration from biopsy was 0.9 months. Other baseline characteristics were similar between arms.

Other baseline characteristics, such as serum creatinine, serum albumin, serologic markers and SLEDAI-2K scores, were similar between treatment arms (Table 7).

Table 7: Patient demographics and baseline characteristics of REGENCY study

Category	OBI (N=135)	Placebo (N=136)	All Patients (N=271)
Age (years)			
n	135	136	271
Mean (SD)	33.0 (10.5)	32.7 (10.0)	32.9 (10.2)
Median	30	31	31
Min - Max	18 – 64	18 – 72	18 – 72
Age group (years)			
n	135	136	271
<65	135 (100%)	135 (99.3%)	270 (99.6%)
≥65	0	1 (0.7%)	1 (0.4%)
Sex			
n	135	136	271

Male	21 (15.6%)	21 (15.4%)	42 (15.5%)
Female	114 (84.4%)	115 (84.6%)	229 (84.5%)
Ethnicity			
n	135	136	271
Hispanic or Latino	71 (52.6%)	85 (62.5%)	156 (57.6%)
Not Hispanic or Latino	54 (40.0%)	48 (35.3%)	102 (37.6%)
Not Stated	9 (6.7%)	1 (0.7%)	10 (3.7%)
Unknown	1 (0.7%)	2 (1.5%)	3 (1.1%)
Race			
n	135	136	271
American Indian or Alaska Native	25 (18.5%)	26 (19.1%)	51 (18.8%)
Asian	9 (6.7%)	7 (5.1%)	16 (5.9%)
Black or African American	20 (14.8%)	20 (14.7%)	40 (14.8%)
White	65 (48.1%)	64 (47.1%)	129 (47.6%)
Multiple	11 (8.1%)	9 (6.6%)	20 (7.4%)
Unknown	4 (3.0%)	6 (4.4%)	10 (3.7%)
Not reported	1 (0.7%)	4 (2.9%)	5 (1.8%)
Race (stratification factor)			
n	135	136	271
Black	15 (11.1%)	17 (12.5%)	32 (11.8%)
Other	120 (88.9%)	119 (87.5%)	239 (88.2%)
Region (stratification factor)			
n	135	136	271
United States and Canada	20 (14.8%)	20 (14.7%)	40 (14.8%)
Latin America and the Caribbean	77 (57.0%)	77 (56.6%)	154 (56.8%)
Other	38 (28.1%)	39 (28.7%)	77 (28.4%)
Region (EU/non-EU)			
n	135	136	271
EU	27 (20.0%)	26 (19.1%)	53 (19.6%)
non-EU	108 (80.0%)	110 (80.9%)	218 (80.4%)
Weight (kg)			
n	135	136	271
Mean (SD)	66.26 (14.03)	68.29 (15.53)	67.28 (14.81)
Median	65	65.5	65.4
Min - Max	36.7 – 106.3	46.0 – 133.6	36.7 – 133.6
Serum Creatinine (µmol/L)			
n	135	136	271
Mean (SD)	73.8 (34.1)	77.5 (42.2)	75.6 (38.4)
Median	70	69.5	69
Min - Max	30 – 332	24 – 388	24 – 388
eGFR (mL/min/1.73m^2)			
n	135	136	271
Mean (SD)	102.1 (39.3)	101.4 (32.2)	108.2 (30.8)
Median	107	109	108
Min - Max	15 – 164	13 – 166	13 – 166
eGFR (mL/min/1.73m^2) category			
n	135	136	271
<30	1 (0.7%)	1 (0.7%)	2 (0.7%)
30 - <60	19 (14.1%)	12 (8.8%)	31 (11.4%)
60 - <90	66 (48.9%)	20 (14.7%)	86 (31.7%)
≥90	96 (71.1%)	96 (70.6%)	192 (70.8%)
24-hour Urine Protein/Creatinine Ratio (mg/mg)			
n	134	136	270
Mean (SD)	3.11 (2.99)	3.52 (2.76)	3.31 (2.87)

Median	2.13	2.76	2.44
Min - Max	0.2 – 21.6	0.1 – 13.3	0.1 – 21.6
24-hour Urine Protein/Creatinine Ratio (mg/mg) category			
n	134	136	270
<3	82 (61.2%)	74 (54.4%)	156 (57.8%)
≥3	52 (38.8%)	62 (45.6%)	114 (42.2%)
Anti-dsDNA category*			
n	135	136	271
Negative	78 (57.8%)	75 (55.1%)	153 (56.5%)
Positive	57 (42.2%)	61 (44.9%)	118 (43.5%)
C3 Complement (g/L) category			
n	135	136	271
<0.9	77 (57.0%)	76 (55.9%)	153 (56.5%)
≥0.9	58 (43.0%)	60 (44.1%)	118 (43.5%)
C4 Complement (g/L) category			
n	135	136	271
<0.1	32 (23.7%)	42 (31.1%)	74 (27.4%)
≥0.1	103 (76.3%)	93 (68.9%)	196 (72.6%)
Serum albumin (g/L)			
n	135	136	271
Mean (SD)	34.7 (6.2)	34.0 (6.3)	34.4 (6.2)
Median	35	35	35
Min - Max	16 – 46	13 – 46	13 – 46
Baseline LN class			
n	135	136	271
Class III	56 (41.5%)	51 (37.5%)	107 (39.5%)
Class IV	79 (58.5%)	85 (62.5%)	164 (60.5%)
Baseline LN concomitant class V			
n	135	136	271
Yes	47 (34.8%)	38 (27.9%)	85 (31.4%)
No	88 (65.2%)	98 (72.1%)	186 (68.6%)
Prior history of LN			
n	135	136	271
Yes	81 (60.0%)	76 (55.9%)	157 (57.9%)
No	54 (40.0%)	60 (44.1%)	114 (42.1%)
Duration of LN for patients who had prior history of LN (months)			
n	81	76	157
Mean (SD)	65.62 (78.64)	59.33 (64.70)	62.58 (72.07)
Median	36.6	34.3	36.5
Min - Max	0.4 – 330.4	0.8 – 217.8	0.4 – 330.4
Duration of LN calculated from time to biopsy for patients who did not have prior history of LN (months)			
n	54	60	114
Mean (SD)	1.61 (1.65)	1.38 (1.18)	1.49 (1.42)
Median	0.9	0.9	0.9
Min - Max	0.2 - 6.8	0.2 - 5.0	0.2 - 6.8
SLEDAI-2K			
n	135	133	268
Mean (SD)	12.1 (8.1)	12.4 (6.7)	12.2 (7.4)
Median	10	12	10
Min - Max	4 – 83	2 – 35	2 – 83

Key: eGFR, estimated glomerular filtration rate; LN, lupus nephritis; SLEDIA-2K, Systematic Lupus Erythematosus Disease Activity Index 2000. *Positive for anti-dsDNA is >120 kU/L. Negative for anti-dsDNA is <=120 kU/L. All patients received standard of care, consisting of MMF and GCs, as per protocol.
Source: Study CA41705 Primary CSR. Report No. 1131275 (115)

2.3.3.2 NOBILITY

Patient demographics and baseline characteristics were generally comparable between the NOBILITY and REGENCY studies. Refer to Appendix K, Section 12.2, for a description of the NOBILITY study population.

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

2.4.1 REGENCY

The analysis populations are defined in Table 8.

Table 8: Definitions of REGENCY analysis populations

Population	Definition
Randomised population	Includes all patients randomised into the study.
Efficacy-evaluable population	Includes all randomised patients regardless of whether they received study drug. Patients are grouped according to randomised (assigned) treatment, rather than treatment received. Patients who received an incorrect therapy are reported under the treatment arm to which they were randomised.
Safety-evaluable Population	Includes patients who received any part of blinded infusion of OBI or placebo. Patients are grouped according to the treatment they actually received rather than the treatment assigned. Patients who received any part of an infusion of OBI as a study treatment (excluding OBI infusion received as a rescue therapy) even if not assigned to the OBI treatment arm at randomisation are reported under the OBI treatment arm.
Pharmacokinetic (PK)-evaluable population	Includes all patients who have been randomised to, and received, any dose of OBI given as study medication, and have at least one post-dose PK sample that is evaluable.

2.4.1.1 Determination of sample size

Based on the phase II NOBILITY study, it was estimated that approximately 30% of patients with proliferative LN who were receiving placebo would achieve CRR at Week 76 and that the addition of OBI to MMF would induce an overall CRR rate of 50% at Week 76. On the basis of these assumptions, a total of 252 patients randomised to OBI and placebo groups in a 1:1 ratio (126 patients in each of the OBI- and placebo-treated groups) stratified by region and race would yield approximately 90% power to compare the combined OBI treatment group with the placebo group at the two-sided $\alpha=0.05$ significance level using a Cochrane-Mantel-Haenszel (CMH) test, assuming the same CRR proportions across the strata. Patients randomised to the OBI-treated group were further randomised to OBI Arm 1 and OBI Arm 2 in a 1:1 ratio stratified by region and race.

2.4.1.2 Efficacy endpoints

The efficacy analyses were performed using the efficacy-evaluable population. The primary efficacy analysis for this trial compared OBI (combined treatment groups) with placebo on the basis of CRR at Week 76 to demonstrate superiority of OBI over placebo.

Secondary endpoints were tested to compare OBI (combined treatment groups) with placebo groups for the superiority of OBI over placebo. To control the overall type I error, a fall-back method maintaining a fixed sequence for testing was used.

The sequence for endpoint testing was the primary endpoint, followed by key secondary endpoints in the following order:

1. Proportion of patients who achieved CRR with successful prednisone taper at Week 76
2. Proportion of patients who achieved a proteinuric response at Week 76
3. Change in eGFR from baseline to Week 76
4. Proportion of patients who experienced death or renal-related events through Week 76
5. Proportion of patients who achieved an ORR evaluated at Week 50
6. Change in FACIT-F scale from baseline to Week 76

If the primary endpoint test was significant at two-sided alpha level 0.05, the first key secondary endpoint in the sequence, CRR with successful prednisone taper, was tested at alpha level 0.05. If the CRR with successful prednisone taper was not significant, the testing stopped and the endpoints after it in the sequence were deemed non-significant. If the CRR with successful prednisone taper was significant, the alpha 0.05 was split as 0.04 and 0.01 to the next two endpoints, the proteinuric response and the change in eGFR, respectively. If the proteinuric response endpoint was significant at 0.04 alpha level, this alpha was unused and was passed to the change in eGFR endpoint giving a total alpha for the change in eGFR endpoint test of 0.05 (0.01+0.04). The change in eGFR endpoint test was then performed at alpha level 0.05. If the proteinuric response endpoint was not significant at level 0.04, the change in eGFR endpoint was tested at the originally reserved alpha of 0.01. If the change in eGFR was not significant at either 0.05 or 0.01 depending on whether the proteinuric response endpoint was significant, the testing stopped. If the change in eGFR was significant, the unused alpha (either 0.05 or 0.01 depending on whether the proteinuric response endpoint was significant) was passed to the next endpoints in the sequence and each endpoint was tested sequentially after achieving the statistical significance on the previous endpoint. Testing stopped as soon as there was a failure of an endpoint in the following sequence to show significance. The endpoints after the non-significant endpoint in the sequence were deemed non-significant. The efficacy endpoints and methodologies are summarised in Table 9.

Table 9: Efficacy endpoint definitions and methodologies in REGENCY study

Endpoint	Analysis methodology
Primary Efficacy Objective	
• Proportion of patients who achieved a complete renal response (CRR) at Week 76, with CRR defined as achievement of all of the following: ○ UPCR < 0.5 g/g ○ eGFR ≥ 85% of baseline, as calculated using the CKD-EPI equation ○ No occurrence of the following intercurrent events[a]: rescue therapy, treatment failure, death, or early study withdrawal	• The proportions of patients achieving CRR in the OBI (combined treatment groups) and placebo groups were compared using the CMH test with region and race as stratification factors. • The proportion of patients achieving CRR in the OBI (combined) and placebo groups were presented along with the adjusted difference, 95% confidence interval (CI) for the adjusted difference, and p-value. • A summary of intercurrent events were be produced as well.
Secondary (Key) Efficacy Objectives[b]	
• Proportion of patients who achieved CRR with successful prednisone taper at Week 76, defined as achievement of CRR (as above) at Week 76 with the following: • No receipt of prednisone > 7.5 mg/day (or equivalent) from Week 64 through Week 76	• The endpoint was analysed using a CMH test with region and race as stratification factors.
• Proportion of patients who achieved a proteinuric response at Week 76, with proteinuric response defined as achievement of all of the following: • UPCR < 0.8 g/g • No occurrence of the following intercurrent events[a]: rescue therapy, treatment failure, death, or early study withdrawal	• The proportion of patients who achieve a proteinuric response at Week 76 were analysed using a CMH test with region and race as stratification factors.
• Mean change in eGFR from baseline to Week 76	• Change in eGFR from baseline at Week 76 was analysed using Analysis of Covariance (ANCOVA) model.
• Proportion of patients who experienced death or renal-related events through Week 76, defined as the proportion of patients with one or more of the following events: • Death • Treatment failure[c] • Worsening proteinuria, defined as a confirmed ≥ 50% increase in UPCR to a value ≥ 3 g/g • Worsening eGFR, defined as a confirmed ≥ 30% decrease in eGFR to a value < 60	• The proportion of patients who experienced death or renal-related events through Week 76 were analysed using a CMH test with region and race as stratification factors.

Endpoint	Analysis methodology

• Proportion of patients who achieved an ORR, defined as achievement of either CRR or PRR, evaluated at Week 50, with PRR defined as achievement of all of the following:
  • ≥ 50% reduction in UPCR from baseline
  • UPCR < 1g/g (or < 3 g/g if the baseline UPCR was ≥ 3 g/g)
  • eGFR ≥ 85% of baseline, as calculated using the CKD-EPI equation
  • No occurrence of the following intercurrent events[a]: rescue therapy, treatment failure, death, or early study withdrawal
  • Change in FACIT-F scale from baseline to Week 76
	• The proportion of patients who achieved an ORR, defined as achievement of either CRR or PRR, evaluated at Week 50 were analysed using a CMH test with region and race as stratification factors.

Supportive Secondary Efficacy Objectives	
• Change in anti-dsDNA titer from baseline to Week 50	• Change in anti-dsDNA from baseline to Week 50 were analysed with ANCOVA model
• Change in C3 from baseline to Week 50	• Change in C3 from baseline to Week 50 were analysed with ANCOVA model
• Change in SLEDAI-2K from baseline to Week 76	• Change in SLEDAI-2K from baseline to Week 76 were analysed with ANCOVA model
• Time to onset of CRR over the course of 76 weeks	• Time to CRR were summarised using Kaplan-Meier curves. • A stratified log-rank test was used to compare the treatment groups (combined OBI vs. placebo) over the 76 weeks treatment period, adjusting for race and region. • Median time to event (when estimable), and their 95% CIs, and a p-value from the log-rank test was presented. • The hazard ratio and its 95% CI was estimated using a Cox regression model stratified by stratification factors. • In fitting the Cox model, ties were handled with the approximate likelihood method of Efron (116).

• Proportion of patients who achieved CRR with serum creatinine criteria at Week 76, with CRR with serum creatinine criteria defined as achievement of all of the following:
  ○ UPCR < 0.5 g/g
  ○ Serum creatinine ≤ ULN (as determined by the central laboratory)
  ○ Serum creatinine not increased from baseline by > 25%
	• The proportion of patients who achieved CRR with serum creatinine criteria at Week 76 were analysed using a CMH test with region and race as stratification factors.

Endpoint	Analysis methodology
○ No occurrence of the following intercurrent events[a]: rescue therapy, treatment failure, death, or early study withdrawal	

Key: anti-dsDNA, anti-double strand DNA; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRR, complete renal response; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; ORR, overall renal response; PRR, partial renal response; SLEDAI-2K, Systematic Lupus Erythematosus Disease Activity Index 2000; ULN, upper limit of normal UPCR, urine protein-to-creatinine ratio

[a]Intercurrent events for the study are the following: rescue therapy, treatment failure, study treatment discontinuation, death, and early study withdrawal. [b]Note that key secondary endpoints are presented in the sequence for endpoint testing. [c]Treatment failure was present if any of the following criteria were met: (a) new ESRD or need for chronic dialysis or renal transplantation, (b) clinically significant, sustained worsening in UPCR and/or eGFR from Week 24 onward that led the investigator to conclude the patient had failed the randomized treatment regimen or (c) receipt of rescue therapy, except for corticosteroid-only rescue.

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2.4.1.3 Safety reporting and analyses

The safety analyses were performed on the safety-evaluable population with data collected in the Week 76 treatment period for each patient. Safety outputs include data until the point of rescue for the patients who received rescue therapy (excluding corticosteroid rescue). Limited key safety outputs were produced for post-rescue data.

Safety data were summarised by the OBI (combined treatment groups) and placebo groups. Additionally, combined OBI treatment groups were further broken down to OBI arm 1 (2-2-2 regimen) and OBI arm 2 (2-2-1 regimen) for selected key safety data up to Week 76. Additional analysis including post Week 76 data collected till CCOD were produced.

2.4.2 NOBILITY

The statistical analyses and definition of study groups in the supportive NOBILITY study are presented in Appendix K, Section 12.3.

2.5 Critical appraisal of the relevant clinical effectiveness evidence

Critical appraisal of the REGENCY and NOBILITY studies was performed using established risk of bias tools recommended for HTA submissions. A summary is presented in Table 10 and Table 11, respectively.

Table 10: REGENCY clinical effectiveness evidence quality assessment

Study question	REGENCY
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

Table 11: NOBILITY clinical effectiveness evidence quality assessment

Study question	NOBILITY
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

2.6 Clinical effectiveness results of the relevant studies

REGENCY serves as the pivotal study in this submission, while NOBILITY primarily plays a supportive role in evaluating primary efficacy. Additionally, NOBILITY provides valuable insights into the B-cell depletive effects of obinutuzumab and helps contextualise the overall and COVID-19 infection rates observed in REGENCY.

2.6.1.1 Study population and disposition

Of 513 patients screened for inclusion, a total of 271 patients were randomised in the REGENCY study. Of these, 135 patients were randomised to the OBI arm and 136 patients to the placebo arm; these patients comprise the efficacy-evaluable population. Patients randomised to the OBI arm were further randomised in a 1:1 ratio to receive one of two OBI dosing schedules (see Section 2.3.1.1): 69 patients were randomized to the OBI arm 1 (2-2-2 regimen) and 66 patients were randomised to OBI arm 2 (2-2-1 regimen).

A total of three patients randomised to the placebo arm were excluded from the safety evaluable population because they did not receive any study treatment after randomisation. One patient randomised to the placebo arm accidentally received OBI and is included in the

OBI arm (2-2-1 regimen) for the safety evaluable population. The safety-evaluable population, therefore, consisted of 268 patients: 136 patients in the OBI arm and 132 patients in the placebo arm.

At the time of the CCOD (15 August 2024) for the REGENCY primary analysis, 122 patients (90%) randomized to the OBI arm and 120 patients (88%) randomised to the placebo arm had completed a Week 76 visit (Figure 3).

A total of 71 patients (52.6%) in the OBI arm and 58 patients (42.6%) in the placebo arm were assessed as adequate responders at Week 76 and, as per the study design, continued blinded treatment after Week 76. In addition, a total of 39 patients in the placebo arm switched to OBI treatment after Week 76 during OLT as allowed per protocol.

As of the CCOD (15 August 2024), 218 patients (80.4%) remained in the study, 116 (85.9%) in the OBI arm and 102 (75.0%) in the placebo arm (Table 21). Among these patients:

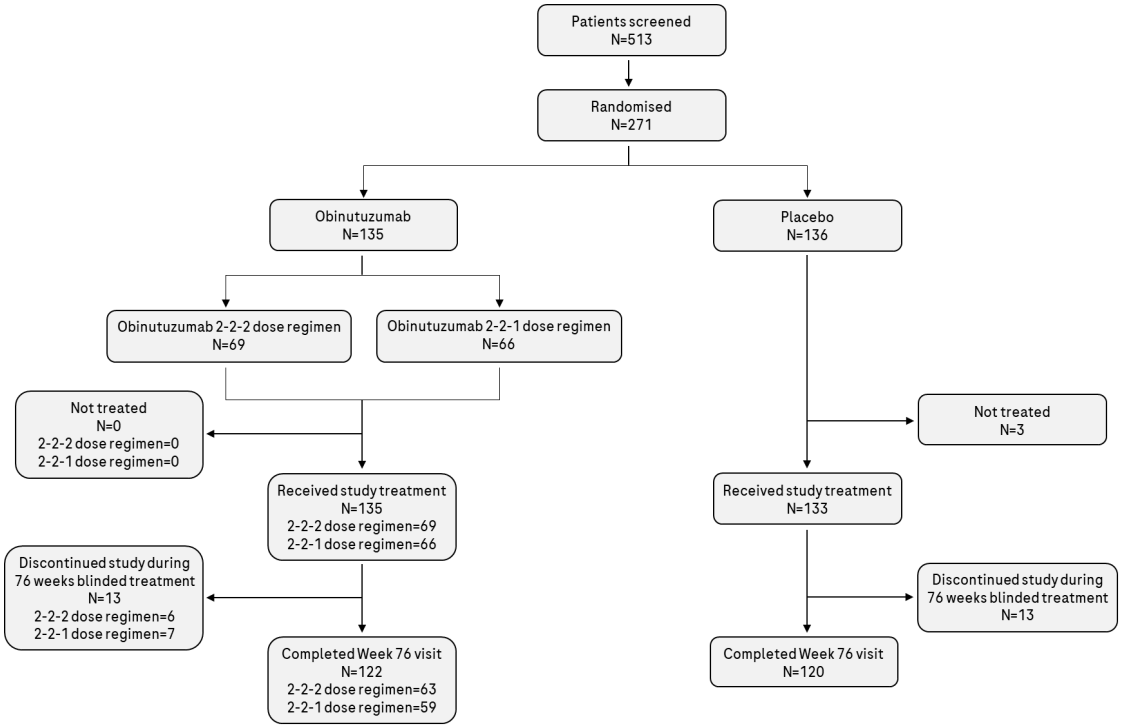
- 67 [49.6%] in the OBI arm and 49 [36.0%] in the placebo arm were ongoing in the post-Week 76 blinded treatment period.
- 26 [19.3%] from the OBI arm and 35 [25.7%] from the placebo arm were in the OLT period.
- 23 [17.0%] from the OBI arm and 18 [13.2%] from the placebo arm were in study follow-up.

Table 12: REGENCY patient disposition at CCOD (randomised population)

	Obinutuzumab (N=135)	Placebo (N=136)	All Patients (N=271)
Completed study, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued study, n (%)	[redacted]	[redacted]	[redacted]
Reasons			
Adverse event	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]
Non-compliance with study drug	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]	[redacted]
Ongoing study, n (%)	[redacted]	[redacted]	[redacted]
Reasons			
Ongoing in blinded treatment after Week 76	[redacted]	[redacted]	[redacted]
Ongoing in OLT period	[redacted]	[redacted]	[redacted]
Ongoing in study follow-up	[redacted]	[redacted]	[redacted]

Key: CCOD, clinical cut-off date; OLT, open-label treatment.
Source: Study CA41705 Primary CSR. Report No. 1131275 (115)

Figure 3: REGENCY patient disposition at CCOD



Source: Study CA41705 Primary CSR. Report No. 1131275 (115)

The percentage of patients who withdrew from the study prior to the Week 76 visit was comparable between treatment arms: 13 (9.6%) patients in the OBI arm and 16 (11.8%) patients in the placebo arm (Table 13).

Table 13: Reasons for study discontinuation during 76-week blinded treatment period (REGENCY; randomised patients)

	Obinutuzumab (N=135)	Placebo (N=136)	All Patients (N=271)
Discontinued study during 76 weeks blinded treatment, n (%)	13 (9.6)	16 (11.8)	29 (10.7)
Reasons			
Adverse event	0 (0.0)	1 (0.7)	1 (0.4)
Death	3 (2.2)	1 (0.7)	4 (1.5)
Lost to follow-up	0 (0.0)	1 (0.7)	1 (0.4)
Non-compliance with study drug	1 (0.7)	0 (0.0)	1 (0.4)
Other	0 (0.0)	2 (1.5)	2 (0.7)
Physician decision	0 (0.0)	5 (3.7)	5 (1.8)
Withdrawal by subject	9 (6.7)	6 (4.4)	15 (5.5)

Source: Study CA41705 Primary CSR. Report No. 1131275 (115)

In the safety-evaluable population, a total of 29 patients (21.3%) in the OBI arm and 38 patients (28.8%) in the placebo arm discontinued blinded OBI treatment up to Week 76. In general, the reasons for discontinuations from study treatment prior to the Week 76 visit were balanced between treatment arms except for discontinuations from study treatment due to lack of efficacy, which were numerically higher in the placebo arm compared with the OBI arm (Table 14).

Table 14: Reasons for study discontinuation from blinded obinutuzumab infusions (safety-evaluable population)

	Obinutuzumab (N=136)	Placebo (N=132)	All Patients (N=268)
Discontinued blinded obinutuzumab up to Week 76, n (%)	29 (21.3)	38 (28.8)	67 (25.0)
Reasons			
Adverse event	7 (5.1)	2 (1.5)	9 (3.4)
Death	3 (2.2)	1 (0.8)	4 (1.5)
Lack of efficacy	6 (4.4)	22 (16.7)	28 (10.4)
Other	2 (1.5)	2 (1.5)	4 (1.5)
Physician decision	4 (2.9)	6 (4.5)	10 (3.7)
Pregnancy	2 (1.5)	0 (0.0)	2 (0.7)
Withdrawal by subject	5 (3.7)	5 (3.8)	10 (3.7)

Source: Study CA41705 Primary CSR. Report No. 1131275 (115)

2.6.1.2 Primary efficacy endpoint

The definition of CRR used in REGENCY is one of the most stringent used for clinical trials, where patients had to achieve all the following for a CRR outcome:

- UPCR <0.5 g/g
- eGFR ≥85% of baseline at Week 76, as calculated using the CKD-EPI equation
- Serum creatinine ≤ULN at Week 76 (as determined by the central laboratory)
- Serum creatinine which did not increase from baseline more than >25%
- No occurrence of the following intercurrent events: Rescue therapy, treatment failure, death, or early study withdrawal

REGENCY met the primary efficacy endpoint of demonstrating a clinically meaningful and statistically significant improvement in CRR at Week 76 in the OBI arm compared with the placebo arm.

The proportion of patients who achieved CRR at Week 76 was greater in the OBI arm (46.4% [95% CI: 37.95, 54.86]) compared with the placebo arm (33.1% [95% CI: 25.18, 41.00]), with an adjusted difference of 13.40% (95% CI: 1.95, 24.84; p = 0.0232, pre-specified alpha of 5%) (Table 15).

Table 15: Difference in proportion of patients in complete renal response at Week 76 (REGENCY; efficacy-evaluable population)

	OBI (N=135)	Placebo (N=136)
Observed data, n (%)		
n	131	135
Responders	60 (45.8)	45 (33.3)
Non-responders	71 (54.2)	90 (66.7)
Main analytical approach (multiple imputation)		
Responders, % (95% CI)	46.4 (37.95, 54.86)	33.1 (25.18, 41.00)
Adjusted difference (95% CI)	13.40 (1.95, 24.84)	
p value (Cochran-Mantel-Haenszel)	0.0232	

Source: Study CA41705 Primary CSR. Report No. 1131275 (115)

2.6.1.3 Secondary efficacy endpoints

2.6.1.3.1 CRR with successful prednisone taper at Week 76

REGENCY met the key secondary efficacy endpoint of demonstrating a statistically significant improvement in CRR with successful prednisone taper (defined as no receipt of prednisone > 7.5 mg/day [or equivalent] from Week 64 through Week 76) at Week 76 in the OBI arm compared with the placebo arm.

A higher proportion of patients achieved CRR with successful prednisone taper at Week 76 in the OBI arm (42.7% [95% CI: 34.32, 51.09]) compared with the placebo arm (30.9% [95% CI: 23.12, 38.65]), with an adjusted difference of 11.88% (95% CI: 0.57, 23.18; p value = 0.0421, pre-specified alpha of 5%) (Table 16).

Table 16: Difference in proportion of patients in complete renal response with successful prednisone taper at Week 76 (REGENCY; efficacy-evaluable population)

	OBI (N=135)	Placebo (N=136)
Observed data, n (%)		
N	131	135
Responders	55 (42.0)	42 (31.1)
Non-responders	76 (58.0)	93 (68.9)
Main analytical approach (multiple imputation)		
Responders, % (95% CI)	42.7 (34.32, 51.09)	30.9 (23.12, 38.65)
Adjusted difference (95% CI)	11.88 (0.57, 23.18)	
p value (Cochran-Mantel-Haenszel)	0.0421	

Source: Study CA41705 Primary CSR. Report No. 1131275 (115)

2.6.1.3.2 Proteinuric response at Week 76

REGENCY met the key secondary efficacy endpoint of demonstrating a statistically significant improvement in proteinuric response at Week 76 in the OBI arm compared with the placebo arm.

The proportion of patients who achieved a proteinuric response at Week 76 was greater in the OBI arm (55.5% [95% CI: 47.09, 63.95]) compared with the placebo arm (41.9% [95% CI: 33.62, 50.20]), with an adjusted difference of 13.68% (95% CI: 2.01, 25.36; p value = 0.0227; pre-specified alpha of 4%) (Table 17).

Table 17: Difference in proportion of patients in proteinuric response at Week 76 (REGENCY; efficacy-evaluable population)

	OBI (N=135)	Placebo (N=136)
Observed data, n (%)		
N	131	134
Responders	72 (55.0)	56 (41.8)
Non-responders	59 (45.0)	78 (58.2)
Main analytical approach (multiple imputation)		
Responders, % (95% CI)	55.5 (47.09, 63.95)	41.9 (33.62, 50.20)
Adjusted difference (95% CI)	13.68 (2.01, 25.36)	
p value (Cochran-Mantel-Haenszel)	0.0227	

Source: Study CA41705 Primary CSR. Report No. 1131275 (115)

2.6.1.3.3 Mean change in eGFR from baseline to Week 76

REGENCY did not meet the key secondary efficacy endpoint of demonstrating a statistically significant improvement in mean change in eGFR from baseline to Week 76 with OBI, compared with placebo. As statistical significance for the third key secondary endpoint in the testing hierarchy was not met, all remaining key secondary endpoints could not be shown to be statistically significant.

However, eGFR numerically improved from baseline in the OBI arm (adjusted mean change: 2.31 mL/min/1.73 m^2 [SE: 2.713]) and numerically declined from baseline in the placebo arm (adjusted mean change: −1.54 mL/min/1.73 m^2 [SE: 2.706]), with a difference in adjusted means of 3.84 mL/min/1.73 m^2 (95% CI: −1.83, 9.51; p value = 0.1842, pre-specified alpha of 5%) (Table 18).

Table 18: Difference in mean change in eGFR from baseline to Week 76 (REGENCY; efficacy-evaluable population)

	OBI (N=135)	Placebo (N=136)
N	135	136
Adjusted mean (SE)	2.31 (2.713)	–1.54 (2.706)
Difference in Adjusted Means (95% CI)	3.84 (–1.83, 9.51)	
p value	0.1842	

Source: Study CA41705 Primary CSR. Report No. 1131275 (115)

2.6.1.3.4 Death or renal-related events through Week 76

Whilst statistical significance could not be claimed (due to an earlier key secondary endpoint in the testing hierarchy not being met), there was a clinically meaningful difference in the proportion of patients who experienced death or renal-related events through Week 76 in the OBI arm (18.9% [95% CI: 12.11, 25.61]) compared with the placebo arm (35.6% [95% CI: 27.50, 43.78]), with an adjusted difference of −16.83% (95% CI: −27.42, −6.23; nominal p value = 0.0026) (Table 19).

Table 19: Difference in proportion of patients in death or renal-related events through Week 76 (REGENCY; efficacy-evaluable population)

	OBI (N=135)	Placebo (N=136)
Observed data, n (%)		
N	135	136
Patients with events	24 (17.8)	46 (33.8)
Patients without events	111 (82.2)	90 (66.2)
Main analytical approach (multiple imputation)		
Patients with events, % (95% CI)	18.9 (12.11, 25.61)	35.6 (27.50, 43.78)
Adjusted difference (95% CI)	–16.83 (–27.42, –6.23)	
p value (Cochran-Mantel-Haenszel)	0.0026	

Source: Study CA41705 Primary CSR. Report No. 1131275 (115).

2.6.1.3.5 Overall renal response (CRR or PRR) at Week 50

Although REGENCY did not meet the secondary efficacy endpoint of demonstrating a statistically significant improvement in ORR at Week 50 in the OBI arm compared with the placebo arm, the proportion of patients who achieved ORR at Week 50 was numerically

greater in the OBI arm (59.1% [95% CI: 50.80, 67.43]) compared with the placebo arm (50.7% [95% CI: 42.16, 59.22]), with an adjusted difference of 8.36% (95% CI: −3.41, 20.12; nominal p value = 0.1670) (Table 20).

Table 20: Difference in proportion of patients in overall response at Week 50 (REGENCY; efficacy-evaluable population)

	OBI (N=135)	Placebo (N=136)
Observed data, n (%)		
n	124	119
Responders	68 (54.8)	56 (47.1)
Non-responders	56 (45.2)	63 (52.9)
Main analytical approach (multiple imputation)		
Responders, % (95% CI)	59.1 (50.80, 67.43)	50.7 (42.16, 59.22)
Adjusted difference (95% CI)	8.36 (–3.41, 20.12)	
p value (Cochran-Mantel-Haenszel)	0.1670	

Source: Study CA41705 Primary CSR. Report No. 1131275 (115)

2.6.1.3.6 Change in FACIT-F scale from baseline to Week 76

FACIT-F is a 40-item measure that assesses self-reported fatigue and its impact upon daily activities and function. Due to the testing hierarchy of the secondary endpoints, statistical significance could not be tested for the improvement in mean change in FACIT-F scale from baseline to Week 76, in the OBI arm compared with the placebo arm.

The adjusted mean change in FACIT-F scale from baseline to Week 76 was similar in the OBI arm (1.76 [SE: 1.223]) compared with the placebo arm [3.11 (SE: 1.212)], with a difference in adjusted means of − 1.35 (95% CI: − 3.89, 1.20; nominal p value = 0.2991) (Table 21).

Table 21: Difference in mean change in FACIT-F scale from baseline to Week 76 (REGENCY; efficacy-evaluable population)

	OBI (N=135)	Placebo (N=136)
N	135	136
Adjusted mean (SE)	1.76 (1.223)	3.11 (1.212)
Difference in Adjusted Means (95% CI)	–1.35 (–3.89, 1.20)	
p value	0.2991	

Source: Study CA41705 Primary CSR. Report No. 1131275 (115).

2.6.1.3.7 Change in anti-dsDNA antibody titre from baseline to Week 50

High titres of anti-dsDNA antibodies are strongly associated with active LN and are often used as a key indicator of disease flares and renal involvement. The adjusted mean change in log anti-dsDNA antibody titres from baseline to Week 50 was greater in the OBI arm (−0.38 [SE: 0.100]) compared with the placebo arm (−0.01 [SE: 0.099]), with a difference in adjusted means of −0.36 (95% CI: 0.57, 0.16; nominal p value = 0.0006) (Table 22).

Table 22: Difference in mean change in anti-dsDNA titre (log-transformed) from baseline to Week 50 (REGENCY; efficacy-evaluable population)

	OBI (N=135)	Placebo (N=136)
N	135	136
Adjusted mean (SE)	–0.38 (0.100)	–0.01 (0.099)
Difference in Adjusted Means (95% CI)	–0.36 (–0.57, –0.16)	
p value	0.0006	

Source: Study CA41705 Primary CSR. Report No. 1131275 (115).

2.6.1.3.8 Change in serum C3 from baseline to Week 50

A low level of serum C3 is indicative of active disease and organ damage in LN. The adjusted mean change in serum C3 from baseline to Week 50 was greater in the OBI arm (0.20 g/L [SE: 0.030]) compared with the placebo arm (0.06 g/L [SE: 0.030]), with a difference in adjusted means of 0.14 g/L (95% CI: 0.08, 0.20; nominal p value < 0.0001) (Table 23).

Table 23: Difference in mean change in serum C3 from baseline to Week 50 (REGENCY; efficacy-evaluable population)

	OBI (N=135)	Placebo (N=136)
N	135	136
Adjusted mean (SE)	0.20 (0.030)	0.06 (0.030)
Difference in Adjusted Means (95% CI)	0.14 (0.08, 0.20)	
p value	< 0.0001	

Source: Study CA41705 Primary CSR. Report No. 1131275 (115).

2.6.1.3.9 Change in SLEDAI-2K from baseline to Week 76

The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) is a widely recognised and validated scoring system that comprehensively assesses disease activity across various organ systems in patients with SLE, including those with LN. Higher scores indicate greater disease activity, making it a crucial tool for monitoring treatment response. [redacted] was noted in the activity of SLE with OBI compared with placebo. The adjusted mean change in SLEDAI-2K from baseline to Week 76 [redacted] in the OBI arm [redacted] compared with the placebo arm [redacted], [redacted] with a difference in adjusted means of [redacted] (95% CI: [redacted]) (Table 24).

Table 24: Difference in mean change in SLEDAI-2K from baseline to Week 76 (REGENCY; efficacy-evaluable population)

	OBI (N=135)	Placebo (N=136)
N	135	136
Adjusted mean (SE)	[redacted]	[redacted]
Difference in Adjusted Means (95% CI)	[redacted]	
p value	[redacted]	

Source: Study CA41705 Primary CSR. Report No. 1131275 (115).

2.6.1.3.10 Time to onset of CRR over the course of 76 weeks

Over the course of 76 weeks, the median time to onset of CRR (defined as the time from randomisation to the achievement of CRR) [redacted] in the OBI arm [redacted][95% CI:[redacted] compared with the placebo arm [redacted] [95% CI:[redacted], with a hazard ratio of [redacted](95% CI: [redacted] (Table 25).

Table 25: Time to onset of complete renal response over the course of 76 weeks (REGENCY; efficacy-evaluable population)

	OBI (N=135)	Placebo (N=136)
Patients with event, n (%)	[redacted]	[redacted]
Patients without event, n (%)	[redacted]	[redacted]
Time to event (weeks)		
Median (95% CI)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Range	[redacted]	[redacted]
Stratified Analysis p value (log-rank)	[redacted]	
Hazard ratio (95% CI)	[redacted]	

Source: Study CA41705 Primary CSR. Report No. 1131275 (115).

2.6.1.3.11 Proportion of patients who achieve CRR with serum creatinine criteria at Week 76

The proportion of patients who achieved CRR with serum creatinine criteria at Week 76 [redacted] in the OBI arm [redacted][95% CI: [redacted] compared with the placebo arm [redacted], with an adjusted difference of [redacted](95% CI: [redacted]. This [redacted] with the primary analysis results that used the eGFR criterion of ≥ 85% of baseline, using the CKD-EPI equation (Table 26).

Table 26: Difference in proportion of patients in complete renal response with serum creatinine criteria at Week 76 (REGENCY; efficacy-evaluable population)

	OBI (N=135)	Placebo (N=136)
Observed data, n (%)		
N	[redacted]	[redacted]
Responders	[redacted]	[redacted]
Non-responders	[redacted]	[redacted]
Main analytical approach (multiple imputation)		
Responders, % (95% CI)	[redacted]	[redacted]
Adjusted difference (95% CI)	[redacted]	
p value (Cochran-Mantel-Haenszel)	[redacted]	

Source: Study CA41705 Primary CSR. Report No. 1131275 (115).

2.6.1.3.12 Exploratory analyses

Time to LN Flare from Week 24 through Week 76

A LN flare from Week 24 through Week 76 was diagnosed if one of the following conditions occurred: eGFR decrease > 20% compared with Week 24 in patients with UPCR > 1 g/g and/or cellular casts; UPCR increase to > 1 g/g if Week 24 UPCR was < 0.2 g/g, or to > 2.0 g/g if Week 24 UPCR was 0.2−1 g/g, or to doubling if Week 24 UPCR was > 1 g/g ; receipt of rescue therapy, except for GC-only rescue

The proportion of patients with a LN flare between Weeks 24 and 76 was [redacted] in the OBI arm ([redacted]%) than the placebo arm ([redacted]%), with a hazard ratio of [redacted] (95% CI: [redacted], [redacted]; nominal p-value = [redacted]), supporting [redacted] of LN flares [redacted] OBI (Table 27). Additionally, the Kaplan-Meier plot of time to LN flare through Week 76 showed separation [redacted] arm beginning at Week 24 through Week 76 (Figure 7).

Table 27: Time to LN flare from Week 24 through Week 76 (REGENCY; efficacy-evaluable population)

	OBI (N=135)	Placebo (N=136)
Patients with event (%)	[redacted]	[redacted]
Patients without event (%)	[redacted]	[redacted]
Time to event (weeks)		
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
25% and 75% ile	[redacted]	[redacted]
Range	[redacted]	[redacted]
Stratified analysis		
p-value (log-rank)	[redacted]	
Hazard ratio (95% CI)	[redacted]	

Source: Study CA41705 Primary CSR. Report No. 1131275 (115).

Figure 4: KM plot of time to LN flare from Week 24 to Week 76 (REGENCY; efficacy-evaluable population)

Primary and key secondary endpoint analyses at Week 76 with 2-2-2 and 2-2-1 obinutuzumab regimens

Descriptive analysis of the OBI 2-2-2 and 2-2-1 regimens showed the point estimate for difference in primary endpoint (CRR at Week 76) versus placebo was numerically slightly higher in the 2-2-2 regimen than the 2-2-1 regimen, while being clinically meaningful for both regimens (Table 28).

Acknowledging the small sample size in each regimen as well as the descriptive nature of the analysis, the two regimens appear comparable and there is no clinically meaningful difference between the two regimens.

The finding that the two regimens are comparable is further supported by the results for the key secondary endpoints, which did not show a consistent direction in favour of one regimen over the other. Overall, the difference in proportions of patients across the key secondary

endpoints is not considered clinically meaningful, suggesting that the efficacy outcomes for the two regimens up to Week 76 are comparable. This, combined with the pooled safety data up to week 76, and the results of the exposure-efficacy and exposure-safety analyses and associated clinical trial simulations, provide sufficient evidence to support the proposed registration dose and schedule of OBI administration (Table 2, Section 1.2) to achieve a favourable clinical benefit-risk profile in patients with active LN.

Table 28: Difference in proportion of patients in complete renal response at Week 76 by obinutuzumab dose regimen (REGENCY; efficacy-evaluable population)

	OBI Arm 1 (2-2-2 Regimen) (N=69)	OBI Arm 2 (2-2-1 Regimen) (N=66)	Placebo (N=136)
Observed data, n (%)			
N	66	65	135
Responders	31 (47.0)	29 (44.6)	45 (33.3)
Non-responders	35 (53.0)	36 (55.4)	90 (66.7)
Main analytical approach (multiple imputation)			
Responders, % (95% CI)	46.9 (35.02, 58.83)	45.5 (33.44, 57.47)	33.1 (25.18, 41.00)
Adjusted difference (95% CI)	13.95 (–0.06, 27.96)	12.67 (–1.49, 26.72)	

Source: Study CA41705 Primary CSR. Report No. 1131275 (115)

Efficacy analyses of blinded treatment beyond Week 76

Overall, [redacted] in the OBI arm and [redacted] in the placebo arm were assessed as adequate responders at Week 76 and continued in the blinded treatment period post-Week 76 (post-Week 76 blinded treatment efficacy-evaluable population). Of these, [redacted] patients in the OBI arm and [redacted] patients in the placebo arm achieved CRR at Week 76. Comparisons between the OBI and placebo arms may not be meaningful given the biased nature of the adequate responder patient population, potential baseline imbalances between treatment arms (since the patients were not re-randomised into the continued blinded treatment period), and small sample sizes, especially at later time points. For this reason, only evaluation of results in the OBI arm are presented below.

A total of [redacted] patients in the OBI arm were included at Weeks [redacted] respectively, in the post-Week 76 analysis population. These patients had reached or would have reached the visit weeks by the primary analysis CCOD unless they discontinued blinded treatment period due to study withdrawals, moving to OLT or SFU. Whilst acknowledging the limitations noted above, results of exploratory analysis in patients in the OBI arm receiving one dose of OBI every 6 months showed that the proportion of patients who met the primary CRR endpoint [redacted] with [redacted] patients [redacted] achieving CRR at Week [redacted] patients [redacted] achieving CRR at Week [redacted] patients [redacted] achieving CRR at Week [redacted] patients [redacted] achieving CRR at Week [redacted], and [redacted] patients [redacted] achieving CRR at Week [redacted].

B-cell depletion

OBI has been shown to achieve deep and sustained B-cell depletion in pre-clinical assays and non-human primate lymphoid tissue compared with the type I antibody RTX (1, 4).

Greater B-cell depletion has also been demonstrated for OBI relative to RTX in in vitro assays using whole blood from patients with SLE (4, 117) and in a pre-clinical mouse model of lupus (118).

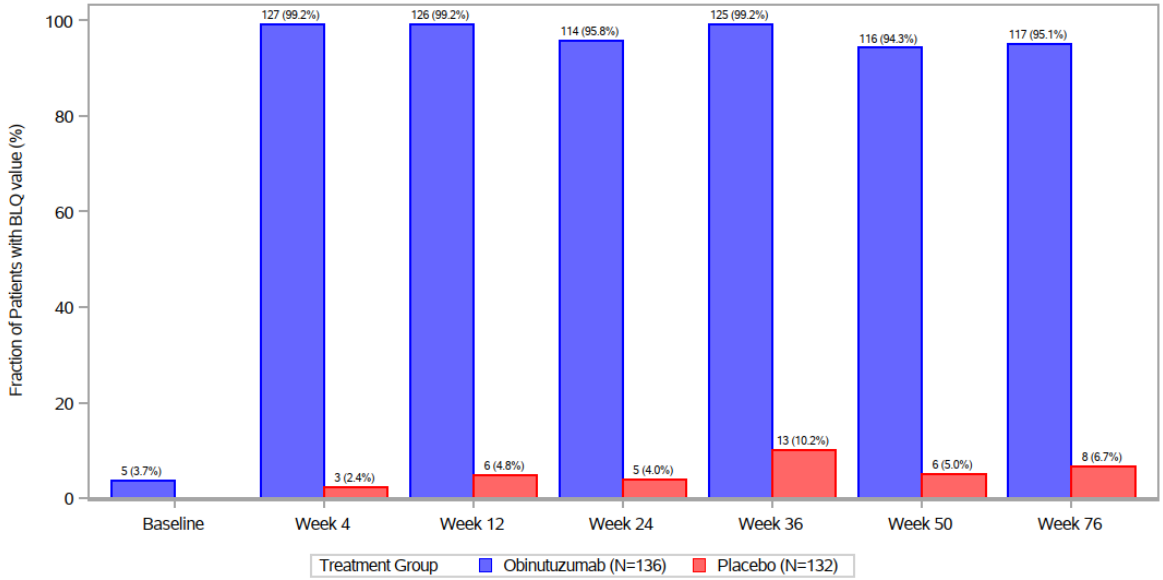
In REGENCY, CD19-positive B-cell levels were measured over time in the safety-evaluable population using flow cytometry assays.

CD19-positive B cells were rapidly and markedly reduced in the blood of patients receiving OBI, with average levels at or below the defined threshold of 10 cells/μL at every time point assessed up to Week 76.

The percentage of patients with peripheral B-cell depletion (defined as CD19-positive B cells below 10 cells/μL) in the OBI arm vs. placebo arm, respectively, were the following: 99.2% vs. 2.4% at Week 4; 99.2% vs. 4.8% at Week 12; 95.8% vs. 4.8% at Week 24 prior to the second course of treatment with OBI; 94.3% vs. 5.0% at Week 50; and 95.1% vs. 6.7% at Week 76.

Additional analysis using a high-sensitivity flow cytometry assay (MRB1.1) showed that a large proportion of patients in the OBI arm had undetectable CD19-positive B-cells (i.e., had peripheral CD19-positive B-cells depleted BLQ of MRB1.1 (LLOQ = 0.441 cells/μL of blood) at every time point tested compared with the placebo arm. The percentage of patients with peripheral B-cells BLQ was (OBI arm vs. placebo arm, respectively) 78.0% vs. 1.7% at Week 4; 60.2% vs. 0.8% at Week 24; 66.9% vs. 1.7% at Week 50; 70.4% vs. 1.7% at Week 76.

Figure 5: Proportion of patients with B-cell depletion by visit (REGENCY; safety-evaluable population)



B-cells were quantified with the TBNK flow cytometry assay. Patients were considered B-cell depleted if their B-cells were below the limit of quantitation (BLQ), defined as 1 cell/μL.
Source: Study CA41705 Primary CSR. Report No. 1131275 (115).

2.6.2 NOBILITY

2.6.2.1 Primary efficacy endpoint

NOBILITY met the primary efficacy endpoint of demonstrating a statistically significant and clinically meaningful improvement in CRR at Week 52 in the OBI arm compared with the placebo arm.

The proportion of patients who achieved CRR at Week 52 was greater in the OBI arm (34.9%) compared with the placebo arm (22.6%), with a difference of 12.3% (80% CI: 2.1%, 22.6%; p = 0.1145, pre-specified alpha of 20%) (Table 29).

Table 29: Difference in proportion of patients who achieved CRR at Week 52 (NOBILITY; mITT population)

	OBI (N=63)	Placebo (N=62)
Observed data, n (%)		
N	63	62
Responders	22 (34.9)	14 (22.6)
Non-responders	41 (65.1)	48 (77.4)
Difference (80% CI)	12.3 (2.1, 22.6)	
p-value (Cochrane-Mantel-Haenzel)	0.1145[a]	

[a]Statistically significant at pre-specified alpha of 20%.
CI, confidence interval; mITT, modified intention-to-treat
Source: Study WA29748 Final CSR. Report No. 1126044 (117)

At Weeks 76 and 104, CRR was also greater in the OBI arm compared with the placebo arm, with CRR response differences to placebo of 20.4% (80% CI: [10.3%, 30.4%], p = 0.0109) at Week 76 and 20.3% (80% CI: [9.8%, 30.8%], p = 0.0162) at Week 104.

Patients who switched to rescue medication prior to Week 52, Week 76 and Week 104 were considered non-responders for those respective time points. A total of nine patients in the OBI arm and 15 patients in the placebo arm received rescue medication after the first treatment. Treatments after baseline that were considered rescue medications were pulse-dose methylprednisolone (≥ 500 mg), cyclophosphamide, RTX or other new immunosuppressive therapies.

2.6.2.2 Secondary efficacy endpoint – proportion of patients who achieved a PRR at Week 52

At Week 52, statistically significant treatment benefits were observed in the OBI arm compared with the placebo arm for PRR (55.6% vs 33.9% [80% CI: 10.6%, 32.8%; p = 0.0150; pre-specified alpha of 20%) (Table 30). This trend persisted at Weeks 76 (31 patients [49.2%] vs 18 patients [29.0%]) and at Week 104 (34 patients [54.0%] vs 18 patients [29.0%]).

Table 30: Differences in proportion of patients who achieved PRR at Week 52 (NOBILITY; mITT Population)

	OBI (N=63)	Placebo (N=62)
Observed data, n (%)		
N	63	62

Responders	35 (55.6)	21 (33.9)
Non-responders	28 (44.4)	41 (66.1)
Difference (80% CI)	21.7 (10.6, 32.8)	
p-value (Cochrane-Mantel-Haenzel)	0.0150[a]	

[a]Statistically significant at pre-specified alpha of 20%. Key: CI, confidence interval, mITT, modified intention-to-treat; PRR, partial renal response. Source: Source: Study WA29748 Final CSR. Report No. 1126044 (117)

2.6.2.3 Exploratory efficacy endpoint – renal flares

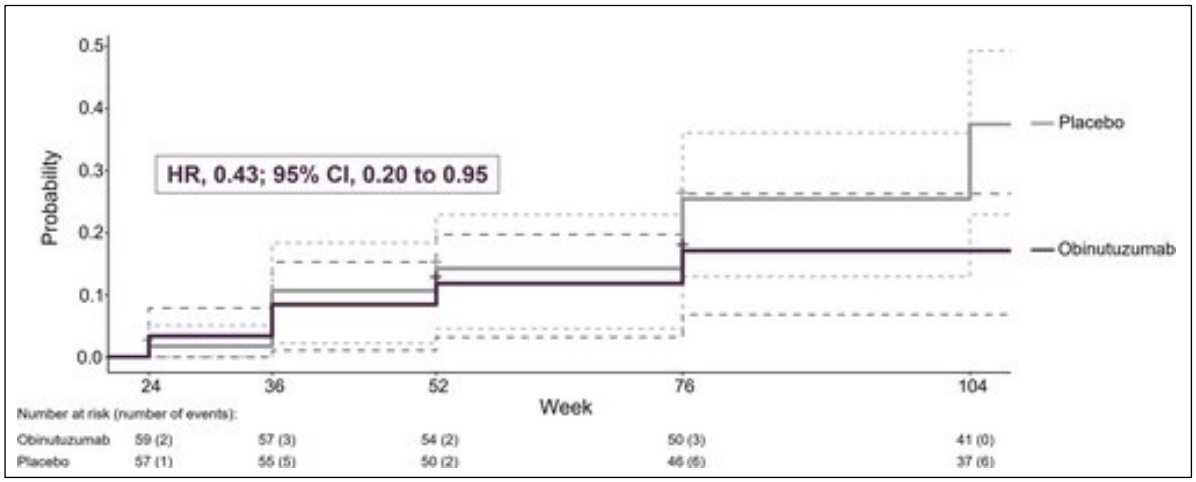
This exploratory endpoint is used to validate and support REGENCY renal flare data to compare with the proportion of patients experiencing renal flares with MMF and VOC+MMF.

Renal flares are defined by the presence of all of the following criteria:

- Stable or increased creatinine
- Worsening active urinary sediment from baseline, as defined by a $\geq$50% increase in RBC/HPF or the appearance of new RBC casts when none are previously present
- Increase in proteinuria, as evidenced by an increase in the UPCR to >2 if the most recent UPCR was <2.

At Week 52, no patients in the OBI arm and 2 patients (3.3%) in the placebo arm experienced a renal flare. At Week 104, 2 patients (3.4%) in the OBI arm and 2 patients (4.3%) in the placebo arm experienced a renal flare (119). Compared to placebo, OBI treatment reduced the risk of a renal flare by 57% (HR 0.43, 95% CI: 0.20-0.95) at Week 104 (Figure 6) (120).

Figure 6: Time to renal flare (NOBILITY; mITT population)



Taken from Rovin et al. 2024 (120)

2.6.2.4 B-cell depletion

In NOBILITY, CD19-positive B-cell levels were measured over time in the safety population using flow cytometry assays.

Baseline CD19-positive B-cell levels were similar for patients in the OBI and placebo arms (208 cells/mL and 187 cells/mL, respectively). From Week 2 through Week 104. CD19-positive B-cells were profoundly reduced in the blood of patients treated with OBI relative to placebo.

At the first time point tested, Week 2, 90% of patients on the OBI arm had B-cells depleted below the limit of quantitation (BLQ) of the assay (lower limit of quantitation = 0.441 cells/μL of blood), compared to 2% of patients on the placebo arm.

The levels of CD19-positive B cells in the OBI arm patients remained profoundly reduced through Week 12. At Week 24, before the second course of treatment with OBI, 72% of patients in the OBI arm had B-cells BLQ. At Week 52, 79.6% of patients on the OBI arm had B-cells BLQ. By Week 104, which was 78 weeks after the last dose of OBI, 91% of patients on the OBI arm had detectable B-cells. At all time points evaluated, >95% of patients on the placebo arm had detectable B-cells.

In samples taken post-Week 104, a small number of patients continued to have undetectable B cells measured by high-sensitivity flow cytometry and were monitored for an additional period. By month 42, all but 1 patient had detectable B-cells. Given the associations between sustained B-cell depletion and response, and the observation of B-cell repletion at Week 104 in NOBILITY, the dosing of OBI in REGENCY was adjusted to maintain B-cell depletion.

2.7 Subsequent treatments used in the relevant studies

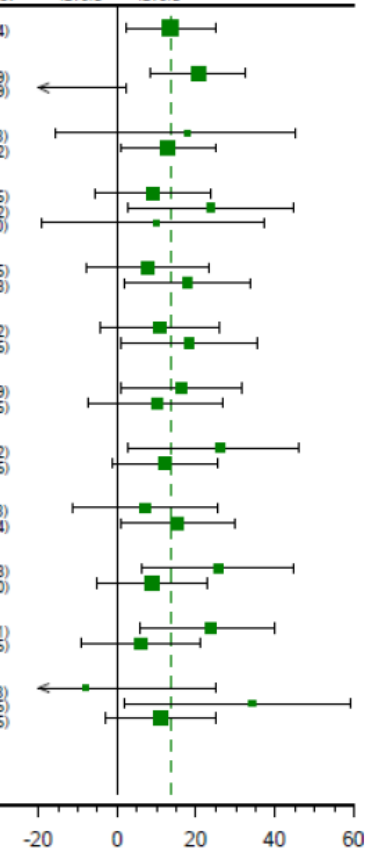
In the REGENCY and NOBILITY studies, management of disease flares with temporary increases in corticosteroid doses whilst continuing the study treatment regimen was permitted. In some cases of worsening or severely active disease, patients would have been deemed to have failed the study treatment, requiring rescue therapy. Because these rescue therapies could have affected subsequent efficacy assessments, patients who received rescue were treated as non-responders for subsequent efficacy analyses. Refer to Section 3.5.1.4 for details of subsequent treatments and their proportions.

2.8 Subgroup analysis

In the REGENCY study, pre-specified subgroup analyses of the primary endpoint based on key baseline risk factors showed a generally consistent treatment benefit in favour of OBI across different subgroups, including subgroups which are indicative of high disease activity at baseline: 24-hour UPCR ≥ 3 g/g, anti-dsDNA > 120 kU/L, C3 < 0.9 g/L, C4 < 0.1 g/L, and presence of concomitant Class V LN (Figure 7). All analyses are exploratory in nature and should be interpreted with caution, particularly for subgroups with a small sample size.

Figure 7: Forest plot of difference in proportion of patients in CRR at Week 76 by subgroup (REGENCY; efficacy-evaluable population)

Baseline Risk Factors	Total n	Placebo (N=136) n	Placebo (N=136) Responders (%)	Obinutuzumab (N=135) n	Obinutuzumab (N=135) Responders (%)	Adjusted Difference (%)	95% CI
All Patients	271	136	33.1	135	46.4	13.40	(1.95, 24.84)
Sex							
Female	229	115	27.0	114	47.1	20.55	(8.42, 32.69)
Male	42	21	66.7	21	42.9	-28.16	(-53.30, 2.29)
Race							
Black	32	17	41.2	15	60.0	17.74	(-15.75, 45.43)
Other	239	119	31.9	120	44.7	12.82	(0.72, 24.92)
Region							
Latin America and the Caribbean	154	77	29.9	77	38.8	9.16	(-5.52, 23.85)
Other	77	39	35.9	38	59.8	23.67	(2.82, 44.52)
United States and Canada	40	20	40.0	20	50.0	10.00	(-19.34, 37.20)
24-hour UPCR at Baseline (mg/mg)							
<3	156	74	45.9	82	52.0	7.77	(-7.71, 23.25)
>=3	114	62	17.7	52	36.5	17.78	(1.63, 33.93)
ds-DNA at Baseline (kU/L)							
<=120	153	75	32.0	78	42.4	10.83	(-4.17, 25.82)
>120	118	61	34.4	57	51.9	18.30	(0.95, 35.66)
C3 Complement at Baseline (g/L)							
<0.9	153	76	34.2	77	52.8	16.40	(1.01, 31.79)
>=0.9	118	60	31.7	58	37.9	10.18	(-7.26, 26.85)
C4 Complement at Baseline (g/L)							
<0.1	74	42	35.7	32	62.5	26.15	(2.43, 46.12)
>=0.1	196	93	31.2	103	41.4	11.95	(-1.36, 25.26)
Lupus Nephritis Class at Baseline							
Class III	107	51	41.2	56	49.5	7.05	(-11.52, 25.63)
Class IV	164	85	28.2	79	44.2	15.17	(0.80, 29.54)
Lupus Nephritis Concomitant Class V at Baseline							
Concomitant Class V	85	38	23.7	47	49.1	25.53	(6.33, 44.73)
No Concomitant Class V	186	98	36.7	88	45.0	8.82	(-5.16, 22.80)
Prior Lupus History at Baseline							
No Prior History of LN	114	60	26.7	54	51.9	23.75	(5.73, 39.81)
Prior History of LN	157	76	38.2	81	42.8	6.03	(-9.19, 21.25)
eGFR at Baseline (mL/min/1.73m2)							
30 - <60	31	19	26.3	12	16.7	-8.03	(-34.09, 25.03)
60 - <90	46	20	15.0	26	53.8	34.33	(1.54, 59.45)
>=90	192	96	38.5	96	48.6	10.93	(-2.99, 24.85)



CRR, complete renal response; ds-DNA, double stranded DNA; eGFR, estimated glomerular filtration rate; LN, lupus nephritis; UPCR, urine protein-to-creatinine ratio. Source: Study CA41705 Primary CSR. Report No. 1131275 (115).

2.9 Meta-analysis

REGENCY investigated OBI versus placebo in an RCT (115). Other head-to-head evidence is not available to compare OBI with other treatments (i.e. VOC and RTX). Therefore, a network meta-analysis (NMA) was performed to estimate the relative efficacy of OBI versus all relevant comparators.

2.10 Indirect and mixed treatment comparisons

2.10.1 Methods

In the absence of direct evidence versus other treatments, an NMA was conducted using published evidence identified from the clinical SLR. The clinical SLR was conducted to evaluate the efficacy, safety, tolerability and HRQoL of OBI and relevant comparators from RCTs involving patients with LN. Initial searches were completed between 22 April and 29 May 2024 and an update of the SLR was performed on 13 February 2025. A full overview of the clinical SLR is presented in Section 2.1 and Appendix B.

Additionally, a feasibility assessment for a subsequent NMA comparing clinical interventions and outcomes across trials was conducted. A robust feasibility assessment is crucial to the relevance and credibility of subsequent statistical analyses for decision-making. The feasibility assessment was undertaken using transparent, stepwise methodology:

- Step 1: Relevant RCTs identified in the SLR were prioritised based on key criteria such as population characteristics (e.g. ≥90% adults), disease classification (e.g. ≥80% with ISN/RPS Class III/IV [with or without Class V]), and alignment with recommended treatments guidelines.
- Step 2: Best-case evidence network was constructed to identify studies that were relevant for indirect comparisons.
- Step 3: Comparability of trials in the network were evaluated in terms of study and patient characteristics and determining whether any heterogeneity may affect the validity of an NMA.
- Step 4: Outcome-specific evidence networks were developed by reviewing the data available for each outcome of interest.

In the feasibility assessment, it was determined whether the RCTs were deemed sufficiently homogeneous to allow comparability of outcomes and if they formed a connected network for each outcome of interest including CRR, PRR, ORR and change in eGFR from baseline. The base case analysis used the endpoint value at the primary analysis time for the study. Values before 48 weeks were excluded, as only studies with the primary analysis at 48 weeks or later were included in the network. A 48-week cut-off was used to differentiate between short-term (<48 weeks) and long-term (≥48 weeks) treatment efficacy, as, in clinical practice treatments such as MMF are generally found to have distinct efficacy over shorter (e.g. 6 months) versus longer durations (e.g. 1.5–2 years).

A Bayesian NMA was conducted. Renal response outcomes (CRR, PRR, and ORR) were analysed using odds ratios (ORs) on the log OR scale and a normal likelihood. Change from baseline (CFB) in eGFR was modelled as continuous data, using the arm level mean CFB

as the outcome. Besides the base case NMA for the best-case network, various scenario and sensitivity analyses (using MMF subgroup data for CRR from BLISS-LN; Week 50 ORR data from REGENCY; using fixed-effects and random effects models with alternative priors) were conducted. The limited number of studies (maximum 6 per network) precluded any network meta-regression.

Deviance information criterion (DIC) was used to compare the relative fit of competing models. Models with a lower DIC were preferred. Differences in DIC of less than 5 points were not considered meaningful. In such cases, the base case RE model was preferred as the priori model because of its ability to incorporate between study variability. To judge the absolute fit, the total residual deviance was calculated and compared against the total number of independent data points. For RE models, the estimate and 95% credible intervals (CrIs) for the between-study SD (tau) were also presented. Inconsistency of direct and indirect evidence in the Bayesian framework was assessed using a node-splitting method, as described in NICE DSU TSD 4 (Dias et al., 2014, Dias et al., 2010) (121). The inconsistency assessment was initially performed for the CRR and PRR independent of CRR outcomes. If evidence of inconsistency was identified for these outcomes, further inconsistency assessment was planned for other outcomes. Further assessment was not required, as node splitting showed no evidence of inconsistency.

The analysis was implemented using R Version 4.3.3 and JAGS Version 4.3.0 (called from R). Models initially used 40,000 iterations, 10,000 burn-in, and thinning parameter of 10. Three parallel chains were run in all model fits. There was a high degree of autocorrelation between study heterogeneity parameter (tau) for PRR independent of CRR and ORR. To address high autocorrelation and improve chain mixing, the number of iterations was increased to 400,000, with a burn-in of 100,000, and a thinning of 100, applied consistently across all outcomes.

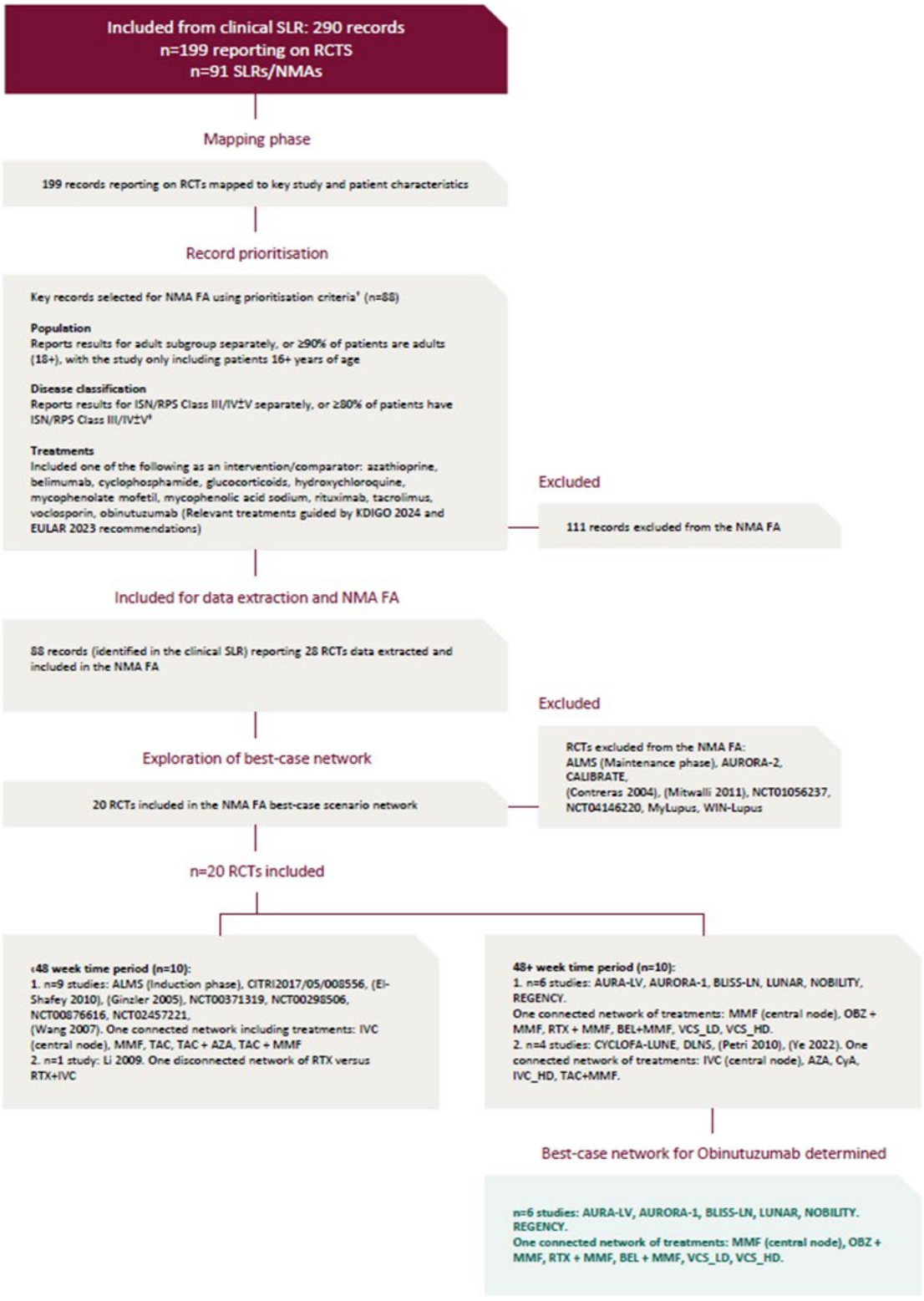
Results of the NMA are presented as ORs or mean difference (MD) with associated 95% credible intervals (CrIs). An OR > 1 indicates a better renal response (CRR, PRR independent of CRR, and ORR) with OBI+MMF relative to other comparators. Similarly, an MD of > 0 indicates a higher eGFR preservation with OBI+MMF relative to other treatments. The results were considered statistically significant if the 95% CrI excluded 1 for binary outcome (CRR, PRR and ORR) and 0 for continuous outcome (CFB in eGFR).

2.10.2 Study selection

82 RCTs from 200 publications were identified as being relevant to the SLR based on the inclusion criteria (Appendix B). The feasibility assessment prioritised the primary population of interest, i.e. adult patients with ISN/RPS Class III/IV (with or without Class V) LN. A total of 28 studies (across 91 publications), including the REGENCY trial, were considered for the feasibility assessment. Eight of these were excluded due to limitations, such as the lack of a clearly defined primary endpoint, inappropriate comparator arms or continuation designs involving responder-only populations. Full limitations detailed in Appendix B. 20 studies were retained for the feasibility assessment. Figure 8 presents a flow diagram detailing the study selection process for the feasibility assessment, and the studies included in the best-case network.

Further details on the overview of the included studies, evidence network, and heterogeneity assessment, including study and baseline characteristics, treatment regimens, outcomes definitions, and risk of bias assessment are available in Appendix B.

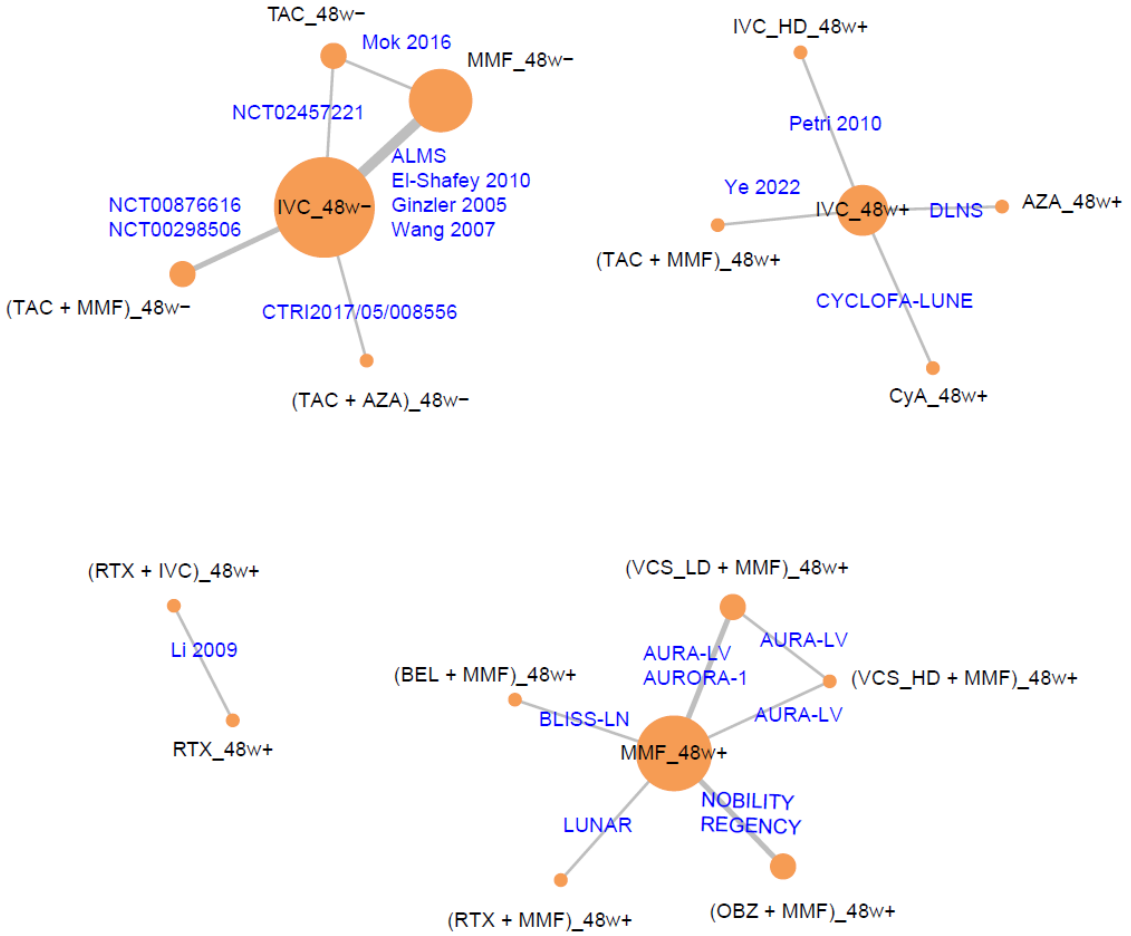
Figure 8: Flow diagram of study inclusion from SLR study identification to best-case network



2.10.3 Overall Network

Of the 20 studies included in the feasibility assessment (Appendix B), 6 studies contributed to the best-case network. These studies all used a primary efficacy analysis time point of 48 weeks or longer, as explained in Section 2.10.1. The 20 RCTs formed three connected networks, plus one disconnected study (122). Figure 9 presents the overall network of studies included in the feasibility assessment (77, 83, 115, 123-126).

Figure 9: Display of the three connected networks and single comparison study based on the 20 eligible RCTs



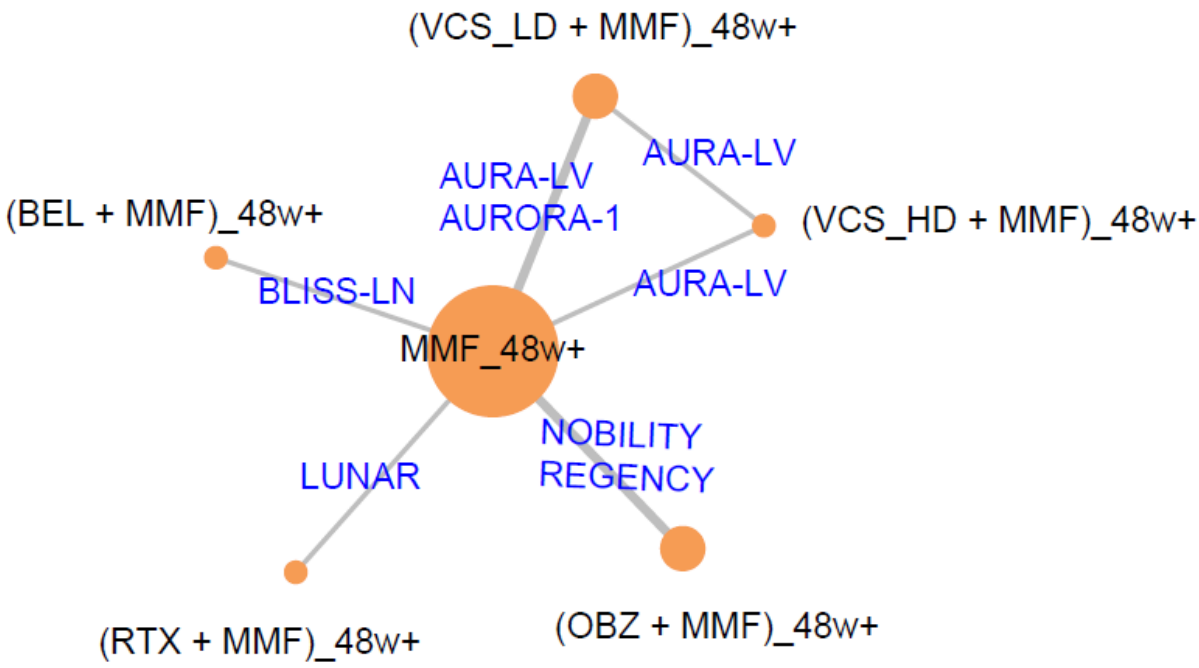
Key: ALMS, Aspreva Lupus Management Study; AZA, azathioprine; BEL, belimumab; CyA, cyclosporine A; DLNS, Dutch Lupus Nephritis Study; HD, high dose; IVC, intravenous cyclophosphamide; LD, low dose; MMF, mycophenolate mofetil; OBZ, obinutuzumab; RCT, randomised controlled trial; RTX, rituximab; TAC, tacrolimus; VCS, voclosporin; 48w+, 48 weeks or more; 48w-, less than 48 weeks.
Notes: The node size indicates how many patients are randomised to each treatment. Study names between interventions indicate how many studies provide direct evidence as represented by the thickness of the connect lines. For the BLISS-LN study, the treatment MMF→MMF or IVC→AZA was assumed to have the same efficacy as MMF. Hence, the treatment and comparator for BLISS-LN is captured in the bottom right network as BEL + MMF_48w+ and MMF_48w+, respectively.

As illustrated in Figure 10, the 20 RCTs formed three connected networks, plus one disconnected study (122). These consisted of one <48-week network (n=9 studies) (127-135), two ≥48-week networks (smaller network [n=4 studies] and larger network [n=6 studies]) (122, 126, 136-144), plus one disconnected study in the ≥48-week period for RTX + intravenous cyclophosphamide (IVC) versus RTX alone (122).

The <48-week network included MMF, tacrolimus (TAC), TAC+MMF, TAC+AZA, and IVC, with the network's main comparator being IVC. One of the ≥48-week networks included high-dose IVC, AZA, cyclosporine A (CyA), IVC and TAC+MMF with the networks main comparator being IVC. The second ≥48-week network was larger in patient size and focused on the newer treatments (MMF, low-dose VOC 23.7 mg [low-dose VOC]+MMF, high-dose VOC 39.5 mg [high-dose VOC]+MMF, BEL+MMF, RTX+MMF, OBI+MMF) with the network common comparator being MMF.

The clinical SLR focused on identifying evidence to allow creation of the largest best-case network feasible for comparing OBI with relevant comparators. Figure 10 presents the base case network for CRR, PRR independent of CRR, ORR and SAEs. Smaller networks were possible for eGFR and Grade 3+ AEs, presented in the NMA report (145) and Appendix B. The network incorporates 6 studies and formed connected networks for all outcomes enabling a comparison of OBI+MMF with BEL+MMF, low-dose VOC+MMF, high-dose VOC+MMF, and RTX+MMF, through MMF as the anchored (common) comparator. A total of 6 RCTs, enrolling 1,608 patients, contributed to the base case network. The network enabled a comparison of OBI with BEL, low-dose VOC, high-dose VOC, and RTX (with all these treatments administered in combination with MMF) (123, 124, 126, 141, 146, 147). The 6 studies in the base case network were judged to be sufficiently homogenous to allow for comparison of the outcomes of interest.

Figure 10: Best-case scenario network based on the 6 studies



Key: AZA, azathioprine; BEL, belimumab; HD, high dose; IVC, intravenous cyclophosphamide; LD, low dose; MMF, mycophenolate mofetil; OBZ, obinutuzumab; RTX, rituximab; VCS, voclosporin; 48w+, 48 weeks or more.
Notes: The node size indicates how many patients are randomised to each treatment. Study names between interventions indicate how many studies provide direct evidence as represented by the thickness of the connect lines. For the BLISS-LN study, the treatment MMF→MMF or IVC→AZA was assumed to have the same efficacy as MMF. Hence, the treatment and comparator for BLISS-LN is captured as BEL + MMF_48w+ and MMF_48w+, respectively.

2.10.4 Efficacy results

The majority of indirect comparisons lack statistical significance and are associated with uncertainty due to wide credible intervals. As detailed in Section 2.10.5, 2.10.6 and 3.3.2.3, there are underlying differences between the trials included that haven't been accounted for, differences in mechanisms of action of treatments included and expected long-term outcomes, and other aspects of the disease to consider, such as extra-renal disease, renal function, impact to renal flares and avoidance of rescue therapy. A full description of the results, uncertainties and limitations is provided in Section 2.10.5 and 2.10.6. When considering outcomes comparing to VOC, it should be noted that VOC is used in a small proportion (5-10%) of patients (Section 1.3.2 and Table 42) who are highly nephrotic to reduce proteinuria. CRR and PRR outcomes presented here for VOC will be largely driven by short term reduction in proteinuria without considering any toxicity impacts to kidney function while on VOC. In addition, outcomes do not account for the reduction in treatment adherence seen in real-world use of tablet formulations such as MMF and VOC+MMF. So, trial outcomes are likely overestimated, and comparative estimates are likely underestimated when compared with OBI+MMF in a real-world NHS setting. Results should be interpreted with caution.

2.10.4.1 Complete Renal Response

Key CRR OR outcomes from the base case network (Figure 10), including the base case random-effects (RE) model and sensitivity analyses are presented in Table 31. CRR forest plots for the base case random-effects model are presented in Figure 11 for OBI + MMF versus other treatments and Figure 12 for all treatments versus MMF. Due to wide credible intervals, and uncertainties highlighted in Section 2.10.4, 2.10.5 and 2.10.6, results should be interpreted with caution. Compared with other treatments (Table 31 and Figure 11), in the base case RE model, OBI + MMF showed an OR of:

- [redacted] (95% CrI: [redacted]) versus MMF
- [redacted] (95% CrI: [redacted]) versus RTX + MMF
- [redacted] (95% CrI: [redacted]) versus high-dose VOC + MMF
- [redacted] (95% CrI: [redacted]) versus low-dose VOC + MMF

Compared with MMF (Figure 12), all treatments, except [redacted], showed [redacted] CRR than MMF, with [redacted] showing statistically significant results (OR: [redacted]; 95% CrI: [redacted]).

Details regarding diagnostic fit and comparative effectiveness based on SUCRA values can be found in Appendix B.

Table 31: OR and 95% CrI of OBI+MMF versus other comparators – CRR, best-case network

OBI+MMF_48w+ versus	Base case, RE model, OR (95% CrI)	Sensitivity 1, FE model, OR (95% CrI)	Sensitivity 2, RE model, alternative prior for tau, OR (95% CrI)
BEL + MMF 48w+	[redacted]	[redacted]	[redacted]
RTX + MMF 48w+	[redacted]	[redacted]	[redacted]
Low-dose VOC + MMF 48w+	[redacted]	[redacted]	[redacted]
High-dose VOC + MMF 48w+	[redacted]	[redacted]	[redacted]

OBI+MMF_48w+ versus	Base case, RE model, OR (95% CrI)	Sensitivity 1, FE model, OR (95% CrI)	Sensitivity 2, RE model, alternative prior for tau, OR (95% CrI)
MMF_48w+	[redacted]	[redacted]	[redacted]

Key: BEL, belimumab; CrI, credible interval; CRR, complete renal response; FE, fixed-effects; HD, high dose; LD, low dose; MMF, mycophenolate mofetil; OBI, obinutuzumab; OR, odds ratio; RE, random-effects; RTX, rituximab; VOC, voclosporin; 48w+, 48 weeks or more.

Figure 11: Forest plot of OR and 95% CrI of OBI+MMF versus other treatments – CRR, best-case network – base case RE model

Key: BEL, belimumab; CrI, credible interval; CRR, complete renal response; HD, high dose; LD, low dose; MMF, mycophenolate mofetil; OBI, obinutuzumab; OR, odds ratio; RE, random-effects; RTX, rituximab; VCS, voclosporin; 48w+, 48 weeks or more.

Figure 12: Forest plot of OR and 95% CrI of all treatments versus MMF – CRR, best-case network – base case RE model

Key: BEL, belimumab; CrI, credible interval; CRR, complete renal response; HD, high dose; LD, low dose; MMF, mycophenolate mofetil; OBI, obinutuzumab; OR, odds ratio; RE, random-effects; RTX, rituximab; VCS, voclosporin; 48w+, 48 weeks or more.

2.10.4.2 Partial Renal Response Independent of CRR

As explained in Section 2.10.3, Figure 10 presents the best-case scenario network for PRR independent of CRR.

PRR OR outcomes from the base case network (Figure 10), including the base case random-effects (RE) model and sensitivity analyses are presented in Table 32. Figure 13 displays forest plots for OBI+MMF versus all other treatments, and Figure 14 shows all other treatments versus MMF. Due to wide credible intervals crossing 1, none of PRR outcomes reached statistical significance. Compared with MMF, all treatments, except [redacted], showed a [redacted] PRR independent of CRR, but, as explained, no statistical significance. As detailed in Section 2.10.4, results should be interpreted with caution. For PRR independent of CRR specifically, results should be interpreted with care, since patients without the event are a mix of patients doing well with CRR and patients doing poorly with neither PRR independent of CRR or CRR. For this reason, although PRR independent of CRR is useful for economic modelling, ORR may be a more clinically meaningful outcome (presented in Appendix B).

Compared with other treatments, in the base case RE model, OBI+MMF showed an OR of:

- [redacted] (95% CrI: [redacted]) versus RTX+MMF
- [redacted] (95% CrI: [redacted]) versus high-dose VOC+MMF
- [redacted] (95% CrI: [redacted]) versus low-dose VOC+MMF
- [redacted] (95% CrI: [redacted]) versus MMF

Details regarding diagnostic fit and comparative effectiveness based on SUCRA values can be found in Appendix B.

Table 32 OR and 95% CrI of OBI+MMF versus other comparators – PRR independent of CRR, best-case network

OBI + MMF_48w+ versus	Base case, RE model, OR (95% CrI)	Sensitivity 1, FE model, OR (95% CrI)	Sensitivity 2, RE model, alternative prior for tau, OR (95% CrI)
(RTX+MMF)_48w+	[redacted]	[redacted]	[redacted]
(high-dose VOC + MMF)_48w+	[redacted]	[redacted]	[redacted]

(low-dose VOC + MMF)_48w+	[redacted]	[redacted]	[redacted]
MMF_48w+	[redacted]	[redacted]	[redacted]

Key: BEL, belimumab; CrI, credible interval; FE, fixed-effects; HD, high dose; LD, low dose; MMF, mycophenolate mofetil; OBI, obinutuzumab; OR, odds ratio; PRR, partial renal response; RE, random-effects; RTX, rituximab; VOC, voclosporin; 48w+, 48 weeks or more.

Figure 13: Forest plot of OR and 95% CrI of OBI+MMF versus other treatments – PRR independent of CRR, best-case network – base case, RE model

[redacted]

Key: BEL, belimumab; CrI, credible interval; HD, high dose; LD, low dose; MMF, mycophenolate mofetil; OBZ, obinutuzumab; OR, odds ratio; PRR, partial renal response; RE, random-effects; RTX, rituximab; VCS, voclosporin; 48w+, 48 weeks or more.

Figure 14: Forest plot of OR and 95% CrI of all treatments versus MMF – PRR independent of CRR, best-case network – base case, RE model

[redacted]

Key: BEL, belimumab; CrI, credible interval; HD, high dose; LD, low dose; MMF, mycophenolate mofetil; OBZ, obinutuzumab; OR, odds ratio; PRR, partial renal response; RE, random-effects; RTX, rituximab; VCS, voclosporin; 48w+, 48 weeks or more.

2.10.4.3 Other endpoints

Full details for the other endpoints included in the NMA can be found in Appendix B. For ORR, results are fairly consistent to CRR and PRR. Compared with MMF, all treatments showed higher ORR, with statistically significant results observed for [redacted] (OR: [redacted]; 95% CrI: [redacted]), [redacted] (OR: [redacted]; 95% CrI: [redacted]), and [redacted] (OR: [redacted]; 95% CrI: [redacted]).

For CFB in eGFR, the differences with both [redacted] were statistically significant in favour of [redacted]. Compared with MMF, [redacted] showed greater eGFR preservation. A statistically significant reduction in eGFR preservation was observed with [redacted] (MD: [redacted]; 95% CrI: [redacted]), relative to MMF.

An ITC for Grade 3+ AEs was only feasible versus RTX+MMF via the common comparator of MMF (network presented in NMA report) (145). For Grade 3+ AEs, OBI+MMF yielded an OR of [redacted] (95% CrI: [redacted]) versus RTX + MMF. Compared with MMF, OBI+MMF showed an OR of [redacted] (95% CrI: [redacted]) and RTX+MMF showed an OR of [redacted] (95% CrI: [redacted]). None of the results reached statistical significance.

For SAEs, the base case network comprising 6 studies was used (Figure 10). None of the comparisons for SAEs demonstrated a statistically significant difference.

As explained above and uncertainties highlighted in Section 2.10.4, 2.10.5 and 2.10.6, results should be interpreted with caution.

2.10.5 Discussion

An SLR and Bayesian NMA was conducted with the aim of evaluating the relative efficacy and safety of OBI+MMF with relevant comparators in the treatment of active LN.

The results of the NMA encompassing 6 RCTs indicated that there were no statistically significant differences between OBI+MMF and any comparators except for MMF for CRR and ORR. However, OBI+MMF was associated with a [redacted] likelihood of achieving CRR and ORR compared with [redacted], while occasionally demonstrating [redacted] likelihood relative to [redacted], specifically [redacted] for CRR. In terms of renal function preservation, as measured by CFB in eGFR, OBI+MMF showed [redacted] than [redacted], whilst comparisons with MMF were not statistically significant. These results were consistent across scenario and sensitivity analyses. Across all efficacy outcomes, OBI+MMF consistently ranked among the top [redacted] treatments.

For safety outcomes, including Grade 3+ AEs and SAEs, none of the results were statistically significant. However, as trials were not powered to detect safety differences, these results should be interpreted with caution. Furthermore, the REGENCY trial was conducted during the COVID-19 pandemic, so our analysis may be conservative as Grade 3+ AEs and SAEs include both confirmed and suspected COVID-19 cases; notably, event rates were more favourable when confirmed and suspected COVID-19 cases were excluded.

In a previously published NMA evaluating efficacy and safety of immunosuppressive therapies in LN, VOC+MMF was ranked highest in achieving CRR, followed by BEL+MMF, and MMF (148). In our NMA for CRR, both VOC combinations (low-dose and high-dose) were similarly ranked first and second, with OBI+MMF ranked third. However, none of the differences reached statistical significance. Importantly, VOC combinations with MMF have been associated with increased risk of infections (149). Another NMA focusing on biologic therapies, after adjusting for time window (differences in follow-up), recommended OBI as the treatment of choice for LN (150). Our results were aligned with the previous NMAs, further supporting OBI+MMF as a clinically relevant treatment option for patients with active LN.

At a recent advisory board experts discussed whether the outcomes of the ITC represented their understanding of current treatment options. Experts expected OBI to be the better-performing treatment of those included in the NMA. Experts discussed how the CRR for VOC is likely to be largely driven by changes in proteinuria as part of the composite CRR endpoint. They agreed that there are other aspects to consider, such as extra-renal disease, renal function, impact to renal flares, avoidance of rescue therapy, etc. They explained that the AURORA trials excluded patients with an eGFR < 30 ml/min/1.73m² (vs. <45 ml/min/1.73m² in REGENCY) and the trials did not have eGFR as a key secondary endpoint. Finally, experts discussed the important impact treatment adherence has on clinical efficacy. They believed that adherence is the most important factor in driving outcomes in LN. The substantial pill burden of 6 tablets of VOC per day, alongside 4 tablets of MMF and corticosteroids, means drug adherence with VOC is difficult in the real world. The AURORA trials report the efficacy of VOC with good drug adherence expected in clinical trials that is extremely difficult to replicate in the real world.

Therefore, experts believe that CRR for VOC from clinical studies and the ITC may not reflect overall real-world efficacy. In their clinical practice with VOC, they often experience a negative effect on kidney function in the short term, and it is known to decrease eGFR. When considering eGFR, NMA results were statistically significant in favour of OBI+MMF compared with VOC regimens. As CRR is a composite outcome of proteinuria and eGFR, experts inferred that the positive impact VOC on proteinuria levels, combined with key exclusion criteria in the AURORA trials is likely driving strong CRR results for VOC. Experts further emphasised that VOC reduces proteinuria without leading to reduction in inflammation in the kidney, and the latter is the most important. They believe OBI achieves both of those things. In their opinion, VOC does not treat the underlying cause, whereas OBI addresses the pathogenesis of LN. Finally, the intravenous administration of OBI will overcome a large portion of adherence issues patients and clinicians currently experience with current treatment options in clinical practice that aren't captured in NMA outcomes.

Clinical advisors suggested that the accompanying cost-effectiveness analysis should attempt to account for other clinical endpoints to capture the expected long-term efficacy associated with each treatment included in the analysis, to not rely entirely on CRR and PRR ITC outcomes. They suggested considering the impact of eGFR, B-cell depletion, the frequency and duration of renal flares, and serological data such as ds-DNA and C3/C4 complements. The cost-effectiveness analysis described in Section 3, 3.2.2 and 3.3.2 attempts to quantify the impact short-term endpoints can have on long-term outcomes.

2.10.6 Uncertainties and limitations in indirect treatment comparisons

Whilst the findings from the NMA offer important insights into the relative efficacy and safety of OBI+MMF compared with other treatments, including standard of care for active LN, several limitations warrant cautious interpretation of results. The evidence comprised only 6 studies, limiting the generalisability of results and interstudy variability was noted in study design, country, and number of patients recruited across the included studies.

Variation in the definition of CRR across the six studies presents a potential limitation for NMAs. While all studies include a UPCR threshold of ≤0.5, they differ in additional criteria such as eGFR thresholds, serum creatinine stability, exclusion of rescue therapy, and steroid tapering requirements. These inconsistencies could not be adjusted for in the analysis, introducing potential uncertainty around the comparability of treatments and the validity of the pooled CRR estimates.

As explained in Section 2.6.1.2, the CRR definition used in REGENCY is one of the most stringent used for clinical trials. In REGENCY, patients had to achieve all the following for a CRR outcome:

- UPCR <0.5 g/g
- eGFR ≥85% of baseline at Week 76, as calculated using the CKD-EPI equation
- Serum creatinine ≤ULN at Week 76 (as determined by the central laboratory)
- Serum creatinine which did not increase from baseline more than >25%
- No occurrence of the following intercurrent events: Rescue therapy, treatment failure, death, or early study withdrawal

However, in other studies e.g. AURORA-2, only a decrease in UPCR to ≤0.5 mg/mg in 2 consecutive first morning urine specimens, plus an eGFR >60 mL/min per 1.73 m^2 or no decrease of ≥20% of baseline eGFR on two consecutive occasions was required. So, while comparative outcomes could be considered conservative when considering the stringent outcome definitions applied in REGENCY, inference on the direction of non-significant ORs for composite outcomes should be treated with caution.

There was noticeable variability in the eGFR outcome data. The reported CFB in eGFR in AURA-LV and AURORA-1 used corrected eGFR, where values were capped at 90 mL/min/1.73 m². Compared to using uncorrected eGFR, this approach may reduce differences between treatments and decrease variability within those studies, as extreme values are excluded. The potential impact of this should be considered when interpreting the NMA results. Additionally, data imputations, such as derivation of mean CFB in eGFR from baseline and endpoint estimates, calculation of missing standard deviations using pooled standard deviations from other studies, and data digitisation of missing values from the graphs may have contributed to additional uncertainty in NMA results. Given the limited number of studies, a sensitivity analysis based on excluding the imputed data could not be performed.

The overall risk-of-bias (Appendix B) for the best-case network was rated as high in all but one study (REGENCY), primarily due to some unexpected imbalances in patient dropouts during the trial analysis phase. Although several studies in the best-case network had a high risk of bias, no study was excluded from the NMA on this basis, which may have further limited the generalisability of our findings.

Lastly, the NMA was limited to primary efficacy outcomes and a limited number of comparators due to lack of connection in the wider evidence network.

2.11 Adverse reactions

The safety data presented in this section are derived from the pivotal REGENCY study, with supportive safety data from the NOBILITY study provided in Appendix K, Section 12.5.

2.11.1 Exposure to study treatments

At the CCOD (15 August 2024) of the REGENCY study, [redacted] patients ([redacted]%) had received [redacted] infusions of OBI and [redacted] patients ([redacted]%) had received [redacted] infusions of OBI (Table 33).

The median duration of exposure to GCs and MMF was balanced between treatment arms. At the CCOD, the median duration of exposure to MMF up to Week 76 was [redacted] days (range: [redacted] days) in the OBI arm and [redacted] days (range: [redacted] days) in the placebo arm. The median cumulative dose was [redacted] in the OBI arm and [redacted] in the placebo arm. The median duration of GC exposure was [redacted] days (range: [redacted] days) in the OBI arm and [redacted] days (range: [redacted] days) in the placebo arm. The median total cumulative GC dose was [redacted] mg (range: [redacted]) in the OBI arm and [redacted] mg (range: [redacted]) in the placebo arm.

Table 33: Blinded obinutuzumab exposure (REGENCY; safety-evaluable population)

Measure of Exposure	OBI (N=136)
Treatment duration (days)	
N	136
Mean (SD)	[redacted]
Median	[redacted]
Min, Max	[redacted]
Number of infusion	
N	136
Mean (SD)	[redacted]
Median	[redacted]
Min, Max	[redacted]
Number of infusions category, n (%)	
N	136
1 dose	[redacted]
2 doses	[redacted]
3 doses	[redacted]
4 doses	[redacted]
5 doses	[redacted]
6 doses	[redacted]

Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
Includes data until the point of rescue for patients who received rescue therapy.
Source: Study CA41705 Primary CSR. Report No. 1131275 (115).

2.11.2 Safety endpoints

The REGENCY safety-evaluable population consisted of patients who received any amount of any study treatment, whether prematurely withdrawn from the study or not. All safety data presented in this section are from the REGENCY study unless otherwise stated.

2.11.2.1 Overview of adverse events

The proportion of patients with at least one adverse event (AE) during the 76-week blinded MMF period was comparable between the OBI (126 patients [92.6%]) and placebo (117 patients [88.6%]) arms. The majority of AEs reported in both arms up to Week 76 were non-serious (680 out of 748 AEs in the OBI arm and 630 out of 665 AEs in the placebo arm). No patients were withdrawn from the study due to AEs (Table 34).

The most commonly reported AE by preferred term (PT; ≥ 10% of patients in either arm) are presented in Table 35.

AEs by PT with notable differences (≥ 5% between arms) were as follows for the OBI and placebo arms, respectively: neutropenia (15 patients [11.0%] vs. four patients [3.0%]), abdominal pain (four patients [2.9%] vs. 11 patients [8.3%]), and COVID-19 pneumonia (seven patients [5.1%] vs. 0 patients).

The AE rate per 100 patient-years was comparable between the OBI arm (378.02 [95% CI: 350.93, 405.11]) and the placebo arm (363.81 [95% CI: 336.15, 391.46]).

Table 34: Overview of deaths and adverse events (REGENCY; safety-evaluable population)

Safety outcome	OBI (N=136)	Placebo (N=132)	All patients (N=268)
Total number of patients with at least one AE, n (%)	126 (92.6)	117 (88.6)	243 (90.7)
Total number of AEs	748	665	1413
Total number of deaths, n (%)	3 (2.2)	1 (0.8)	4 (1.5)
Total number of patients withdrawn from study due to an AE	0 (0.0)	0 (0.0)	0 (0.0)
Total number of patients with at least one, n (%)			
AE with fatal outcome[a]	3 (2.2)	2 (1.5)	5 (1.9)
SAE	44 (32.4)	24 (18.2)	68 (25.4)
Serious infection AE	23 (16.9)	10 (7.6)	33 (12.3)
SAE leading to discontinuation from blinded OBI	8 (5.9)	4 (3.0)	12 (4.5)
SAE leading to discontinuation from MMF	2 (1.5)	0 (0.0)	2 (0.7)
SAE leading to discontinuation from blinded OBI or MMF	9 (6.6)	4 (3.0)	13 (4.9)
SAE leading to blinded OBI dose interruption`	[redacted]	[redacted]	[redacted]
SAE leading to MMF dose modification/interruption	[redacted]	[redacted]	[redacted]
SAE leading to blinded OBI or MMF dose modification/interruption	[redacted]	[redacted]	[redacted]
SAE related to blinded OBI	[redacted]	[redacted]	[redacted]
SAE related to MMF	[redacted]	[redacted]	[redacted]
SAE related to blinded OBI or MMF	[redacted]	[redacted]	[redacted]
Infection AE	98 (72.1)	81 (61.4)	179 (66.8)
AE leading to discontinuation from blinded OBI	10 (7.4)	5 (3.8)	15 (5.6)
AE leading to discontinuation from MMF	3 (2.2)	1 (0.8)	4 (1.5)
AE leading to discontinuation from blinded OBI or MMF	12 (8.8)	5 (3.8)	17 (6.3)
AE leading to blinded OBI dose interruption	[redacted]	[redacted]	[redacted]
AE leading to MMF dose modification/interruption	[redacted]	[redacted]	[redacted]
AE leading to blinded OBI or MMF dose modification/interruption	[redacted]	[redacted]	[redacted]
AE related to blinded OBI	[redacted]	[redacted]	[redacted]
AE related to MMF	[redacted]	[redacted]	[redacted]
AE related to blinded OBI or MMF	[redacted]	[redacted]	[redacted]
Grade 3–5 AE	44 (32.4)	22 (16.7)	66 (24.6)
AEs of special interest: patients with, n (%)			
Infusion-related reactions (IRRs)	21 (15.4)	15 (11.4)	36 (13.4)
Grade 3–5 infection	21 (15.4)	9 (6.8)	30 (11.2)

Safety outcome	OBI (N=136)	Placebo (N=132)	All patients (N=268)
Any Hepatitis B reactivation and PML	0 (0.0)	0 (0.0)	0 (0.0)
Drug-related neutropenia	17 (12.5)	5 (3.8)	22 (8.2)
Drug-related thrombocytopenia	1 (0.7)	0 (0.0)	1 (0.4)
Gastrointestinal perforations	0 (0.0)	0 (0.0)	0 (0.0)
Worsening of pre-existing cardiac conditions	0 (0.0)	2 (1.5)	2 (0.7)
Hy's law	0 (0.0)	0 (0.0)	0 (0.0)
Suspected transmission of an infectious agent by the study drug	0 (0.0)	0 (0.0)	0 (0.0)

Investigator text for AEs encoded using MedDRA version 27.0. Percentages are based on N in the column headings. Only treatment emergent AEs are displayed. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately. Includes AEs through 76 weeks blinded treatment period. Includes AEs until the point of rescue for patients who received rescue therapy (except GC-only rescue).
[a]There were 3 deaths (2.2%) in the OBI arm and 1 death (0.8%) in the placebo arm. In addition, there was 1 patient in the placebo arm with fatal AE onset during the 76-week treatment period but who died after the Week 76 data cut; therefore, there were 3 patients (2.2%) with fatal AEs in the OBI arm and 2 patients (1.5%) with fatal AEs in the placebo arm.
Source: Study CA41705 Primary CSR. Report No. 1131275 (115).

Table 35: Adverse events by preferred term (≥ 10% of patients in either arm; REGENCY; safety-evaluable population)

MedDRA Preferred Term	OBI (N=136)	Placebo (N=132)	All patients (N =268)
Total number of patients with at least one AE, n (%)	126 (92.6)	117 (88.6)	243 (90.7)
Total number of events, n	748	665	1413
COVID-19, n (%)	[redacted]	[redacted]	[redacted]
Diarrhoea, n (%)	[redacted]	[redacted]	[redacted]
Urinary tract Infection, n (%)	[redacted]	[redacted]	[redacted]
IRR, n (%)	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection, n (%)	[redacted]	[redacted]	[redacted]
Neutropenia, n (%)	[redacted]	[redacted]	[redacted]

Investigator text for AEs is coded using MedDRA version 27.0. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes AEs through 76 weeks blinded treatment period. Includes AEs until the point of rescue for patients who received rescue therapy (except GC-only rescue).
Source: Study CA41705 Primary CSR. Report No. 1131275 (115).

2.11.2.2 AEs related to OBI

Overall, the proportion of patients who experienced at least one AE assessed by the investigator as related to blinded OBI or MMF was higher in the OBI arm ([redacted] patients [redacted%]) compared with the placebo arm ([redacted] patients [redacted%]).

The proportion of patients who experienced at least one AE assessed by the investigator as related to blinded OBI was [redacted] in the OBI arm ([redacted] patients [redacted%]) compared with the placebo arm ([redacted] patients [redacted%]) (Table 36).

Table 36: Adverse events related to blinded obinutuzumab (REGENCY; safety-evaluable population)

MedDRA System Organ Class MedDRA Preferred Term	OBI (N=136)	Placebo (N=132)	All patients (N=268)
Total number of patients with at least one AE, n (%)	[redacted]	[redacted]	[redacted]
Total number of events	173	102	275
Infections and infestations, n (%)			
Total number of patients with at least one AE	[redacted]	[redacted]	[redacted]
Total number of events	[redacted]	[redacted]	[redacted]
Urinary tract infections	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications			
Total number of patients with at least one AE	[redacted]	[redacted]	[redacted]
Total number of events	[redacted]	[redacted]	[redacted]
IRR	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders			
Total number of patients with at least one AE	[redacted]	[redacted]	[redacted]
Total number of events	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]

Investigator text for AEs encoded using MedDRA version 27.0. Only treatment-emergent AEs related to blinded OBI are displayed. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes AEs through 76 weeks blinded treatment period. Includes AEs until the point of rescue for patients who received rescue therapy (except GC-only rescue).
Source: Study CA41705 Primary CSR. Report No. 1131275 (115).

2.11.2.3 AEs by severity

The majority of patients in both OBI and placebo arms reported AEs that were NCI CTCAE Grade 1−2 in intensity (82 patients [60.3%] in the OBI arm vs. 95 patients [72.0%] in the placebo arm).

The proportion of patients with at least one NCI CTCAE Grade 3−5 AE was higher in the OBI arm (44 patients [32.4%]) compared with the placebo arm (22 patients [16.7%]). The majority of AEs were Grade 3 in both treatment arms (OBI arm and placebo arm, respectively):

- Grade 3 ([redacted] patients [redacted%] and [redacted] patients [redacted%])
- Grade 4 ([redacted]patients [redacted%] and [redacted]patients [redacted%])
- Grade 5 ([redacted]patients [redacted%] and [redacted]patients [redacted%])

Grade 5 (fatal) AEs (five patients) are described further in Section 2.11.2.5.

Grade 3−5 AEs by PT with notable differences (≥ 5% between arms) were as follows for the OBI and placebo arms, respectively: COVID-19 pneumonia ([redacted]patients [redacted%] vs. [redacted]patients) and neutropenia ([redacted]patients [redacted%] vs. [redacted]patients).

2.11.2.4 AEs that led to dose modification or treatment and/or study withdrawal

Dose modification for blinded OBI was not permitted during REGENCY as per protocol; however, the rate of infusion could be adjusted in the event of an IRR. OBI and placebo infusions could be slowed or held for patients who experienced toxicity considered to be related to OBI or placebo. Additionally, dose modifications for MMF were allowed.

A [redacted] proportion of patients experienced at least one AE leading to dose modification/ interruption of blinded OBI or MMF in the OBI arm ([redacted]patients [redacted%]) compared with the placebo arm ([redacted]patients [redacted%]). Of these, [redacted]patients [redacted%] in the OBI arm and [redacted]patients [redacted%] in the placebo arm experienced at least one AE leading to dose interruption of blinded OBI alone. The difference in the proportion of patients with AEs leading to dose modification/interruption of blinded OBI or MMF versus interruption of blinded OBI alone suggests that the majority of AEs led to dose modification or interruption of MMF and not blinded OBI.

The proportion of patients with at least one AE leading to discontinuation from blinded OBI treatment was low in both arms (10 patients [7.4%] in the OBI arm vs. five patients [3.8%] in the placebo arm).

The most frequent AE by PT (≥ 1% of patients in either arm) that led to discontinuation of blinded OBI was neutropenia ([redacted]patients [redacted%] in the OBI arm and [redacted]patients in the placebo arm).

The proportion of patients with at least one AE leading to discontinuation from the study was low in both arms ([redacted]patient [redacted]%] in the OBI arm vs. [redacted]patients [redacted]%] in the placebo arm).

2.11.2.5 Deaths

Through the 76-week blinded treatment, four patients died (three patients [2.2%] in the OBI arm and one patient [0.8%] in the placebo arm). By PT, these events were COVID-19 pneumonia (two patients [1.5%]) and nephrotic syndrome (one patient [0.7%]) in the OBI arm, and COVID-19 (one patient [0.8%]) in the placebo arm.

In addition, in the placebo arm, there was one patient with fatal AE onset (PT: B-cell lymphoma) during the 76-week blinded treatment period but who died after the Week 76 data cut. Therefore, there were three patients (2.2%) with fatal AEs in the OBI arm and two patients (1.5%) with fatal AEs in the placebo arm.

All fatal events were considered related to blinded OBI treatment, except for the nephrotic syndrome, which was considered unrelated to OBI treatment.

2.11.2.6 Serious adverse events

A higher proportion of patients experienced at least one SAE in the OBI arm (44 patients [32.4%]) compared with the placebo arm (24 patients [18.2%]) during the 76-week blinded treatment period. The REGENCY trial was conducted during the global COVID-19 pandemic and this increase in rate of SAEs was primarily driven by serious infections AEs of COVID-19.

The only PT with a notable difference (≥ 5%) in the SAE incidence in the OBI arm versus the placebo arm was COVID-19 pneumonia (seven patients [5.1%] and no patients, respectively).

Excluding COVID-19 AEs, the number of patients with SAEs remained higher in the OBI arm (37 patients [27.2%]) than the placebo arm (24 patients [18.2%]); however, the difference in the number of patients with serious infections was less pronounced between the OBI (15 patients [11.0%]) and placebo arms (10 patients [7.6%]).

The proportion of patients requiring blinded OBI dose interruptions due to SAE was low in both arms ([redacted]patients [redacted]%] in the OBI arm vs. [redacted]patients [redacted]%] in the placebo arm) (Table 34). In addition, the proportion of patients requiring discontinuation from blinded OBI due to SAE in both arms was [redacted]([redacted] patients [redacted]%] in the OBI arm vs. [redacted] patients [redacted]%] in the placebo arm) (Table 34).

Overall, the majority of SAEs (67/114 events) were Grade 3−5, and were considered serious as they required prolonged in-patient hospitalisation. SAEs in all patients, except for one patient with SAE of weight decreased and those with fatal outcomes, had resolved or were resolving at the time of CCOD.

2.11.2.7 SAEs related to obinutuzumab

Overall, a higher proportion of patients experienced at least one SAE that was assessed by the investigator as related to blinded OBI in the OBI arm (18 patients [13.2%]) compared with the placebo arm (seven patients [5.3%]) (Table 37).

The most frequent SAEs by PT (≥ 2% in either arm) that were assessed by the investigator as related to blinded OBI were the following (OBI arm and placebo arm, respectively):

- COVID-19 pneumonia ([redacted] patients [redacted]%] and [redacted] patients)
- Neutropenia ([redacted] patients [[redacted]%] and [redacted]patients)

Table 37: Serious adverse events related to blinded obinutuzumab (REGENCY; safety-evaluable population)

MedDRA System Organ Class MedDRA Preferred Term	OBI (N=136)	Placebo (N=132)	All patients (N=268)
Total number of patients with at least one AE, n (%)	18 (13.2)	7 (5.3)	25 (9.3)
Total number of events, n	27	9	36
Infections and infestations, n (%)			
Total number of patients with at least one adverse event	11 (8.1%)	6 (4.5%)	17 (6.3%)
Total number of events	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]
Peritonsillar abscess	[redacted]	[redacted]	[redacted]
Post-acute COVID-19 syndrome	[redacted]	[redacted]	[redacted]
Pyelonephritis	[redacted]	[redacted]	[redacted]
Pyelonephritis acute	[redacted]	[redacted]	[redacted]
Urethritis	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders			
Total number of patients with at least one AE	[redacted]	[redacted]	[redacted]
Total number of events	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps), n (%)			
Total number of patients with at least one AE	[redacted]	[redacted]	[redacted]
Total number of events	[redacted]	[redacted]	[redacted]
B-cell lymphoma	[redacted]	[redacted]	[redacted]
Vulvovaginal warts	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders, n (%)			
Total number of patients with at least one AE	[redacted]	[redacted]	[redacted]
Total number of events	[redacted]	[redacted]	[redacted]
Organizing pneumonia	[redacted]	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complaints, n (%)			

MedDRA System Organ Class MedDRA Preferred Term	OBI (N=136)	Placebo (N=132)	All patients (N=268)
Total number of patients with at least one AE	[redacted]	[redacted]	[redacted]
Total number of events	[redacted]	[redacted]	[redacted]
IRR	[redacted]	[redacted]	[redacted]

Investigator text for AEs encoded using MedDRA version 27.0. Only treatment emergent SAEs related to blinded OBI are displayed. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes AEs through 76 weeks blinded treatment period. Includes AEs until the point of rescue for patients who received rescue therapy (except GC-only rescue).
Source: Study CA41705 Primary CSR. Report No. 1131275 (115).

2.11.2.8 AEs of special interest and selected AEs

2.11.2.8.1 Infusion-related reactions

Overall, the proportion of patients who experienced at least one AE of special interest (AESI) of IRRs was higher in the OBI arm (21 patients [15.4%]) compared with the placebo arm (15 patients [11.4%]); however, IRR is an expected risk for OBI. The IRR rate per 100 patient-years was comparable in the OBI arm (12.63 [95% CI: 7.68, 17.59]) and in the placebo arm (10.39 [95% CI: 5.72, 15.07]).

2.11.2.8.2 Grade 3–5 infections

Overall, a higher proportion of patients reported at least one AESI of Grade 3–5 infection in the OBI arm (21 patients [15.4%]) compared with the placebo arm (nine patients [6.8%]); however, Grade 3−5 infection is an expected risk for OBI. The most frequent Grade 3−5 infections by PT (≥ 2% of patients in either arm) were as follows (OBI arm and placebo arm, respectively):

Overall Grade 3−5 infections were balanced between arms (≤ 2% difference between arms), except for COVID-19 pneumonia and COVID-19 which were reported in more patients in the OBI arm compared with the placebo arm as described above.

When COVID-19 AEs were excluded, the number of Grade 3−5 infections remained higher in the OBI arm (15 patients [11.0%]) than the placebo arm (nine patients [6.8%]); however, the difference between arms was less pronounced.

A higher proportion of patients experienced serious Grade 3−5 infections in the OBI arm (18 patients [13.2%]) compared with the placebo arm (eight patients [6.1%]). One patient in the OBI arm had a serious Grade 4 infection of COVID-19 that resolved with treatment. Three patients (1.1%) experienced Grade 5 (fatal) infections: two patients (1.5%) with COVID-19 pneumonia in the OBI arm and one patient (0.8%) with COVID-19 in the placebo arm.

Apart from the Grade 5 (fatal) infections, all Grade 3−5 infections resolved.

In the NOBILITY study, which was conducted before the COVID-19 pandemic, infections (all grades) occurred more frequently in the OBI arm (48 patients [75%]) than the placebo arm (38 patients [62.3%]). However, Grade ≥ 3 infections were less frequent in the OBI arm (four patients [6.3%]) compared with the placebo arm (11 patients [18.0%]). All grade ≥ 3 infections in the OBI arm were SAEs, and were assessed by the investigator as being related to OBI treatment, except for the event of respiratory tract infection. In both arms, all Grade ≥ 3 infections resolved (Appendix K, Section 12.5.2).

Serious infections occurred less frequently in the OBI arm than in the placebo arm (7.8% vs.16.4%, respectively).

2.11.2.8.3 Drug-related neutropenia

Overall, the proportion of patients who experienced at least one AESI of drug-related neutropenia was higher in the OBI arm (12.5% [17 patients]) compared with the placebo arm (3.8% [five patients]). Neutropenia is an expected risk for B-cell depleting therapies such as OBI, and management of this is well understood through experience with RTX and other B-cell therapies.

The majority of events reported in both arms were Grade 1−2 in intensity ([redacted]) in the placebo arm. Grade 3−4 drug-related neutropenia (including PT febrile neutropenia) was reported in [redacted]; there were no Grade 5 (fatal) events of drug-related neutropenia.

2.11.2.8.4 Drug-related thrombocytopenia

One patient (0.7%) experienced an AESI of drug-related thrombocytopenia in the OBI arm; this was a serious Grade 4 event that was assessed as related to blinded OBI and led to dose interruption of blinded OBI and MMF; this event resolved by the CCOD. There were no reports of patients who experienced drug-related thrombocytopenia in the placebo arm.

2.11.2.8.5 Worsening of existing cardiac conditions

No worsening of pre-existing cardiac conditions was observed in patients in the OBI arm. Two patients (1.5%) experienced worsening of pre-existing cardiac conditions in the placebo arm, with [redacted] experiencing non-serious Grade 2 pericardial effusion that resolved with treatment, and [redacted] experiencing non-serious Grade 2 sinus tachycardia that resolved without intervention. Neither of these events resulted in discontinuation of study treatment or dose interruptions/modifications.

2.11.2.8.6 COVID-19 AEs

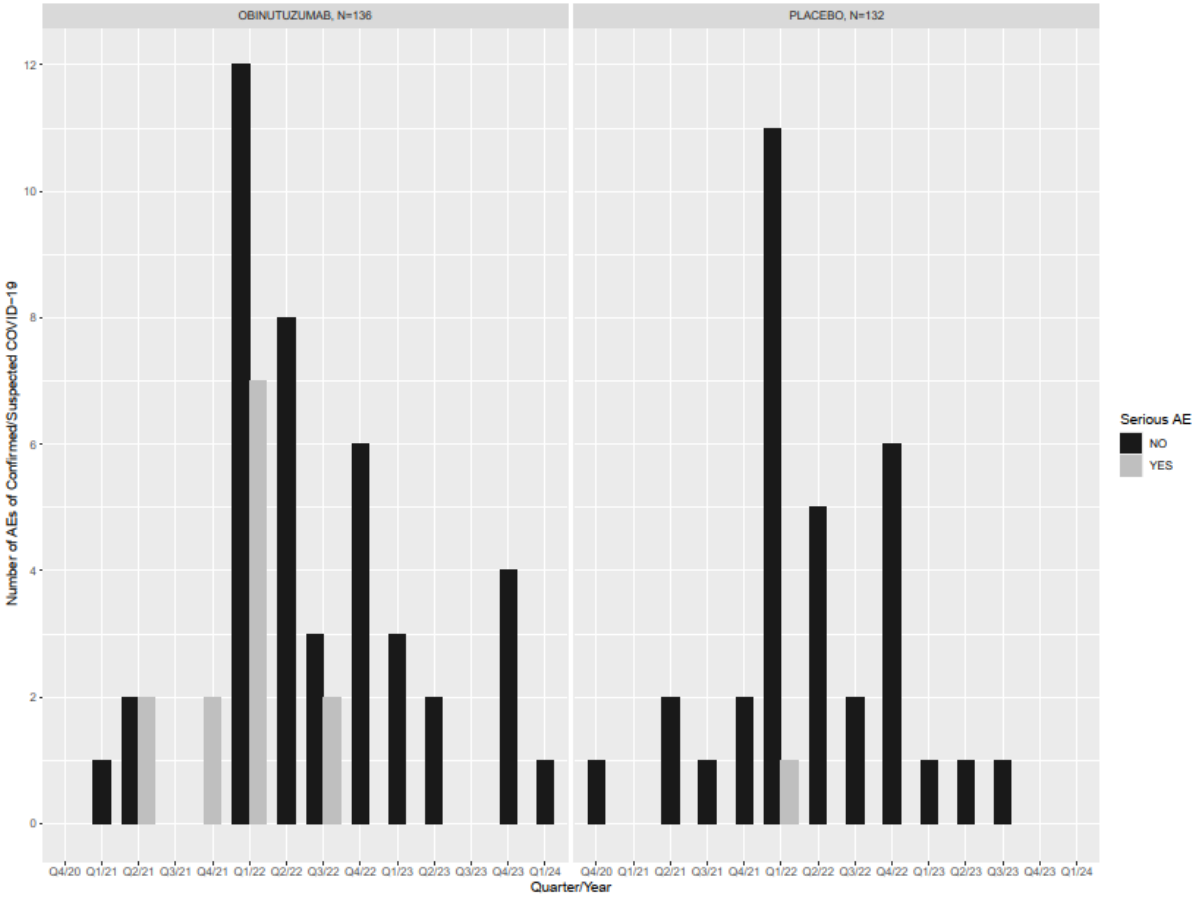
The REGENCY trial was conducted during the global COVID-19 pandemic. A higher proportion of patients reported at least one COVID-19 AE in the OBI arm (45 patients [33.1%]) compared with the placebo arm (31 patients [23.5%]).

The number of patients reporting Grade 3−5 COVID-19 AEs was higher in the OBI arm than in the placebo arm (10 patients vs. one patient). Of these, two patients in the OBI arm and one patient in the placebo arm reported AEs with fatal (Grade 5) outcome. Other than these

3 AEs with fatal outcome, all COVID-19 events were manageable and had resolved by the CCOD).

Confirmed or suspected COVID-19 AEs were more common in the earlier stages of the study and became less common with the global vaccine rollout (Figure 15). It is noteworthy that no COVID-19 infections were reported in NOBILITY since this study was conducted prior to the COVID-19 pandemic (Appendix K, Section 12.5.2).

Figure 15: Number of AEs of confirmed/suspected COVID−19 by treatment arm and seriousness over time (REGENCY; safety-evaluable population)



Source: Study CA41705 Primary CSR. Report No. 1131275 (115).

2.11.2.8.7 Comparison of AEs reported in 2-2-2 and 2-2-1 obinutuzumab regimens

The incidence of AEs up to Week 76 [redacted] across both OBI regimens (64 patients [92.8%] in the 2-2-2 regimen and 62 patients [92.5%] in the 2-2-1 regimen).

The incidence of SAEs, serious infections, Grade 3−5 AEs, AEs with fatal outcome as well as the majority of reported AESIs up to Week 76 were [redacted] in the [redacted] regimen compared with the [redacted] regimen.

Given that the two regimens only differed at Week 50 (where an additional OBI dose was administered in the 2-2-2 regimen), an analysis of AEs reported in the OBI arm up to Week 50 was performed and results showed

[redacted] to Week 50 (Table 38). This suggests that the observed [redacted] of events in patients randomised to the [redacted] regimen compared with the [redacted] regimen up to Week 76 was [redacted] by the [redacted] or [redacted] of an additional dose of OBI at Week 50.

Table 38: Overview of key adverse events reported in OBI 2-2-2 and 2-2-1 regimens (REGENCY; safety-evaluable population)

	Up to Week 50		Up to Week 76	
	OBI Arm 1 (2-2-2 Regimen) (N=69)	OBI Arm 2 (2-2-1 Regimen) (N=67)	OBI Arm 1 (2-2-2 Regimen) (N=69)	OBI Arm 2 (2-2-1 Regimen) (N=67)
Total number of patients with at least one, n (%)				
AE	[redacted]	[redacted]	[redacted]	[redacted]
Infection AE	[redacted]	[redacted]	[redacted]	[redacted]
Serious AE	[redacted]	[redacted]	[redacted]	[redacted]
Serious Infection AE	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3–5 AE	[redacted]	[redacted]	[redacted]	[redacted]
AE with fatal outcome	[redacted]	[redacted]	[redacted]	[redacted]
AESI:[a] patient with, n (%)				
IRR	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3–5 infection	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]

[a]Only select categories of AESIs are presented.
Source: Study CA41705 Primary CSR. Report No. 1131275 (115)

2.12 Ongoing studies in LN

The NOBILITY study has reached completion (151). The REGENCY study is currently in the OLE phase, with patients able to remain on the study for up to 5 years in total. The study end date is yet to be confirmed but is expected in 2028. The POSTERITY study is a phase II, randomised, double-blind, placebo-controlled, multicentre study evaluating the efficacy, safety and pharmacokinetics of OBI in adolescent patients with active Class III or IV LN. The study is ongoing and has a primary completion date of May 2027 (152).

2.13 Interpretation of clinical effectiveness and safety evidence

Achieving rapid and sustained remission is key to the long-term preservation of renal function and avoidance of ESRD in patients with LN, and this is reflected in recent clinical guidelines that recommend upfront triple immunosuppressive therapy, along with UK clinical expert opinion (68, 72, 74, 75, 153). There is a lack of targeted immunosuppressive drugs that offer rapid efficacy along with convenience of administration, with current treatments placing a significant pill burden on patients, requiring frequent administration, or taking lengthy periods of time to reach full therapeutic effect (68, 77, 83). Since patient adherence is a significant challenge associated with poor clinical outcomes in LN (101), there is a need for treatments that can reduce treatment burden by offering rapid and sustained efficacy with infrequent administration (68), a need that OBI is well positioned to address.

B-cells are central to the initiation and perpetuation of autoimmune processes driving LN (154). Clinicians recognise the importance of B-cell depletion, a therapeutic strategy widely employed through the off-label use of RTX (68). Despite its widespread use, the efficacy of RTX is constrained by its inability to achieve complete B-cell depletion and its relatively short duration of action, as demonstrated in the LUNAR study (88). A post-hoc analysis suggested that greater B-cell depletion correlated with a higher percentage of patients having a CRR (88). OBI is a monoclonal antibody that targets the CD20 receptor on B-cells, featuring enhanced antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis due to its glycoengineered Fc region. This engineering offers deeper and more sustained B-cell depletion compared to RTX, providing a potentially more effective therapeutic option for patients with LN (1).

2.13.1 Efficacy

The phase III REGENCY study affirmed the efficacy of OBI in achieving rapid and deep B-cell depletion in patients with Class III/IV ± V LN, where 99.2% of patients receiving OBI combined with SOC therapy experienced complete peripheral CD19+ B-cell depletion by Week 4 (115). The durability of this effect was confirmed at Week 76, where 95.1% of patients remained depleted of B-cells 24 to 26 weeks following the final dose administered at Week 50 or Week 52 (115). UK clinical experts consulted by Roche agree that the B-cell depletive effects of OBI, as evidenced by this data, are superior to those of RTX (68).

REGENCY met its primary endpoint, with OBI plus SOC therapy demonstrating a significant and clinically meaningful improvement in CRR at Week 76 compared with placebo plus SOC therapy (115). Subgroup analyses based on key baseline characteristics of baseline proteinuria and biopsy class showed higher CRR rates with OBI compared with placebo, further supporting the robustness of the treatment effect (115). This treatment benefit in CRR was consistent with findings from NOBILITY (125), including post-hoc analyses that compared REGENCY and NOBILITY data, and evaluated multiple CRR definitions. Furthermore, extended follow-up in NOBILITY showed that CRR rates remained higher in the OBI arm compared with the placebo arm up to Week 104, indicating a sustained renal response over two years (125).

In addition to CRR, OBI demonstrated benefits in GC-sparing and proteinuric response as key secondary efficacy endpoints, which further support its efficacy (115). While not statistically significant, REGENCY results for the remaining key secondary efficacy endpoints, excluding the FACIT-Fatigue endpoint, showed directionally consistent treatment effects in favour of OBI. Notably, there was a clinically meaningful difference in favour of OBI for the proportion of patients with death or renal-related events through Week 76 between the two arms (115). Furthermore, an exploratory analysis of renal flares from Week 24 to Week 76 indicated a nominally significant trend of fewer renal flares in the OBI arm. At a recent advisory board organised by Roche, UK clinical experts agreed that the flare data demonstrates the ability of OBI to delay flares and consequently preserve nephrons earlier in the disease course. Thus, initiating treatment with OBI early would preserve nephrons and delay disease progression, reducing the need to cycle through other drugs (68).

A post-hoc analysis of NOBILITY assessed whether OBI provided long-term benefits in preserving kidney function and reducing GC use (120). The results indicated that OBI provides sustained renal protection and may help reduce GC dependence in LN. Findings indicate a lower risk of kidney deterioration and LN flare, with greater improvements in proteinuria and long-term renal response compared to placebo (120).

2.13.2 Safety

Across REGENCY and NOBILITY, OBI was generally well tolerated in patients with LN (115, 125). No new safety concerns were identified, and the safety data was consistent with the known safety profile of OBI and/or the underlying disease of the patient population. UK clinical experts consulted by Roche commented that the long-term safety profile of OBI is well known from oncology studies and is not of particular concern (68).

In REGENCY, the incidence of AEs during the 76-week blinded treatment period was comparable between OBI and placebo arms, with most AEs being mild to moderate in severity (115). SAEs occurred more frequently in the OBI arm. REGENCY was conducted during the global COVID-19 pandemic and this increase in rate of SAEs was primarily driven by serious infection AEs of COVID-19. Importantly, when excluding COVID 19 SAEs, the difference between treatment arms was less pronounced. Moreover, in the NOBILITY study, which was conducted before the COVID-19 pandemic, OBI was associated with fewer SAEs, serious infections and deaths than placebo. In REGENCY, infusion-related reactions, Grade 3–5 infections and drug-related neutropenia occurred more frequently with OBI compared with placebo. There were three fatal AEs in the OBI arm and two fatal AEs in the placebo arm. The proportion of patients with at least one AE leading to discontinuation from blinded OBI was low in both arms, and no patients were withdrawn from the study due to AEs (115). Safety findings in NOBILITY were consistent with REGENCY (125).

2.13.3 Conclusion

In summary, OBI in combination with standard therapy has demonstrated a significant clinical benefit in patients with LN in terms of CRR, reduction of proteinuria and glucocorticoid sparing, underpinned by a rapid, deep and sustained depletion of peripheral B-cells. Moreover, OBI is well-tolerated and has a manageable safety profile. The clinical data supporting the efficacy and safety of OBI have led to its inclusion in the 2025 BSR and EULAR guidelines on management of LN before achieving marketing authorisation in any jurisdiction, highlighting its role as an innovative treatment offering rapid and sustained efficacy with the potential to alleviate treatment burden in patients with LN.

3 Cost effectiveness

3.1 Published cost-effectiveness studies

An SLR was conducted to identify published cost-effectiveness studies of OBI or other interventions for the treatment of adults with active LN. A full description of the SLR, including detailed descriptions of the search strategy and extraction methods, as well as an overview of the identified studies, is provided in Appendix E. A clinical SLR has also been conducted in conjunction with this economic review (Section 2.1 and Appendix B), as well as a NMA feasibility assessment (Section 2.9 and Appendix B).

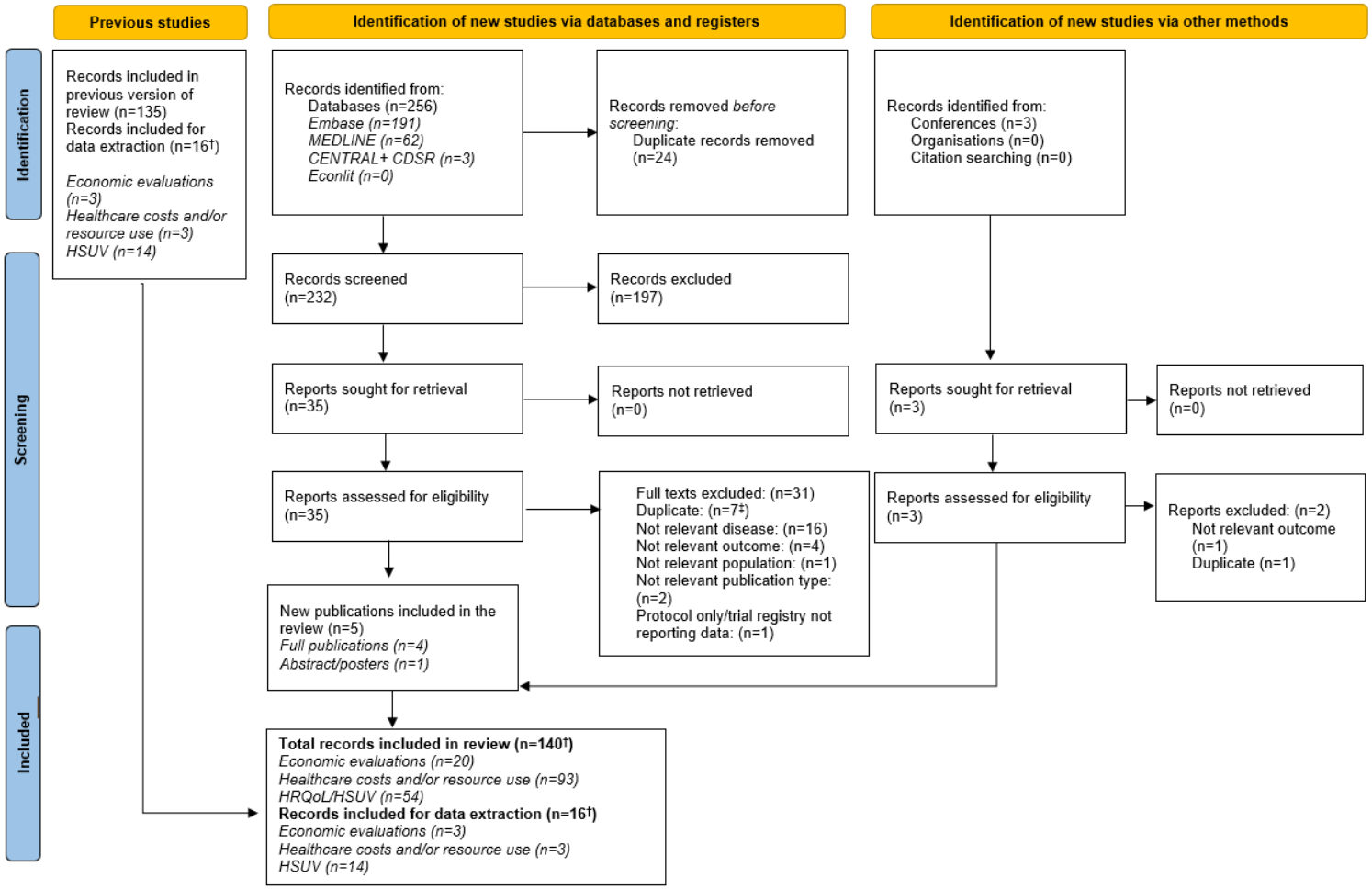
3.1.1 Summary of identified studies and results

For the economic SLR, bibliographic database searching was performed (24th June 2024) alongside searches of conference proceedings, trial registries, HTA/regulatory body websites, additional websites to identify records of interest. All searches were conducted between 30th May and 24th June 2024. 2,661 records were retrieved from the bibliographic databases following removal of duplicates. Following primary (title/abstract) screening, 685 records were included for secondary (full-text) review, of which 123 were considered relevant for inclusion against the specified inclusion/exclusion criteria (population, intervention, comparator(s), outcomes, study design/publication type [PICOS]) criteria (Table 39). A further 12 records were included from supplementary searches, resulting in an evidence base including 135 records across the three economic components (economic evaluation, HRQoL and cost and resource use).

An update to the economic SLR was conducted in 2025, with bibliographic database searching performed on 3rd March 2025, alongside searches of the same conference proceedings, trial registries, HTA/regulatory body websites, and additional websites as the original SLR. 232 records were retrieved from the bibliographic databases following removal of duplicates. Following primary (title/abstract) screening, 35 records were included for secondary (full-text) review, of which 4 were considered relevant for inclusion against the specified inclusion/exclusion criteria. One further record was included from supplementary searches, resulting in 5 additional records identified in the update, and 140 records included across the three economic components for both the original and SLR update.

Of the included records (n=140), the majority (n=104/140) did not report the percentage of patients that were ISN/RPS Class III/IV ±V LN (population of interest). Just over half of the included records (n=79/140) had a primary focus on LN patients, whereas a large proportion of studies related to SLE more generally, with patients having renal involvement/LN. Of the included records (n=140), 20 represented economic evaluations. The flow of studies through the review is summarised in the PRISMA flow diagram in Figure 16.

Figure 16: PRISMA flow diagram detailing the record identification process for the original SLR and update



Key: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; HSUV, health state utility value; HTA, health technology assessment; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.
Notes: † Included articles may be relevant to more than one economic component (cost effectiveness, healthcare cost and/or resource use, HSUV). ‡ Duplicates included publications that were identified in the original review that were not deduplicated in KiaKia due to the update being run as a separate review.

The SLR identified only three economic evaluations relevant to a UK population; of those, two were recent HTA submissions to NICE and the SMC from 2023 assessing VOC plus MMF. Both applied a Markov model over a lifetime horizon from a UK (England and Wales/Scotland) NHS perspective, with health states defined by level of chronic kidney disease (CKD), to estimate the cost-effectiveness of VOC. The third relevant economic evaluation compared MMF to intravenous cyclophosphamide (IVC) and used a simulation (time to event) model with less than a year time horizon. It was also dated, being a 2007 publication with the analysis based on 2005 costs/inputs. All economic evaluations were generally conducted in the population of interest; however, pure Class V patients were included in all. A summary of the three relevant economic evaluations is presented in Table 40. It is expected that the HTAs will be the most useful source of evidence to inform data gaps in an economic model. These are the most recent publications identified relevant to a UK population and provide a comprehensive overview of the evidence that has been submitted to UK HTA bodies to date.

In conclusion, although a large number of records identified economic evidence, a paucity of economic evidence was found for the ISN/RPS Class III/IV ±V LN population. There is potential to use data from similar or proxy LN populations such as those also including pure Class V patients, or even broader LN populations, but the generalisability to the population of interest would need to be considered. Recent economic evaluations conducted from a UK perspective generally support the use of a Markov model with a lifetime horizon and 6-monthly cycles.

Further details and results for the identified cost effectiveness studies and abstracts can be found in Appendix E.

Table 39: Economic SLR eligibility criteria (PICO)

Criteria category	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years) with active/chronic proliferative LN (ISN/RPS Class III or IV ±V)†	Children/adolescents Non-proliferative LN of either Class I, II, or VI
Interventions	Any (restricted to pharmacological therapies)	-
Comparators	Any (restricted to pharmacological therapies)	-
Outcomes	**Economic evaluations** Summary (total and incremental) costs, including by category (e.g. health states, adverse events) Summary (total and incremental) health outcomes (QALYs, LYs) ICERs/ICURs (cost per QALY gained, cost per LY gained) NMB Model summary (e.g. type of economic analysis, model type/structure, model diagram, model perspective, time horizon, discounting) Transition probabilities **Cost and/or HCRU data** **Costs:** Direct health and social care total and unit costs (e.g. cost per outpatient appointment, cost per adverse event) Indirect health and social care total and unit costs (e.g. patient travel, out-of-pocket expenses) **HCRU:** Health and social care resource use frequencies (e.g. number of outpatient visits) LoS/readmissions Work productivity (e.g. absenteeism, presenteeism, lost work days, lost wages) **HRQoL/HSUVs** Utility/disutility values associated with health states or disease classification (e.g. ISN/RPS Class III±V, ISN/RPS Class IV±V, ESRD) and health events (e.g. adverse events, dialysis, transplantation) HRQoL non-utility values associated with health states (from non-preference-based measures, e.g. SF-36) Mapping algorithms that allow mapping from non-preference-based measures to utility values (A record only needs to include one outcome of interest across any of the three components to be eligible for inclusion)	Records reporting only medicine acquisition (total and unit) costs will be excluded. Medicine acquisition costs are not a relevant outcome.‡
Study design	**Economic evaluations**	Animal/*in vitro* studies

Criteria category	Inclusion criteria	Exclusion criteria
	CEA CUA CMA/cost comparison CCA COI CBA Budget impact **Costs and/or HCRU data** RCTs Non-randomised trials (comparative) Single-arm studies (non-comparative) Observational studies Registries Chart reviews Claims data analyses EAPs Economic evaluations (as listed above) **HSUVs/HRQoL** HRQoL elicitation studies HRQoL validation studies Economic evaluations (as listed above) Study types as per 'Costs and/or resource use data' (as listed above)	Case series studies Case reports Studies with <20 participants
Publication type	Full-text peer-reviewed publications Conference abstracts/proceedings (including posters) HTA guidance/documents Trial protocols reporting original data (e.g. model structure) Horizon scanning documents Guidance documents	Systematic reviews and network meta-analyses§ Non-systematic reviews§ Letters¶ Comment/opinion pieces Editorials¶ Press releases¶ Trial protocols not reporting original data
Geography	No restriction	
Publication date	Date limit applied to conference abstracts/proceedings, for the last 3 full years (2021–present) No other date restrictions are applied	Pre-2021 conference abstracts/proceedings

Criteria category	Inclusion criteria	Exclusion criteria
Language	No restriction††	

Key: BNF, British National Formulary; CBA, cost-benefit analysis; CCA, cost-consequence analysis; CEA, cost-effectiveness analysis; CMA, cost-minimisation analysis; COI, cost of illness; CUA, cost-utility analysis; EAP, early access programme; ESRD, end-stage renal disease; HCRU, healthcare resource use; HRQoL, health-related quality of life; HSUV, health state utility value; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; ISN/RPS, International Society of Nephrology/Renal Pathology Society; LN, lupus nephritis; LoS, length of stay; LY, life year; NMB, net monetary benefit; PICO, population, intervention, comparators, outcomes; QALY, quality-adjusted life year; RCT, randomised controlled trial; SF-36, Short Form-36; SLR, systematic literature review.
Key: † SLR searches capture all adults with active LN for increased sensitivity, but the primary aim of the review is to identify clinical evidence in active LN (ISN/RPS Class III or IV), for which relevant data from these studies will inform the OBI economic model.
‡ Medicine acquisition costs are not considered relevant as these would be sourced for an economic model from national cost databases, e.g. BNF (UK).
§ Systematic reviews were identified for cross-checking/reference-tracking purposes only.
¶ Press releases, letters, and editorials were excluded unless they clearly reported new, yet to be published, primary data relevant to the PICO and economic model/decision problem.
†† Attempts to translate records identified in non-English language were made using Google translate; where translations could not be adequately conducted, these were detailed in deliverables.

Table 40: Summary of published cost-effectiveness studies

Study, country, design	Summary of model	Intervention / comparator	Patient population	Base case costs, currency (year),	Base case health outcomes	Base case ICER	Model assumptions	Reported study limitations
Wilson 2007 (155) UK CEA/CUA	Model type: Simulation model (time to event) Health states: 1) Treatment: MMF, IVC, none Disease status: Active, PR, CR Minor infection: Yes/No Major infection: Yes/No Adverse event leading to discontinuation: Yes/No Time horizon: <1 year Perspective: UK NHS Cycle length: 12 weeks Use of half-cycle correction: NR Discount rate for costs: Not applied	MMF IVC	Adults with active LN (ISN/RPS Class III, IV, V)	Total costs, GBP (2005): MMF: 1,338 IVC: 2,994	Total QALYs: MMF: 0.262 IVC: 0.223	Cost/ QALY: MMF versus IVC: MMF dominant	The transition period of the model is 12 weeks and costs and outcomes were summed over 24 weeks (6 months) representing the induction period of therapy Following the Cochrane review evidence, it was assumed that the infection rates for steroid treatment were equal to those for IV, but varied this assumption in a scenario analysis, setting the infection rates for steroid treatment equal to those for MMF The treatment variable was MMF, IVC or 'none' Patients switched or discontinued immunosuppressants (due to AEs) at rates determined from the literature. It was assumed that such patients received a course of intravenous methylprednisolone administered as a monthly bolus of 1 g/m2 (average	A limitation of the model is that this effect (major infections may lead to dose reduction) is not captured; but as MMF has a lower frequency of major infection, excluding this effect will bias the model against MMF It should be noted that this model considered only the first 6 months of a patient's therapy (induction treatment). It is therefore not possible to comment on the cost effectiveness of longer-term maintenance therapy at this stage Long-term experience with MMF is still quite limited and further work is ongoing to determine the longer-term clinical outcomes of using

Study, country, design	Summary of model	Intervention / comparator	Patient population	Base case costs, currency (year),	Base case health outcomes	Base case ICER	Model assumptions	Reported study limitations
	Discount rate for outcomes: Not applied Health benefits: QALYs						monthly dose of 1.75 g, range: 1.6–1.9 g) The disease status variable relates to the effectiveness of the treatment at inducing remission	MMF as a maintenance therapy. Additionally, the model does not consider the critical outcomes of renal failure and death A limitation in developing this model was the lack of a strictly defined dosing regimen for IVC in common practice. For the purpose of this model, the authors defined an explicit regimen
SMC 2023 (156) UK CUA	Model type: Markov model Health states: 2) CKD Stages 1–3a (with substates of AD, PR and CR) CKD Stages 3b–4 CKD Stage 5 (ESRD) Death	VOC + MMF MMF (main comparator) Other comparators included: CYC, RTX + MMF, and TAC	Active Class III/IV ±V LN	Total costs, GBP (2023): NR	Total QALYs: NR	Cost/QALY for VOC + MMF versus: MMF (main comparator): £19,794 Cost/QALY for VOC + MMF versus: L-CYC: £3,717	Cost and resource use: for indirect comparators it was assumed to continue on therapy to a maximum timepoint of 36 months, with subsequent maintenance therapy conditional on type of prior therapy	The clinical data from AURORA-1 and 2 was represented though non-parametric count-based methods applied for individual model cycles; due to patient/event numbers this may lead to uncertainty that the submitting company was unable to overcome its attempts to employ alternative methods

Study, country, design	Summary of model	Intervention / comparator	Patient population	Base case costs, currency (year),	Base case health outcomes	Base case ICER	Model assumptions	Reported study limitations
	Time horizon: Lifetime (67 years) Perspective: NHS Scotland Cycle length: NR Use of half-cycle correction: NR Discount rate for costs: NR Discount rate for outcomes: NR Health benefits: QALYs					H-CYC: £2,870 AZA £16,264 RTX + MMF: £7,480 TAC + MMF: £15,205 TAC: £14,238		Longer-term extrapolation relies on arbitrary assumptions relating to application of Year 3 data from AURORA 2. This risks conflation of short-term outcomes following induction therapy with long-term maintenance therapies There is uncertainty over anticipated treatment durations, which the submitting company acknowledged The model structure did not address the potential for longer-term treatment involving attempted re-induction of response, adding to the uncertainty over long-term model outcomes There is some uncertainty as to whether the Kaplan–Meier for discontinuation fully

Study, country, design	Summary of model	Intervention / comparator	Patient population	Base case costs, currency (year),	Base case health outcomes	Base case ICER	Model assumptions	Reported study limitations
								aligns with response. Discontinuation was not applied for secondary comparators
NICE 2023(82) UK CEA/CUA	Model type: Markov model Health states: 3) CKD Stages 1–3a (with substates of PR, CR, AD) CKD Stages 3b–4 (with substates of PR, CR, AD) CKD Stage 5 (dialysis), CKD Stage 5 (after kidney transplant) death (the absorbing health state) Time horizon: Lifetime (72 years) Perspective: UK NHS and PSS Cycle length: 6 months	VOC + MMF MMF (main comparator) Other comparators : L-CYC, H-CYC, AZA, RTX + MMF, TAC + MMF, TAC	Active Class III, IV, or V (including mixed Class III/V and IV/V) LN	Redacted (GBP, NR)	Redacted	ICER (£/QALY) for VOC + MMF versus MMF: 20,001 ICER (£/QALY) for VOC +MMF versus L-CYC: 10,701 ICER (£/QALY) for VOC + MMF versus H-CYC: 10,221 ICER (£/QALY) for VOC + MMF versus AZA: 15,009	Initial treatment duration: 3-year (36-month) stopping rule applied for initial treatments in the base case, apart from a 1-year (12-month) stopping rule for TAC Long-term treatment effect: treatment waning effect applied following treatment discontinuation for all treatments Transition from CKD 1–3a to CKD 3b–4: it is assumed that patients do not progress from CKD 1–3a to CKD 3b–4 in the first 3 years TTD: TTD extrapolations based on combined AURORA 1 and AURORA 2 trial data were used to estimate VOC + MMF and MMF discontinuation over 36-month treatment period	The rarity of the disease means that there is generally limited published clinical, humanistic, and economic data available for LN and/or SLE. Therefore, there is some uncertainty in terms of long-term transitions to advanced CKD stages The chronic, progressive nature of the disease means that patients typically remain on treatment for a number of years and there is some variation in clinical practice in terms of treatment duration on a treatment-by-treatment basis There is currently limited knowledge of

Study, country, design	Summary of model	Intervention / comparator	Patient population	Base case costs, currency (year),	Base case health outcomes	Base case ICER	Model assumptions	Reported study limitations
	Use of half-cycle correction: Yes Discount rate for costs: 3.5% Discount rate for outcomes: 3.5% Health benefits: QALYs, LYs					ICER (£/QALY) for VOC + MMF versus RTX +MMF: 20,742 ICER (£/QALY) for VOC + MMF versus TAC + MMF: 17,864 ICER (£/QALY) for VOC + MMF versus TAC: 16,737	TTD: It is assumed that no other treatments were discontinued in the model Patient response status and utility for CKD 1–3a: it is assumed that patients in the AURORA-1 and 2 trials are reflective of LN patients with CKD 1–3a Patient response status and utility for CKD 1–3a: it is assumed that only consistent and confirmed eGFR changes over time were reflective of patient response status and CKD progression Utility for CKD 3b–4: it is assumed that a CKD 1–3a to CKD 3b–4 progression-related utility decrement is reflective of LN-related CKD 3b–4 utility AE disutility and AE-related costs: it is assumed that only Grade III/IV TEAEs identified in ≥1% of patients in the AURORA-1 are associated with disutility and costs	treatment waning effects in the field of LN Among the nine health states, the base case analysis excluded CKD 3b–4 PR and CKD 3b–4 CR states due to a lack of available data and in line with KOL feedback, which highlighted response to be rare among these patients

Study, country, design	Summary of model	Intervention / comparator	Patient population	Base case costs, currency (year),	Base case health outcomes	Base case ICER	Model assumptions	Reported study limitations
							Among the nine health states, the base case analysis excludes CKD 3b–4 PR and CKD 3b–4 CR states due to a lack of available data and in line with KOL feedback, which highlighted response to be rare among these patients	

Key: AD, active disease; AE, adverse event; AZA, azathioprine; CEA, cost-effectiveness analysis; CKD, chronic kidney disease; CR, complete response; CUA, cost-utility analysis; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; H-CYC, high-dose cyclophosphamide; ICER, incremental cost-effectiveness ratio; ISN/RPS, International Society of Nephrology/Renal Pathology Society; IVC, intravenous cyclophosphamide; KOL, key opinion leader; L-CYC, low-dose cyclophosphamide; LN, lupus nephritis; LY, life year; MMF, mycophenolate mofetil; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NR, not reported; QALY, quality-adjusted life year; PR, partial response; PSS, Personal Social Services; QALY, quality-adjusted life year; RTX, rituximab; SLE, systemic lupus erythematosus; SMC, Scottish Medicines Consortium; TAC, tacrolimus; TEAE, treatment-emergent adverse event; TTD, time-to-treatment discontinuation; VOC, voclosporin.

3.2 Economic analysis

As explained in Section 3.1, the economic analyses used to inform the VOC UK health technology appraisals (NICE TA882 and SMC2570) will be the most useful sources of evidence to inform data gaps in an economic model (82, 156). These are the most recent publications identified relevant to a UK population and provide a comprehensive overview of what has been submitted to UK HTA bodies to date.

In TA882, it was concluded that, although the model still had uncertainties, the company submitted model to assess VOC for the treatment of LN was appropriate for decision making. Key uncertainties and limitations described by the committee included heterogeneity across trial populations included in the underlying network meta-analysis, treatment discontinuation assumptions and the company's and External Assessment Group (EAG)'s approaches to the long-term treatment effect extrapolations (82).

Some of these uncertainties will be difficult to address in the assessment of OBI for the treatment of LN, including long-term treatment effects and their impact on LN and ESRD. This is a difficulty often associated with clinical data collection and long-term economic modelling of chronic diseases. In the absence of data in the comparator arms, this analysis makes use of assumptions that have a conservative impact on the cost-effectiveness of OBI treatment in this indication. However, the company-submitted analysis will undertake scenario analyses to investigate the impact of alternative assumptions and data sources for the modelling of long-term treatment effect on cost-effectiveness outcomes.

3.2.1 Patient population

In line with the final NICE scope, the economic analysis evaluates the cost-effectiveness of OBI in combination with immunosuppressive therapies for the treatment of LN. Specifically adult patients with active class III or IV LN, with or without concomitant class V disease, consistent with the REGENCY trial population.

3.2.2 Model structure

The economic model developed to assess the cost-effectiveness of OBI for this population follows a Markov state-transition modelling approach. There is only one published NICE technology appraisal for the treatment of patients with LN. The cost-effectiveness model in TA882 was based on previously published models and the clinical pathway for LN (82). The model comprised 9 health states to capture the transitions between active disease and response health states within CKD stages and the progression between CKD stages and death.

The company submission for OBI will also follow a Markov state-transition modelling approach and comprises of the same 9 health states. In TA882, the company model structure was deemed appropriate for decision making (82). Clinical experts consulted for this submission considered that the model structure captures health states relevant to UK clinical practice. LN is a chronic and progressive condition, and Markov state-transition models are well-suited for chronic diseases where patients transition between different health states over time. Markov models operate in fixed cycles, in this case 6 months, which

capture the dynamic progression of LN over time including the eventual progression through different stages of CKD to ESRD.

The health states considered are presented below:

1. CKD1-3b: Active Disease (CKD_1_3b_AD)
2. CKD1-3b: Partial Response (CKD_1_3b_PR)
3. CKD1-3b: Complete Response (CKD_1_3b_CR)
4. CKD4: Active Disease (CKD_4_AD)
5. CKD4: Partial Response (CKD_4_PR)
6. CKD4: Complete Response (CKD_4_CR)
7. CKD5: Dialysis (CKD_5_D)
8. CKD5: Transplant (CKD_5_T)
9. Death (Death)

Based on the KDIGO LN 2024 guideline (50, 74), the following CKD categories are defined:

- CKD 1: eGFR >= 90 ml/min/1.73m^2
- CKD 2: eGFR 60 - 89 ml/min/1.73m^2
- CKD 3a: eGFR 45 - 59 ml/min/1.73m^2
- CKD 3b: eGFR 30 - 44 ml/min/1.73m^2
- CKD 4: eGFR 15 - 29 ml/min/1.73m^2
- CKD 5: eGFR < 15 ml/min/1.73m^2

REGENCY included patients with an eGFR > 30 ml/min/1.73m^2, i.e. CKD Stage 1-3b.

The final model structure is presented in Figure 17. All patients enter the model in the CKD_1_3b_AD health state, in line with the inclusion criteria in the REGENCY pivotal trial (115).

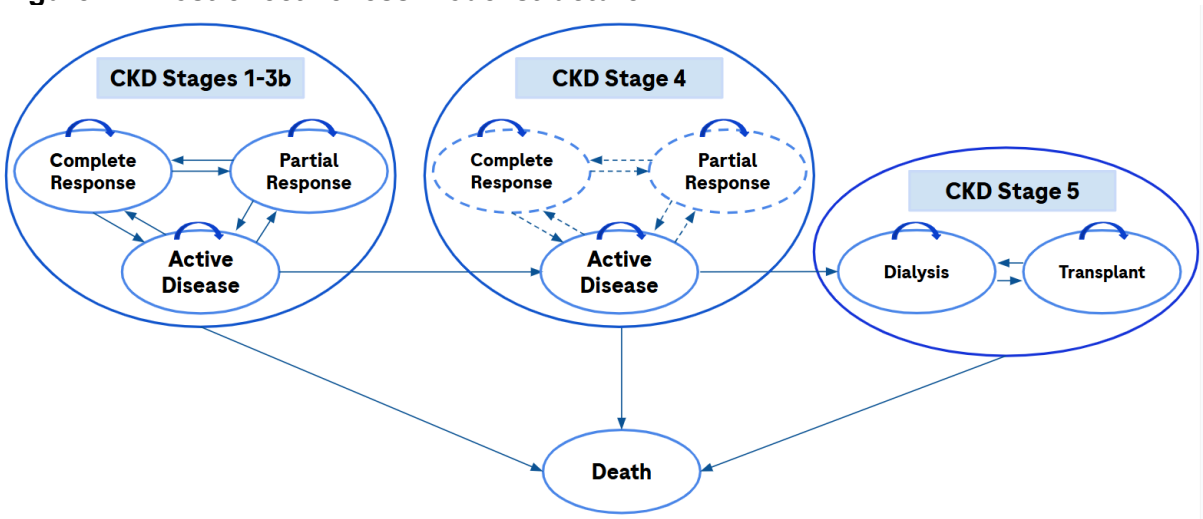
People were excluded from REGENCY if they exhibited severe renal impairment, as defined by eGFR < 30 mL/min/1.73 m^2 (as estimated using the CKD-EPI equation) or the need for dialysis or renal transplantation (157).

Mapping LN classes to CKD stages is difficult, because the classification is based on the histological features seen in kidney biopsies.

- Class I and II LN: These early classes often correspond to CKD Stage 1 or 2. Kidney function is typically well-preserved.
- Class III and IV LN: These classes indicate more significant inflammation and potential for substantial kidney damage. Patients can range from CKD Stage 2 to Stage 4, depending on the severity and duration of the disease.
- Class V LN: Membranous LN can lead to nephrotic syndrome, which can result in CKD Stage 1 to Stage 4, mainly progressing depending on the response to treatment and control of symptoms.
- Class VI LN: This indicates advanced disease and sclerosis, often corresponding to CKD Stage 4 or 5 due to significant loss of kidney function.

Because REGENCY excludes patients with eGFR >30, we can conclude that patients up to CKD Stage 3b are included in this trial. So, patients enter the cost-effectiveness model in CKD Stage 3b and present with active disease (CKD_1_3b_AD).

Figure 17: Cost-effectiveness model structure



Key: CKD, chronic kidney disease.

The Markov state transition model applies transition probabilities at each 6-month model cycle.

From the entry model health state of CKD_1_3b_AD, patients can transition either to partial response (CKD_1_3b_PR) or complete response (CKD_1_3b_CR) health states, remain in an active disease health state (CKD_1_3b_AD), progress to Stage 4 CKD via worsening eGFR (CKD_4_AD), or die (death).

In the subsequent model cycles, the proportion of patients that are partially responding can completely respond and transition to CKD_1_3b_CR, lose response and transition to CKD_1_3b_AD, remain in CKD_1_3b_PR, or die (death). Similarly, those who have completely responded to initial treatment can either remain completely responding (CKD_1_3b_CR), revert to partial response (CKD_1_3b_PR) lose response altogether (CKD_1_3b_AD), or die in each subsequent model cycle.

As in TA882, the model assumes that progression along CKD health states (i.e. from CKD Stage 1-3b to CKD Stage 4 and CKD Stage 4 to CKD Stage 5) can only occur in the proportion of patients with active LN (AD health states). This assumption is consistent with the analysis presented in TA882 (82). If the patient is responding to the treatment (that is, in PRR or CRR), we can assume their disease is not active. The correlation between these is strong, but not perfect. This means that, in theory, there could be a small minority of patients who could progress to CKD Stage 4 from CRR or PRR. However, there were no observable cases of patients transitioning from response health states to CKD Stage 4 in REGENCY and none were cited in TA882, so this simplification assumption is considered appropriate and transitions from CRR or PRR to CKD Stage 4 are not possible in the cost-effectiveness model.

The model has the functionality to include the same ‘response-based’ transitions in the CKD Stage 4 health states as in CKD Stage 1-3b. But, as in TA882 due to lack of available data and in line with clinical expert opinion, these transitions are disabled in the model base case (presented with dashed lines in Figure 17). So, from CKD_4_AD, patients can only progress

onwards to CKD Stage 5 and associated complications. Patients cannot transition back to CKD Stage 3 and, because response-based transitions are switched off in the base case, patients cannot further respond from the CKD_4_AD health state in the model.

Once a proportion of patients have transitioned to CKD Stage 5, they have a probability of receiving dialysis or a kidney transplant. The model assumes that all patients transition from CKD Stage 4 to CKD Stage 5 into the dialysis health state (CKD_5_D). From the dialysis health state, patients can transition to transplant (CKD_5_T) or die. The proportion of patients that receive a kidney transplant remains as a standalone health state, due to the impact transplants have on the population and the lack of available data on mortality and quality of life of this population. All assumptions relating to later-stage CKD transitions (i.e. CKD Stage 4 and 5) are in line with those made in TA882 (82).

Cost effectiveness was modelled over a lifetime horizon (70 years) from an NHS and Personal Social Services perspective. A lifetime horizon was chosen in order to simulate long-term outcomes, including the progression to ESRD. Most supportive costs in LN occur in the late stages of kidney disease, where either dialysis or kidney transplant are the only viable treatment options. These procedures have important cost and resource implications for the NHS and have the potential to be cost drivers in the economic analysis. So, it is important that the time horizon is long enough to capture these impacts appropriately. The model utilises a six-month cycle length, which was used and accepted in the only relevant UK economic analyses found as part of the economic SLR (TA882 and SMC2570), detailed in Section 3.1 and Table 40 (82, 156). A six-monthly cycle also matches the dosing pattern of OBI and was deemed sufficiently granular to accurately capture the clinical and cost outcomes for patients with LN. Half-cycle correction is applied to account for events not occurring at the beginning or end of each 6-month cycle, and costs and benefits are discounted an adjustable annual rate of 3.5%.

Table 41: Features of the economic analysis

Factor	TA882	Current evaluation, chosen values	Current evaluation, justification
Time horizon	Lifetime, with the option to consider reduced time horizons.	Lifetime, with the option to consider reduced time horizons.	Long enough to capture all costs and benefits associated with the treatment of LN.
Model structure and health states	Nine-state Markov cohort state transition model (seven states utilised in the base case analysis).	Nine-state Markov cohort state transition model (seven states utilised in the base case analysis).	Consistent with NICE TA882 and previous LN cost-effectiveness analyses, validated by clinical experts. As in TA882, the model comprises 9 health states. However, response-based transitions within CKD stage 4 are switched off due to lack of available data. (82)
Stopping rule and treatment effect waning	Applied 36-month stopping rule for VOC + MMF and all other treatments apart from TAC containing regimens (12 months). Assumed that, upon discontinuation of VOC + MMF, patient health state transition probabilities wane to an average (i.e. midpoint) of those recorded with VOC + MMF and those MMF. For all other treatments, long-term health state transition probabilities wane to an average of those derived from ITC data and those for MMF.	Applied 36-month stopping rules for all treatments included in the model. Treatment effect waning applied to all treatments following discontinuation. Following discontinuation of OBI + MMF, the treatment effect is maintained for 12 months before waning to MMF transitions over the next 12 months. Following discontinuation of VOC + MMF, the treatment effect wanes to equal MMF transition probabilities over 6 months. For rituximab + MMF, the treatment effect is maintained for 6 months before waning to MMF transitions over the next 6 months. The model has the flexibility to consider alternative treatment effect waning scenarios.	Unlikely that treatment effect will be maintained for lifetime time horizon upon discontinuation. So, treatment waning assumptions applied for all add-on triple therapy treatments. OBI B-cell depleting mechanism of action expected to result in a better duration of response following discontinuation, supported by NOBILITY and REGENCY clinical trial evidence and clinical expert opinion (68, 115, 120, 125). Once patients discontinued from VOC, clinical experts do not expect any treatment benefit over MMF transitions. Conservative assumption to wane VOC transitions to MMF over a period of 6 months. Waning not included in TA882 decision-making assumptions (82). Less effective B-cell depleting mechanism of rituximab likely to result in some maintenance of treatment effect, but not equal to OBI.
Source of utilities	AURORA 1 and AURORA 2 trials and literature estimates.	Utility health state utility estimates used in TA882 (i.e. AURORA trials) and literature estimates.	Utility estimates were collected in REGENCY but lacked face validity, where patients responding to treatment had

			lower utility than those in active disease (115). Clinical experts explained that this was counterintuitive. So, the base case model utilises utility values from AURORA-1 and AURORA-2 used in the appraisal of VOC for Stage 1-3b health states. For subsequent model health states, the analysis utilises estimates from the literature. Maintains consistency with TA882 in the absence of alternative data and assumptions (82, 83, 124) .
Source of costs	eMIT, BNF, National Schedule of NHS costs (2019–2020), PSSRU unit costs (2020), published literature.	eMIT, BNF, National Schedule of NHS costs (2023-24), PSSRU unit costs (2023), published literature.	In line with the NICE reference case.

Key: BNF, British National Formulary; CKD, chronic kidney disease; eMIT, electronic market information tool; EQ-5D, EuroQol-5 Dimension; ITC, indirect treatment comparison; KOL, key opinion leader; LN, lupus nephritis; NHS, National Health Service; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; SoC, standard of care; TA, Technology Appraisal; TAC, tacrolimus; VOC, voclosporin.

3.2.3 Intervention technology and comparators

The intervention relevant to this economic analysis is OBI (1000 mg) in combination with MMF (2g per day) and low-dose corticosteroid (0.5 mg/kg per day until Day 15, then tapered to a target dose of 5 mg per day by Week 24 and maintained until Week 80). OBI+MMF is implemented in the analysis according to the proposed marketing authorisation described in Section 1.2, and the REGENCY trial (please see Section 2.3.1.1 and Section 2.4.1 for further information about OBI+MMF and the clinical trial protocol) (115).

The NICE final scope included a range of comparators:

- cyclosporin with or without MMF
- cyclophosphamide
- mycophenolate (hereby referred to as MMF)
- rituximab with MMF (hereby referred to as RTX+MMF)
- tacrolimus with or without MMF
- voclosporin with MMF (hereby referred to as VOC+MMF)
- belimumab with MMF (hereby referred to BEL+MMF)

Clinical expert opinion highlighted that:

- It is important to note that, while BEL is licensed for SLE and LN, BEL is not reimbursed in England for LN and its NICE appraisal was terminated.
- While RTX is used in the UK for LN, it does not have a license so it must be demoted in treatment guidelines, despite its use. RTX is predominantly used for refractory disease when other treatment options have failed.
- The ALMS study showed equivalent efficacy between MMF and cyclophosphamide for induction therapy, but that MMF is less toxic (158, 159). MMF is used in the vast majority of first line patients, and guidelines state that if MMF is not working then you can switch to cyclophosphamide, however cyclophosphamide is probably only used in 15% of patients compared to MMF's 85%.
- VOC is predominantly used in a small proportion of highly nephrotic patients with a high chance of relapse.

Clinical experts also indicated the likely usage in clinical practice of each comparator (Table 42) (68).

Table 42: Estimated usage of treatments in UK clinical practice

Treatment	Estimated usage
MMF	80-90%
MMF alone	20-30%
MMF in combination	50-60%
Rituximab	70%
Voclosporin	5-10%
Cyclophosphamide	10-20%
Belimumab	10-20%

Key: MMF, mycophenolate mofetil; UK, United Kingdom.

The comparators included in this economic analysis are limited to MMF, VOC+MMF and RTX+MMF, all in combination with corticosteroids.

BEL+MMF was not included as a comparator because it is not a NICE-recommended and reimbursed treatment in England, so inference on cost-effectiveness results versus BEL+MMF would be of little value to the reimbursement system in England (80). It is likely that the 20% of patients included in the estimated usage in Table 42 are patients originally treated for SLE, where BEL+MMF is a recommended and reimbursed treatment, who then go on to develop renal involvement. So, the proportion of patients estimated to be receiving BEL+MMF are a different standalone population of patients who have been heavily pre-treated. So, the cost-effectiveness of OBI versus BEL+MMF is not a relevant comparison in LN.

Cyclophosphamide was not included as a comparator in the cost-effectiveness analysis for simplicity and pragmatism. Cyclophosphamide is used in a much smaller proportion of patients compared with MMF, and as explained above, clinical experts indicated that cyclophosphamide is predominantly used in patients who have first failed on MMF. Additionally, the ALMS study showed that cyclophosphamide could be considered equivalent to MMF but with more adverse events (158, 159). So, any clinical- and cost-effectiveness outcomes comparing OBI with MMF are likely to be conservative when comparing to cyclophosphamide. Finally, as presented in Section 2.10.3 and Appendix B, it was not possible to generate comparative effectiveness estimates versus cyclophosphamide alone through a connected network meta-analysis. So, any comparative effectiveness would be associated with high uncertainty.

Tacrolimus is not included as a comparator as clinical experts did not indicate tacrolimus was used in a substantial proportion of patients in clinical practice (Table 42). As with cyclophosphamide, and as presented in Section 2.10.3 and Appendix B, it was not possible to generate comparative effectiveness estimates versus tacrolimus through a connected network. However, the cost-effectiveness model does consider a comparison towards the most relevant calcineurin inhibitor in VOC, so a comparison to tacrolimus and/or cyclosporin would offer limited additional value.

3.2.4 Outcomes

Evidence from the REGENCY study and the literature was used to model benefits associated with OBI and other treatments for LN. The model calculates benefits in terms of life years (LYs) and quality-adjusted life years (QALYs) over a lifetime horizon, in line with the NICE reference case. Total costs were calculated and summed from an NHS and PSS perspective. Base case results were generated as incremental cost-effectiveness ratios (ICERs) in terms of incremental cost per QALY gained.

3.3 Clinical parameters and variables

3.3.1 Overview of clinical data sources and outcomes in the economic model

The clinical outcomes used to inform the economic analysis are based on patient-level data from the REGENCY study, investigating OBI+MMF versus MMF (115). These data are included in the NMA (Section 2.9), along with published RCTs included in the SLR (Section 2.1), to inform the ITC of OBI+MMF, VOC+MMF and RTX+MMF (Section 2.10). The REGENCY trial and ITC provide the most robust and best available evidence for conducting comparative cost-effectiveness analysis (145).

The following clinical outcomes are included in the economic model:

- CRR (described in Section 2.6.2.1 and 3.3.2.1)
- PRR (described in Section 2.6.2.1 and 3.3.2.1)
- Transition to ESRD (described in Section 3.3.2.3 and 3.3.2.4)
- Survival (described in Section 3.3.2.5)
- AEs (described in Section 2.11, 3.4.4 and 3.5.3)
- HRQoL (described in Section 3.4.1)

For consistency between treatments, 'forward' health state transitions from CKD Stage 1-3b AD to PR, AD to CR, and PR to CR were estimated based on the outputs of the ITC for OBI+MMF, MMF and other comparators (Section 2.10.4.1 and 2.10.4.2), while 'backwards' transitions from Stage 1-3b CR to PR, CR to AD and PR to AD were informed by REGENCY patient-level data for OBI+MMF and MMF and assumptions made for other treatments (115).

As the REGENCY patient population was limited to CKD Stage 1-3b, and the lack of evidence regarding the long-term impact of LN intervention on CKD progression to end-stage renal disease, transitions through other CKD stages are informed by the literature (115).

Key uncertainties highlighted by the EAG in TA882 included transitions and relative-effectiveness estimates used to model long-term progression to ESRD (82). In this analysis, in line with clinical expert opinion on key predictive endpoints and to attempt to better capture disease progression, the cost-effectiveness model considers the impact of renal flares on long-term progression to ESRD. The inclusion of renal flare data in the analysis aims to capture the effect add-on therapy has on long-term outcomes and cost effectiveness. In the base case, renal flare data from REGENCY and AURORA-2 is used to adjust the probability of transitioning from CKD Stage 1-3b to CKD Stage 4 for OBI and VOC, respectively (described in Section 3.3.2.3) (83, 115).

Overall survival is informed by health state specific transitions to death probabilities, informed by REGENCY and the literature (115).

3.3.2 Health state transition probabilities

An NMA was performed to indirectly compare OBI to other treatments not included in the REGENCY trial. Full details of the NMA and ITC are presented in Section 2.9 and 2.10.

A summary of transition probabilities for all treatments included in the cost-effectiveness analysis is presented in Appendix H.

3.3.2.1 CKD stages 1-3b response

As explained in Section 3.2.2, to align with the REGENCY inclusion criteria, the model assumes that the cohort of patients enter the model in the CKD Stage 1-3b AD health state (115). Transitions from CKD Stage 1-3b AD to either PR or CR for OBI and MMF alone are ultimately informed by REGENCY CRR and PRR outcomes, which were then used in the ITC.

Estimates of transition probabilities from "CKD_1_3b_AD" to "CKD_1_3b_PR" and "CKD_1_3b_CR" for each treatment were obtained from the ITC (Section 2.10). It is assumed that the analysis time point of the ITC is 3 years, which is the likely treatment duration for targeted therapies before clinical review.(75) From the ITC we obtain the median CRR odds ratio for each treatment (OBI+MMF, VOC+MMF and RTX +MMF) compared to the reference treatment (MMF).

The CRR estimates for OBI+MMF were obtained using the formula:

$$CRR\_OBI_{3y} = \frac{CRR\_OR\_OBI \ \frac{CRR\_MMF_{3y}}{1 - CRR\_MMF_{3y}}}{CRR\_OR\_OBI \ \frac{CRR\_MMF_{3y}}{1 - CRR\_MMF_{3y}} + 1}$$

Where CRR_OBI_{3y} denotes the CRR estimate at 3 years for OBI+MMF and CRR_OR_OBI denotes the average CRR odds ratio estimate for OBI+MMF vs. MMF, obtained from the ITC. The CRR estimates at 3 years for the other regimens (VOC+MMF and RTX+MMF) are calculated in a similar way. To calculate the CRR estimates at 6 months to match the cycle length used in the model, the CRR estimates at 3 years are extrapolated using a Weibull distribution. The same ITC methodology is used to generate the transition probabilities of partially responding (i.e. from AD to PR) for OBI+MMF, MMF, VOC+MMF and RTX+MMF. For the probability of remaining in AD, the analysis simply takes 1 minus the two response transitions described above, minus the probability of transitioning to CKD 4, described in Section 3.3.2.3.

Six-monthly response transition probabilities calculated with the ITC for all treatments included in the cost-effectiveness model are presented in Table 43. As detailed in Section 2.10, 2.10.5 and 2.10.6, there are key differences between trials and treatments, and uncertainties associated with the ITC. Particularly when considering the extrapolation of VOC+MMF short-term proteinuria driven CRR outcomes with treatment adherence expected in clinical trials, to long-term transitions in the Markov model with an NHS perspective. Transition probabilities presented here should be treated as conservative, especially when considering the difference between OBI+MMF and VOC+MMF transitions.

Table 43: CKD stages 1-3b six-monthly active disease to response health states transition probabilities calculated from the ITC – base case

Transition	OBI+MMF	MMF	VOC	RTX	References
AD → PR	[redacted]	[redacted]	[redacted]	[redacted]	REGENCY / ITC

AD → CR	[redacted]	[redacted]	[redacted]	[redacted]	REGENCY / ITC
AD → AD	[redacted]	[redacted]	[redacted]	[redacted]	Calculation (1 – others) *

*, AD to AD transitions further impacted by CKD 1-3b to CKD 4 transition (Section 3.3.2.3)
Key: AD, active disease; CKD, chronic kidney disease; CR, complete response; ITC, indirect treatment comparison; MMF, mycophenolate mofetil; OBI, obinutuzumab; PR, partial response; RTX, rituximab + MMF; VOC, voclosporin + MMF.

For OBI+MMF and MMF, the model also has the flexibility to consider transition probabilities directly derived from REGENCY. A multi-state model was fitted considering no response (AD), CR, PR and death health states. Individual REGENCY patient movements through defined states at 3 post baseline time points every 24 weeks were captured. Six-monthly response transition probabilities informed by REGENCY used in scenario analysis using OBI+MMF, MMF and pooled datasets are presented in Table 44. These transition probabilities are considered for OBI+MMF and MMF in scenario analysis only, where, in the absence of patient level data to derive transitions, other treatments are still informed by the ITC.

Table 44: CKD stages 1-3b six-monthly response transition probabilities calculated from REGENCY – scenario analysis

Transition	OBI+MMF	MMF	Pooled	References
AD → PR	[redacted]	[redacted]	[redacted]	REGENCY
AD → CR	[redacted]	[redacted]	[redacted]	REGENCY
AD → AD	[redacted]	[redacted]	[redacted]	Calculation (1 – others) *

Key: *, AD to AD transitions further impacted by CKD 1-3b to CKD 4 transition (Section 3.3.2.3); VOC and RTX transitions informed by ITC values described in Table 43. AD, active disease; CKD, chronic kidney disease; CR, complete response; ITC, indirect treatment comparison; MMF, mycophenolate mofetil; OBI, obinutuzumab; PR, partial response; RTX, rituximab + MMF; VOC, voclosporin + MMF.

The base case analysis uses transition probabilities derived from the ITC, as this ensures consistency in methods between treatments included in the analysis.

During the recent clinical advisory board and subsequent model validation teleconferences, clinical experts explained that they would expect OBI+MMF to have more favourable long-term renal response outcomes when compared with other treatments in the network, including VOC+MMF. They explained that, due to the mechanism of action of both drugs, the anticipated disease-modifying effects of OBI and observed VOC+MMF outcomes, they would anticipate patients treated with OBI would have more favourable outcomes over the long term. The Markovian assumption applied in the cost-effectiveness model assumes that transition probabilities are memoryless, i.e. time independent. So, when the ITC is used to capture patient transitions, the same transitions apply while patients are on treatment and the model cannot explicitly capture any expected differences in response transition probabilities potentially driven heterogeneity in outcomes, populations or expected differences driven by mechanism of action. The cost-effectiveness analysis tests the impact of adjusting other transition probabilities (e.g. loss of response or progression to CKD 4) using key secondary endpoints that are predictive of progression to ESRD (further described in Section 3.3.2.2 and 3.3.2.3).

3.3.2.2 CKD stages 1-3b loss of response

Due to a lack of data reported for the loss of complete or partial response for key comparators, an ITC could not be completed to inform transitions from CR to AD, CR to PR

and PR to AD. Instead, the model relies on probabilities directly derived from REGENCY. As described in Section 3.3.2.1, a multi-state model was fitted considering no response (AD), CR, PR and death health states, and patient movements through defined states were captured. As all patients enlisted in the REGENCY trial can be assumed to be in the AD health state, any patient movements informing transitions from CR or PR health states back to PR or AD health states first had to initially respond to treatment. Transition probabilities for loss of CRR and PRR calculated from REGENCY are notably higher than the ITC and seen in other sources from the literature (160). These transitions are based on observations over a 76-week period measured at baseline and every 24 weeks. There are few observations for PRR in REGENCY, so these numbers are uncertain. The model has the flexibility to consider 'by treatment' transitions, informed by the patients in the OBI+MMF and MMF arms independently, or pooled transitions, informed by the combined arms. REGENCY-derived transitions for OBI+MMF, MMF and the pooled datasets are presented in Table 45.

Table 45: CKD stages 1-3b six-monthly loss of response transition probabilities calculated from REGENCY

Transition	OBI+MMF	MMF	Pooled	References
CR → AD	[redacted]	[redacted]	[redacted]	REGENCY
CR → PR	[redacted]	[redacted]	[redacted]	REGENCY
PR → AD	[redacted]	[redacted]	[redacted]	REGENCY

Key: AD, active disease; CKD, chronic kidney disease; CR, complete response; ITC, indirect treatment comparison; MMF, mycophenolate mofetil; OBI, obinutuzumab; PR, partial response; RTX, rituximab + MMF; VOC, voclosporin + MMF.

In line with treatment arm transitions presented in Table 45, clinical experts indicated that patients treated with MMF would likely revert to active disease quicker than patients treated with OBI+MMF. Clinical experts during model validation affirmed that they would expect OBI+MMF to lower the relapse rate compared to MMF alone, citing common observations with combination therapies and improved adherence with OBI's dosing. They also explained that the disease modifying potential of OBI when considering the B-cell depleting mechanism of action (further described in 2.6.1.3.12, 2.6.2.4 and 3.3.2.6) leads to deeper and longer B-cell depletion and this would likely result in a better duration of response (68). This is supported by the clinical trial evidence for OBI+MMF in NOBILITY and REGENCY (115, 125). In NOBILITY, patients received 26 weeks of OBI treatment before cessation and results indicated that OBI+MMF was associated with improved preservation of kidney function. Post-hoc analyses of the NOBILITY study at Week 104 showed that of the 51 patients with long-term B-cell recovery data, 48 (96.1%) took >26 weeks until B-cell recovery and 11 (21.6%) took >93 weeks and, of these, 23/48 (47.9%) and 5/11 (45.5%) achieved complete response at B-cell repletion (120, 161, 162). The strength of OBI+MMF's efficacy is likely due, at least in part, to the depth and duration of B-cell depletion (120). When considering REGENCY, a numerically higher proportion of patients in the OBI+MMF group achieved complete peripheral CD19+ B-cell depletion than was observed in the placebo group from 4 up to 76 weeks (115). Clinical experts anticipate that the longer dosing schedule in REGENCY will lead to more prolonged deep B-cell depletion and longer duration of response following treatment cessation (68). Ultimately, clinical experts believe that there is more chance of sustained response when treated with OBI+MMF than MMF alone. This is

consistent with treatment transitions presented in Table 45. So, the base case analysis utilises transition probabilities generated for the OBI+MMF and MMF arms independently.

A conservative assumption is used in the base case to apply OBI+MMF transitions to other comparators. Clinical opinion on the mechanism of action of all treatments indicate that B-cell repletion and loss of response is likely to be quicker on the VOC+MMF and RTX+MMF arms. Clinical experts also noted that adherence in trials tends to be better than in real-world clinical practice due to factors like monthly visits and motivated patients, suggesting that the relapse rate on MMF alone (and other tablet-based regimens like VOC) would be higher in the real world due to non-adherence. Experts also explained that patients treated with RTX often experience a common problem with anti-drug antibodies that leads to loss of efficacy and therefore response. However, in the absence of alternative data, the model conservatively assumes VOC+MMF and RTX+MMF equivalence to OBI+MMF. The model has the flexibility to test the impact of assuming VOC+MMF and RTX+MMF follow MMF transitions or the midpoint of the transitions associated with OBI+MMF and MMF arms. These are tested in scenario analysis.

The model also has the option to adjust loss of response transitions using key renal flare data. Time to renal flare is an outcome that is predictive of long-term disease progression. A single flare can cause irreversible damage to kidney function and push patients on a faster path to ESRD (92). Renal flare outcomes from REGENCY for OBI+MMF and MMF and AURORA-2 for VOC+MMF and MMF are used to generate relative effectiveness hazard ratios (HRs) (68, 83). These renal flare HRs can be applied to loss of response transitions to test the impact avoidance of renal flares has on long-term disease course and cost effectiveness. The methods and rationale for the application of renal flare HRs are fully described in Section 3.3.2.3. The model considers the impact of renal flares on loss of response in scenario analysis.

3.3.2.3 CKD stage 4

Transition to CKD Stage 4

As explained in Section 3.2.2, patients can only transition to CKD Stage 4 from the CKD Stage 1-3b AD health state.

In the TA882 base case analysis, for patients with AD, the risk of progressing to CKD stage 3b-4 was fixed at 3.05% per 6-monthly model cycle (82). This value was estimated using clinical expert opinion that approximately 6% of patients in CKD stage 1-3a will progress to CKD stage 3b-4 per year. The EAG noted that, as this probability was not estimated using empirical evidence but relied on clinical expert opinion, it is subject to uncertainty. However, the EAG acknowledged that there is limited evidence concerning long-term disease progression for patients with LN. The EAG did not run any additional analyses around this fixed transition probability in the absence of alternative data or methods.

The base case analysis for this appraisal applies the same 3.05% transition probability, derived from clinical expert opinion in TA882. This proportion has been validated again by clinical experts as part of the model development process for this appraisal. Clinical experts explained that, while the general probability is reasonable, they would expect the probability of progression through CKD stages to be dependent on treatment received. They explained

that, due to the totality of the efficacy outcomes (CRR, proteinuria, eGFR and renal flares) and underlying mechanism of action of OBI, they would expect lower rates of progression to CKD stage 4 and ESRD when compared with other treatments.

In REGENCY, there were 26 instances of eGFR values below 30 ml/min/m^2 from a total of 14 patients of the 268 in the safety-evaluable population (115). Appendix H presents spaghetti plots of eGFR rates over the 76-week data collection period for the pooled and by treatment populations, respectively. We observe that there are numerically more observed instances of CKD Stage 4 in the MMF arm compared with OBI+MMF, however numbers are small.

In TA882, the company noted that key limitations of previous economic models for LN are that they did not fully capture the LN disease pathway (82). The company cost-effectiveness model for this appraisal looks to utilise key predictive secondary endpoints to understand the impact of short-term clinical outcomes on long-term disease course. One predictive endpoint is the time to and frequency of renal flares. The TA882 company submission presented renal flare outcomes from AURORA-2 and attempted to consider the cost of LN flares within economic model health states. However, it failed to consider the efficacy impact of reducing renal flares on long-term progression and prognosis.

Repeat episodes of nephritis and renal flares significantly worsen outcomes. The cumulative impact of renal flares over time were not captured by modelling LN progression through the advanced CKD stages prior to reaching ESRD. A recent review of risk factors and strategies for prevention of renal flares (34) presented that, despite advances in LN management guidelines, the definition of treatment goals associated with improved outcomes, and the approval of novel therapies (106-108) LN patients are still burdened with increased morbidity and mortality (32, 34, 43). In addition, rates of lupus-associated ESRD are stable and haven't improved in line with these advances (109, 110). The review explains that, while several factors may contribute to these trends, exacerbations (flares) of renal activity are a well-recognized driver for adverse kidney and long-term patient prognosis.

In NOBILITY and REGENCY, treatment with OBI+MMF reduced the risk of renal flare by 57% and 56%, respectively when compared with MMF (115, 125). However, VOC+MMF in AURORA-2 only reduced renal flares by 12% (83). Renal flare outcomes are presented in Table 46. When comparing the HRs associated with OBI versus MMF+MMF and VOC+MMF versus MMF in a standard Bucher comparison, it is predicted that OBI+MMF reduces renal flare rate [redacted] when compared with VOC+MMF (HR: [redacted] / 0.88 = [redacted]).

Table 46: Renal flare outcomes from clinical trials

	Intervention	Placebo	HR	Source
OBI+MMF	11.1%	23.5%	0.44 (0.24, 0.82)	REGENCY(115)
			0.43 (0.20, 0.95)	NOBILITY(120, 125)
VOC+MMF	23.8%	26.0%	0.88 (0.49, 1.45)	AURORA-2; OR: 0.85; HR (95% CI) calculated using formula: HR = OR / (1 - p + p * OR)(83)

Key: HR, hazard ratio; MMF, mycophenolate mofetil; OBI, obinutuzumab; OR, odds ratio; VOC, voclosporin.

As data suggest that duration and frequency of LN renal flare is a predictor of poor long-term kidney outcome and progressive CKD, the difference in these outcomes are likely to be clinically meaningful for patients and the healthcare system. Clinical experts at the advisory board agreed on the importance of renal flares on long-term clinical outcomes and indicated that low adherence levels associated with VOC is likely to exacerbate this issue. However, the cost-effectiveness analysis cannot account for low adherence levels on clinical outcomes (detailed in Section 3.5.1.2), so the HR calculated using renal flare data is potentially conservative.

The base case analysis in this submission utilises HRs versus MMF associated with time to renal flare (Table 46) to adjust the probability of transitioning from CKD Stage 1-3b to CKD Stage 4. These HRs are applied to OBI+MMF and VOC+MMF to account for the expected differences in long-term outcomes associated with avoiding frequent renal flares and resulting damage to kidney function. For MMF and RTX +MMF, the elicited probability in TA882 is assumed to be relevant for standard of care at the time of the elicitation (i.e. MMF and RTX+MMF) (82) The model also has the option to apply HRs versus OBI+MMF in scenario analysis, and as explained in Section 3.3.2.2, the model has the option to test the impact of renal flare HRs on loss of response transitions in place of or in addition to the application to transition to CKD Stage 4. Base case transition probabilities from CKD Stage 1-3b AD to CKD Stage 4 AD are presented in Table 47.

Table 47: Base case CKD Stage 1-3b AD to CKD Stage 4 AD transition probabilities

Treatment	Transition probability	Justification
OBI+MMF	[redacted]	Underlying TA882 clinical informed transition probability adjusted for impact of renal flares (82, 83, 115).
MMF	3.05%	TA882 clinical opinion informed estimate assume to be relevant to treatments available at the time of elicitation (82).
VOC+MMF	[redacted]	Underlying TA882 clinical informed transition probability adjusted for impact of renal flares (82, 83, 115).
RTX+MMF	3.05%	TA882 clinical opinion informed estimate assume to be relevant to treatments available at the time of elicitation (82).

Key: AD, active disease; CKD, chronic kidney disease; MMF, mycophenolate mofetil; OBI, obinutuzumab; RTX, rituximab; TA, technology appraisal; VOC, voclosporin.

Transitions within CKD Stage 4

Once patients lose kidney function through worsening eGFR they do not improve. So, when patients transition out of Stage 1-3b to Stage 4, they cannot transition back. They either remain in CKD Stage 4, transition to CKD stage 5, or die. As in TA882, the model has the functionality for transitions within CKD Stage 4 AD, PR and CR health states but, in the absence of data, these functions are switched off (described in Section 3.2.2). So, the 100% of patients in CKD Stage 4 are assumed to have active disease.

3.3.2.4 CKD stage 5

3.3.2.4.1 Transition to CKD Stage 5

The cost-effectiveness model utilises transition probabilities from the wider CKD literature to inform transition to CKD Stage 5 and ESRD (163). The model assumes that patients can only transition from the CKD Stage 4 AD health state to the CKD Stage 5 dialysis health state. The model assumes that patient's kidney function deteriorates while with active LN and that the first complication associated with CKD Stage 5 is likely to be dialysis. This assumption is consistent with the analysis presented in TA882.

Sugrue et al., 2019 provides an estimate of the annual transition rate from "CKD 4" to "CKD 5" of 0.067 (163). We assume that this is the annual rate from CKD_4_AD to CKD_5_D, and the 6-month transition probability from CKD_4_AD to CKD_5_D can be calculated as 0.0329. In TA882, the probability of moving into 'Dialysis' from CKD stage 3b-4 was fixed at 13.91% per 6-month model cycle, informed by clinical expert feedback and applied equally to all treatments (82). Clinical experts estimated that 95% or patients would have transitioned to dialysis over 10 years, and the per-cycle probability was then calculated to be 0.139.

The base case analysis uses transition probabilities informed by Sugrue et al (0.0329) applied to all treatments (163).

3.3.2.4.2 Transitions within CKD Stage 5

As with CKD Stage 4, described in Section 3.3.2.3, once patients lose kidney function through worsening eGFR they do not improve. So, when patients transition out of Stage 4 to Stage 5, they cannot transition back. They either remain in CKD Stage 5 dialysis, transition to CKD stage 5 transplant, or die.

Sugrue et al., 2019 provides an estimate of the annual transition rate from CKD 5 Dialysis to CKD 5 Transplant of 0.055 (163). So, the 6-month transition probability from CKD 5 D to CKD 5 T can be calculated as $(-0.055/2) = 0.0271$. This estimate is much lower than the TA882 company analysis (43.77%, presented in Table B.3-5), derived from a 90% kidney transplantation rate over 2 years. The EAG in TA882 considered that the rate used by the company was too high and suggested and amended rate of 65% over two years (equivalent to 23.08% every 6 months). The company base case for this appraisal utilises the TA882 EAG estimate of 23.08% for consistency in the absence of alternative literature-derived estimates (82). Uncertainties in longer-term outcomes are inherent to cost-effectiveness modelling in chronic conditions such as LN and ESRD. The transition probability is applied equally to all treatments included in the model, so any uncertainty associated with the probability does not bias in favour of or against any specific treatment.

Sugrue et al 2019 provides an estimate of the reverse transition, i.e. the annual rate from CKD 5 Transplant to CKD 5 Dialysis, to be 0.082, which the 6-month transition can be calculated as $(-0.082/2) = 0.0402$ (163). Again, this estimate is different from TA882 which was sourced from Palmer et al 2004 (2.96%, see table B.3-5) (82, 164). The company base case for this appraisal utilises the value from Sugrue et al (4.02%) to utilise a consistent source of transition probabilities, where possible.

3.3.2.5 Death

Transition probabilities from CKD Stage 1-3b AD, PR and CR was estimated from REGENCY (115). There were [redacted] deaths recorded in the REGENCY study over a total follow-up of [redacted] periods of 6-month cycles. In the base case, a multi-state model is used to estimate movements to the death health state. The pooled population data are used, as the possibility of transitioning to death is assumed to be equal across all treatments in the model. Using the pooled data, an overall transition probability can be estimated by $\underline{1 - exp\ exp\left(-\frac{[redacted]}{[redacted]}\right) = [redacted]}$ for the whole CKD Stage 1-3b population. However, the model base case stratifies by response status. Transition probabilities to death for each of the CKD 1-3b health states are presented in Table 48.

Sugrue et al., 2019 provides estimate of the annual transition probabilities for all other CKD stages to death (163). All transitions to death are presented in Table 48.

- For CKD Stage 4, the annual transition to death is given as 0.080 (163). Then, we can calculate the 6-month transition probability to death as $(-0.080/2) = 0.0392$ (165). The model assumes that the transition probabilities from CKD Stage 4 AD, PR and CR to death are all the same in the absence of health state specific estimates. The transition probability and assumptions used is consistent with TA882 (82).

  For CKD Stage 5 Dialysis to death, the annual probability was 0.177 and the 6-month transition probability can be calculated as $(-0.177/2) = 0.0847$. (163)

- For CKD Stage 5 Transplant to death, the annual probability was 0.053 and the 6-month transition probability can be calculated as $(-0.053/2) = 0.0262$. (163)

Table 48: Health state transition probabilities to death

Health state	Transition probability	Reference
CKD Stage 1-3b AD	[redacted]	REGENCY(82)
CKD Stage 1-3b PR	[redacted]	REGENCY(82)
CKD Stage 1-3b CR	[redacted]	REGENCY(82)
CKD Stage 4 AD	0.0392	Sugrue et al., 2019(163)
CKD Stage 4 PR	0.0392	Sugrue et al., 2019(163)
CKD Stage 4 CR	0.0392	Sugrue et al., 2019(163)
CKD Stage 5 D	0.0847	Sugrue et al., 2019(163)
CKD Stage 5 T	0.0262	Sugrue et al., 2019(163)

Key: AD, active disease; CKD, chronic kidney disease; CR, complete response; D, dialysis; PR, partial response; T, transplant.

Transitions to death from each health state in the cost-effectiveness model are applied consistently to all treatments included in the model. So, any associated uncertainty does not bias in favour of or against any specific treatment.

3.3.2.6 Treatment duration and effect waning

Treatments for LN are typically administered for a defined period before an assessment of clinical benefit. In TA882, stakeholders highlighted that a long-term treatment effect is an unproven assumption, but that short-term benefits can be predictive of improved longer-term outcomes (82).

In TA882, the company model assumed treatment stops at 36 months, in line with the available AURORA data (83, 124). Clinical advice to the EAG also supported stopping treatment at 36 months in the TA882 model (82). Clinical experts suggested treatment would last roughly 12 months. However, the committee also recalled that retreatment would be expected, meaning it was difficult to determine whether the model accurately reflected treatment durations expected in clinical practice. Recent updates to the clinical guidelines call for clinical review at around 3 years and a total therapy duration of 3-5 years for those achieving complete renal response.(50, 72, 75) In line with TA882, recent clinical guidelines and clinical expert opinion, the model assumes that all treatments are administered for 3 years in the base case analysis (82).

Following treatment cessation, OBI+MMF, VOC+MMF and RTX+MMF arms are all subject to treatment effect waning assumptions. In TA882, the EAG expressed that they would have liked to have explored different durations of treatment effect for VOC+MMF but model functionality didn't allow (82). The cost-effectiveness model for this appraisal includes functionality to test the impact of alternative treatment effect waning scenarios. All treatments wane linearly over a user-defined period until ultimately following MMF transition probabilities for the remainder of the time horizon. The specific assumptions and duration of treatment effect waning assumptions differ for each treatment, informed by their clinical data, mechanism of action and clinical expectations following treatment cessation.

For OBI+MMF, as explained in Section 3.3.2.2, the B-cell depleting mechanism of action is likely to result in a better duration of response. This is supported by the clinical trial evidence for OBI+MMF in NOBILITY and REGENCY (115, 125).

In REGENCY, over 99% of patients treated with OBI+MMF had B-cell depletion at 4 weeks, this level of B-cell depletion was maintained to over 95% by Week 76, compared with 2.4% and 6.7% for MMF alone at the respective timepoints. B-cell depletion was defined as an absolute CD19-positive B-cell count <10 cells/μL (115).

In NOBILITY, patients received 26 weeks of OBI treatment before cessation and results indicated that OBI+MMF was associated with improved long-term preservation of kidney function, with the majority of patients recovering B cells within 93 weeks of the last dose. Post-hoc analyses of the NOBILITY study at Week 104 showed that of the 51 patients with long-term B-cell recovery data, 48 (96.1%) took >26 weeks until B-cell recovery and 11 (21.6%) took >93 weeks and of these 23/48 (47.9%) and 5/11 (45.5%) achieved complete response at B-cell repletion (125).

Response to OBI+MMF is largely influenced by the level of B-cell depletion. As a reasonable proportion of patients (21.6%) had not repleted by 93 weeks following stopping treatment in NOBILITY and ~50% of patients still had complete response at B-cell repletion, the base case analysis considers that the OBI+MMF treatment effect continues for 2 cycles (1 year) following treatment cessation. Then, the treatment effect wanes to that of MMF alone over another 2 cycles (1 year). After which, OBI+MMF transitions are equivalent to MMF. At the recent advisory board, clinical experts explained that it is reasonable to assume a patient will stay within the same state on OBI+MMF for at least 6 months after stopping treatment. As explained in Section 3.3.2.2, clinical experts also anticipate that the longer dosing schedule

in REGENCY will lead to more prolonged deep B-cell depletion and longer duration of response following treatment cessation (68). So, while uncertainty remains as to the duration of treatment effect following stopping treatment, it is possible – and expected by clinical experts – that OBI treatment waning assumptions are conservative.

For VOC+MMF, in TA882 the company assumed that VOC+MMF had a lasting treatment effect when compared with MMF, implemented as the midpoint between VOC+MMF and MMF transition probabilities (82). The EAG expressed considerable uncertainty in off-treatment long-term outcomes and assumed VOC+MMF and MMF were equal for all health states following stopping treatment. Clinical experts believe that there is no clinical rationale why the treatment effect associated with VOC would continue once treatment with VOC is stopped. Clinicians indicated that, once nephrotic patients treated with VOC have responded and then stopped treatment, they are not likely to progress differently to MMF patients. They also highlighted that, as VOC is administered daily along with MMF, it is unlikely for there to be a long 'wash out' period and you could expect they would present similarly to MMF-treated patients within 3 months (68). For this analysis, the base case cost-effectiveness model assumes that VOC+MMF transitions wane to those of MMF over a period of 6 months following stopping treatment. This is a conservative assumption as it applies treatment effect waning for VOC+MMF in this analysis where the EAG could not and had to assume equivalence in TA882.

For RTX, clinical experts indicated that, while RTX is another B-cell depleting intervention, it is not as proficient at depletion as OBI. Mendez et al., 2018 investigated peripheral blood B-cell depletion after RTX in LN and its correlation with CRR (88). The study found that median complete peripheral depletion was 71 days. In addition to the duration depletion, the study found that the proportion of patients with depletion lasting longer than the median was associated with a greater likelihood of complete response at week 78 compared with proportion with depletion lasting fewer days than the median. This study highlights the shorter expected duration of B-cell depletion associated with RTX and the association with CRR. The study also concludes that treatments that enhance B cell depletion may result in increased efficacy in LN. NOBILITY has shown better B-cell depletion and duration until repletion when compared to outcomes for RTX+MMF, in line with clinical expectations. Clinical experts consider B-cells to replete faster with RTX+MMF than OBI+MMF, and noted that levels of anti-drug antibodies can lead to a quick loss of response for a reasonable proportion of patients treated with RTX. The model assumes that the RTX+MMF treatment effect continues for 1 cycle (6 months) following treatment cessation. Then, the treatment effect wanes to that of MMF alone over another 1 cycle (6 months). These are likely conservative assumptions.

A summary of treatment effect waning assumptions is presented in Table 49.

Table 49: Treatment effect waning assumptions

Treatment	Assumption	Justification
OBI+MMF	Maintain treatment effect for 2 cycles (12 months) after stopping treatment at 3 years; then treatment effect wanes over 2 cycles (12 months); then transitions equal to MMF	Deep B-cell depletion observed in REGENCY and NOBILITY; maintenance of complete response in large proportion of NOBILITY (115, 125).

MMF	Maintain MMF treatment effect	NA
VOC+MMF	No maintenance of treatment effect (i.e. 0 cycles) after stopping treatment at 3 years; then treatment effect wanes over 1 cycle (6 months); then transitions equal to MMF	Clinical opinion indicated limited rationale or expectation for maintenance of treatment effect. Conservative as no treatment waning included in TA882 (68, 82).
RTX+MMF	Maintain treatment effect for 1 cycle (6 months) after stopping treatment at 3 years; then treatment effect wanes over 1 cycle (6 months); then transitions equal to MMF	B-cell depleting agent, but less efficacious compared with OBI; Mendez et al., 2018 (88).

Key: MMF, mycophenolate mofetil; OBI, obinutuzumab; RTX, rituximab; TA, technology appraisal; VOC, voclosporin.

3.4 Measurement and valuation of health effects

LN is the most common severe organ manifestation of SLE and results in impaired kidney function. There is a large HRQoL burden in patients with LN, in particular symptoms of fatigue and pain (14). However, there are likely to be other domains which has an impact on a patient's HRQoL such as family planning, professional life and the burden of medication (166). There is unmet need for tolerable and effective treatment options for patients with LN that not only provides improvement in response outcomes but also reduces treatment burden and the reliance on corticosteroids.

Currently, there are no standard treatment options that directly target the underlying mechanism of disease. OBI+MMF has demonstrated statistically significant superior efficacy in REGENCY when compared with MMF (115). This statistically significant benefit is paired with a manageable safety profile and a convenient dosing regimen and administration.

Treatments for LN are often used in combination with corticosteroids. However, the beneficial anti-inflammatory effects of corticosteroids must be balanced with their adverse effect, such as cardiovascular events, weight gain, sleep disorders and long-term bone weakness. Newer treatments have aimed to decrease corticosteroid dose, and allow tapering, to control disease activity with a lower cumulative corticosteroid exposure. REGENCY showed the potential of utilising OBI+MMF treatment to taper corticosteroid use while maintaining treatment effect, reducing the overall burden and adverse reactions to treatment (115).

OBI represents a step-change improvement in the treatment pathway for patients with LN. OBI will provide patients with a disease-modifying treatment option that has the potential to treat the underlying mechanism of the disease, while allowing patients to live with freedom from the burden of additional daily medication. The superior response-based efficacy associated with OBI will improve lifetime quality of life for patients with LN by avoiding progression to more-burdensome CKD stages. In addition, the avoidance of renal flares, tapering of corticosteroids and a more infrequent, manageable dosing regimen is likely to further enhance the quality of life for patients treated with OBI+MMF, however these factors are uncaptured in this analysis.

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

HRQoL data was collected in the REGENCY study (115). The exploratory utility objective for REGENCY was to evaluate health status utility scores of patients treated with OBI+MMF. The key endpoints considered were change from baseline in EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) index-based and Visual Analog Scale (VAS) scores at Weeks 0, 24, 50, and 76, presented in Table 50.

Table 50: EQ-5D Summary of VAS score by visit in the efficacy evaluable patients

[redacted]

3.4.2 Mapping

At baseline, median (OBI+MMF: [redacted] and MMF: [redacted]) and mean (OBI+MMF: [redacted] and MMF: [redacted]) utility scores were generally similar for OBI+MMF and MMF alone arms, respectively, but slightly higher in the MMF alone arm. The proportions of patients reporting 'no problems' across the five dimensions were generally balanced at baseline between the OBI+MMF arm and the MMF arm; no notable differences were observed for the five dimensions between the two arms from baseline to Week 76. A graphical representation of the per-patient health state utility data collected in REGENCY for OBI and MMF alone is presented in Figure 18.

Figure 18: REGENCY per-patient health state utility values

[redacted]

Post-baseline utility values (excluding baseline values), mapped to the UK tariff, are presented in Figure 19. These utility values have been categorized by health state: complete response, partial response, and active disease. As with baseline utility, the post-baseline summary shows that values are generally similar for OBI+MMF and MMF alone arms. However, the general trends are slightly different, and both lack face validity, where complete response values are lower than partial response and active disease.

Figure 19: REGENCY post-baseline utility values

[redacted]

A formal statistical analysis of the REGENCY-based utilities was conducted using a linear mixed-effects model to predict post-baseline, utility incorporating random intercepts for the subjects. Specifically, to model post-baseline utility as a function of baseline utility and the health state (comparing complete response and partial response with active disease), including random intercepts for each subject using a linear mixed-effects model analysis. The model was used to generate health state-specific utility values for the CKD_1_3b_CR, CKD_1_3b_PR and CKD_1_3b_AD health states used in the cost-effectiveness analysis.

Predicted utility values by health state are presented for the pooled REGENCY population in Table 51 and stratified by treatment in Table 52. Model fit, as assessed by AIC and BIC criteria, is presented in Table 53. The predicted means in the complete response, partial

response and active disease health states are given or adjusted for an overall baseline utility of [redacted].

Table 51: Health state utility values calculated using linear mixed-effects model – REGENCY pooled

Health state	Predicted utility	SE
Pooled		
Complete response	[redacted]	[redacted]
Partial response	[redacted]	[redacted]
Active disease	[redacted]	[redacted]

Key: SE, standard error.

Table 52: Health state utility values calculated using linear mixed-effects model – REGENCY by treatment

Health state	Predicted utility	SE
OBI+MMF		
Complete response	[redacted]	[redacted]
Partial response	[redacted]	[redacted]
Active disease	[redacted]	[redacted]
MMF alone		
Complete response	[redacted]	[redacted]
Partial response	[redacted]	[redacted]
Active disease	[redacted]	[redacted]

Key: MMF, mycophenolate mofetil; OBI, obinutuzumab; SE, standard error.

Table 53: Model goodness of fit statistics

	AIC	BIC
Model 1 (pooled)	-649.0913	-612.8020
Model 2 (separated by treatment)	-641.5998	-609.7623

Key: AIC, Akaike information criteria; BIC, Bayesian information criteria.

As with the summary post-baseline utilities presented in Figure 19, utility values calculated using the linear mixed-effects model follow a counter-intuitive pattern and lack simple face validity. The numerically highest utility value is observed in the 'worst' health state (active disease), and the lowest utility value in the 'best' health state (complete response) for both pooled and by treatment health state utility values. By treatment health state utility values show slight differences between OBI+MMF and MMF arms, however the addition of treatment status did not improve model fit.

Clinical experts expressed surprise at the generally high utility values, believing LN significantly impairs quality of life, not just from fatigue, and questioned the small difference between complete responders and active disease and the ordering of utility values by health state.

3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify published studies reporting HRQoL data for patients with LN. A full description of the SLR, including detailed descriptions of the search strategy and extraction methods, as well as an overview of the identified studies, is provided in Appendix G.

A summary of the general search strategy is provided in Section 3.1.1 and presented in Figure 16. Of the included records (n=140), 54 reported HRQoL data and/or health state utility values (HSUVs). However, the majority (n=104/140) did not report the percentage of patients that were ISN/RPS Class III/IV ± Class V LN and just over half (n=79/140) had a primary focus on LN patients, whereas a large proportion of studies related to SLE more generally, with patients having renal involvement/LN.

Considering a further review of the included records in relation to the decision problem of supporting an HTA submission to NICE and the development of an economic model, 16 records were identified as being of most relevance. These records consisted of 12 records for HSUVs (160, 167-177).

Following prioritisation of included records, only half of the HSUV studies (n=7/14) elicited utility values, and the remaining studies sourced utilities from published literature. Disutility values were reported by very few studies and when reported, were not specific to SLE/LN patients. This highlights that there is a paucity of utility data in the relevant population of ISN/RPS Class III/IV ±V LN.

Table 54: HSUVs identified in SLR

HSUV	Health state/ event	
Mandrik et al (2022); Institute for Clinical and Economic Review (2021); Kennedy et al (2024)		
Chronic disease HSUVs	Notes on methods	*Mohara et al (2014) (15) was referenced and used to estimate utility decrements by subtracting the corresponding decrements from the utility value for the CR state*
	AD	0.624 (lower, upper values: 0.6, 0.7)
	CR	0.8 (lower, upper values: 0.72, 0.9)
	PR	0.71 (lower, upper values: 0.63, 0.79)
	Renal failure (ESRD)	0.549
Mohara et al (2014); Kim et al (2019)		
Chronic disease HSUVs	Notes on methods	*Mohara et al (2014) (15) collected utility values in a cohort of Thai patients with active, severe LN. Kim et al (2019) mostly sourced utilities directly from Mohara et al (2014) (15)*
	AD	0.764 (SE: 0.071) (Min, Max: 0.069, 1)
	CR	0.940 (SE: 0.109) (Min, Max: 0.106, 1.000)
	PR	0.850 (SE: 0.113) (Min, Max: 0.087, 1)
	Renal failure (ESRD)	ESRD: 0.689 (SE 0.048) (Min, Max: 0.054, 1.000)
	Post-transplantation/ Kidney transplantation	0.87 (Min, Max: 0.092, 1.000) Kim et al (2019)
Acute disease HSUVs	Major infection	0.223 (SE: 0.128) Mohara et al (2014) *(15)*
Wilson (2007)		
Chronic disease HSUVs	Notes on methods	*AD and PR assumed as Major Infection and Minor Infection, respectively, and CR assumed as perfect health*
	AD	0.39 (SE: 0.005)
	CR	1
	PR	0.72 (SE: 0.012)
	Dead	0
Acute disease HSUVs	Major infection	0.39 (SE: 0.012)

	Minor infection	0.72 (SE: 0.005)
Dai et al (2021)		
Chronic disease HSUVs	Notes on methods	*Sourced from literature – methods and population(s) unclear*
	CR	Mean utility (lower, upper values) CYC to CYC: 0.80 (0.75–0.85) MMF to CYC: 0.89 (0.84–0.95) CYC to AZA: 0.89 (0.84–0.95) MMF to AZA: 0.94 (0.88–0.99) CYC to MMF: 0.89 (0.84–0.95) MMF to MMF: 0.94 (0.88–0.99)
	Post-transplantation/ Kidney transplantation	0.81 (lower, upper values: 0.72–0.90)
	Renal relapse	Mean utility (lower, upper values) CYC to CYC: 0.62 (0.56–0.69) MMF to CYC: 0.72 (0.65–0.80) CYC to AZA: 0.72 (0.65–0.80) MMF to AZA: 0.76 (0.68–0.84) CYC to MMF: 0.72 (0.65–0.80) MMF to MMF: 0.76 (0.68–0.84)
	Renal dialysis	0.56 (lower, upper values: 0.49–0.62)
	Dead	0
Utility values relating to specific patient populations	Lupus nephritis	0.76 (lower, upper values: 0.68–0.84)
Barbosa-Arana et al (2024)		
Chronic disease HSUVs	Notes on methods	*Collected directly from Class III/IV ±V LN patients aged 16+ years in Colombia*
Treatment-specific utility values (includes response to therapy)	Response to rituximab	0.830 (95% CI: 0.738, 0.922)
	No response to rituximab	0.668 (95% CI: 0.551, 0.785)
Nee et al (2015)		
Chronic disease HSUVs	Notes on methods	*Sourced from literature – methods and population(s) unclear*
	PR	Remission: 0.70 (Range: 0.65–0.80)
	Renal failure (ESRD)	On dialysis: 0.67 (Range: 0.54–0.85)
	Renal relapse	On MMF or AZA: 0.60 (Range: 0.50–0.70)

	Renal dialysis	0.67 (Range: 0.54–0.85)
	Dead	0
NICE (2023)		
Chronic disease HSUVs	Notes on methods	*Sourced directly from AURORA–1/AURORA-2 or published literature*
	AD	CKD 1–3a: 0.710 (SE: 0.192) (95% CI: 0.277, 0.979) CKD 3b–4: 0.655 (SE: 0.131) (95% CI: 0.380, 0.882)
	CR	CKD 1–3a: 0.830 (SE: 0.155) (95% CI: 0.433, 0.997) CKD 3b–4: 0.775 (SE: 0.155) (95% CI: 0.409, 0.983)
	PR	CKD 1–3a: 0.800 (SE: 0.181) (95% CI: 0.345, 0.997) CKD 3b–4: 0.745 (SE: 0.149) (95% CI: 0.406, 0.964)
	Renal failure (ESRD)	CKD 5 on dialysis: 0.485 (SE: 0.33) (95% CI: 0.005, 0.993)
	Post-transplantation/ Kidney transplantation	0.710 (SE: 0.27) (95% CI: 0.100, 0.999)
	Renal dialysis	CKD 5 on dialysis: 0.485 (SE: 0.33) (95% CI: 0.005, 0.993)
Utility values relating to specific timepoints	Baseline	0.70 (SD: 0.19) Median: 0.73 (Q1: 0.58, Q3: 0.86; Range: -0.02–0.97)
	Month 6	0.77 (SD: 0.17) Median: 0.80 (Q1: 0.66, Q3: 0.90; Range: -0.00–0.99)
	Month 12	0.80 (SD 0.16) Median: 0.85 (Q1: 0.71, Q3: 0.92; Range: 0.18–0.99)
	Month 18	0.80 (SD 0.16) Median: 0.85 (Q1: 0.72, Q3: 0.92; Range: 0.18–0.99)
	Month 24	0.80 (SD 0.16) Median: 0.85 (Q1: 0.70, Q3: 0.93 ; Range: 0.07–0.99)
Sebastiani et al (2021)		
Chronic disease HSUVs	Notes on methods	*Collected directly from SLE patients aged 16+ years (21.4% with LN) in Colombia*
Treatment-specific utility values (includes response to therapy)	Non-biologic immunosuppressant cohort (NBC)	0.67 (SD: 0.28)
	Biologic immunosuppressant cohort (BC)	0.59 (SD: 0.33)†
Utility values relating to specific patient populations	Overall (all patients in the study population)	SLE aged 16+ years (21.4% with LN): 0.63 (SD: 0.31)
Cho et al (2014)		

Chronic disease HSUVs	Notes on methods	*Collected directly from SLE patients with renal involvement in South Korea using the KEQ-5D*
Utility values relating to specific patient populations	SLE patients with renal involvement	0.655 (SD: 0.215)
	SLE without renal involvement	0.693 (SD: 0.180)
	Overall (all patients in the study population)	SLE patients: 0.670 (SD 0.203)
Anderson et al (2023) (7)		
Chronic disease HSUVs	Notes on methods	*Collected directly from Class III–V LN patients internationally*
eGFR utility values	eGFR <15	0.74 (SD: 0.22)
	eGFR 15–29	0.52 (SD: 0.30)
	eGFR 30–59	0.71 (SD: 0.23)
	eGFR ≥60	0.81 (SD: 0.19)
Utility values relating to specific patient populations	Lupus nephritis	0.72 (SD: 0.24)
Chanloung et al (2023)		
Chronic disease HSUVs	Notes on methods	*Collected directly from active LN patients (class unclear) in Thailand*
Utility values relating to specific timepoints	Baseline	0.790 (SD: 0.170)
	Month 1	0.830 (SD: 0.208)
	Month 2	0.829 (SD: 0.198)
	Month 3	0.881 (SD: 0.133)
	Month 6	0.891 (SD: 0.126)

Key: AD, active disease; AZA, azathioprine; BC, biologic immunosuppressant cohort; CI, confidence interval; CKD, chronic kidney disease; CR, complete response; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HSUV, health state utility value; KEQ-5D, Korean EuroQol-5 dimension; LN, lupus nephritis; MMF, mycophenolate mofetil; NBC, non-biologic immunosuppressant cohort; NICE, National Institute for Health and Care Excellence; PR, partial response; SE, standard error; SLE, systemic lupus erythematosus.
† Median utility values also reported – see separate Excel data extraction table document.

3.4.4 Adverse reactions

It is assumed that any impact to HRQoL associated with AEs are captured within health state utility estimates. So, additional decrements are not accounted for in the economic base case analysis.

The analysis includes the option to consider the impact of utility decrements associated with adverse events (82). Utility decrements associated with adverse reactions when considered outside of health state utilities, are presented in Table 55. Where specific disutility values and durations associated were missing, the model assumes extreme values of 0.5 decrement to patient utility and 10 days until resolution of adverse reaction as conservative assumptions.

When included in scenario analysis, adverse events are applied per cycle to the proportion of patients on treatment. The proportion of patients experiencing adverse events on each treatment is described in Section 3.5.3.

Table 55: Utility decrements associated with adverse events – scenario analysis

Adverse event	Disutility	Duration (days)	Reference
Acute kidney injury	0.38	10.0	TA942: Table 36; duration assumption(178)
COVID-19	0.31	3.5	TA882: Table B.3-12(82)
COVID-19 pneumonia	0.31	3.5	TA882: Table B.3-12(82)
Gastroenteritis	0.01	8.0	TA882: Table B.3-12(82)
Gastroenteritis viral	0.01	8.0	TA882: Table B.3-12(82)
Hypertension	0.15	8.0	TA882: Table B.3-12(82)
Infusion related reaction	0.2	3.5	TA882: Table B.3-12(82)
Intervertebral disc disorder	0.5	10.0	Assumption
Large intestinal stenosis	0.006	10.0	Kim (2019); duration assumption(167)
Nephrotic syndrome	0.5	10.0	Assumption
Neutropenia	0.09	15.1	TA882: Table B.3-12(82)
Pneumonia	0.31	3.5	TA882: Table B.3-12(82)
Small intestinal obstruction	0.006	10.0	Kim (2019); duration assumption(167)
Urinary tract infection	0.2	3.5	TA882: Table B.3-12(82)
Cholecystitis	0.2	3.5	TA882: Table B.3-12(82)
Pain in extremity	0.5	10.0	TA942: Table 36; duration assumption(178)

Key: COVID, coronavirus disease; TA, technology appraisal

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

3.4.5.1 CKD Stage 1-3b

Many people with LN in these CKD stages can often experience few, if any, symptoms and can maintain a relatively normal lifestyle (i.e. working and being able to perform physical activity), which can result in higher utility values. Clinical opinion to the company explained that they would expect utility values to be somewhat similar between response health states, but that it was counter-intuitive to expect that people with active disease would have lower quality of life to those responding to treatment.

Utility estimates derived from REGENCY presented in Table 51 and Table 52 lacked face validity, and the order of health state utilities were not reflective of utility data identified in published literature (Table 54, Section 3.4.3) or expected by clinical experts. For example, the CR health state was estimated to have lower utility values than the PR and the AD health states. This did not follow the expected pattern when considering response-based health states over time. It was also observed that utility values post baseline are higher than at baseline, even if the patient remains in active disease.

So, utility values sourced from the previous NICE TA882, considering VOC+MMF for LN, were utilised in the base case analysis (82). Utility values were considered an area of uncertainty in TA882, and the EAG undertook some additional analyses to assess the impact of alternative assumptions. In the company approach, utility values were sourced only from 36-month data from AURORA 2. The EAG considered this approach to be inappropriate as it ignored all data from Month 0 to Month 36, i.e. the company had not conducted a regression using all the data. In the absence of AURORA-2 patient-level data, the EAG produced a weighted average utility value per health state (CKD stage 1-3a for AD, PR and CR) based on the information provided within the company submission. The publicly available utility values considered during TA882 by the company and EAG are presented in Table 56.

Table 56: Health state utility values considered in TA882 – Stage 1-3a

Health state	Predicted utility	SE
Company submitted (mean values)		
Complete response	**0.830**	0.155
Partial response	0.800	0.181
Active disease	0.710	0.192
EAG adjusted (weighted approach)		
Complete response	0.814	0.155*
Partial response	0.800	0.181*
Active disease	0.749	0.192*

*, assumed equal to company approach in absence of SE provided.
Key: SE, standard error.

The company undertook alternative regression analysis of the utility data collected in AURORA 1 and AURORA 2 during technical engagement in TA882, as recommended by the EAG, which were included in their revised base case. However, these regression-based utility values were redacted so cannot be used in this cost-effectiveness analysis.

So, for CKD Stage 1-3 health state utilities, the base case analysis considers the TA882 EAG adjusted utility values (Table 56). Alternative assumptions are tested in scenarios analyses, including pooled and by treatment REGENCY data and company submitted values from TA882 (82, 115).

3.4.5.2 CKD Stage 4

For CKD Stage 4 active disease, partial response and complete response health states, the base case analysis follows the same methodology as applied in TA882 (82). Namely, applying a decrement to the CKD Stage 1-3b utility values presented above. The decrement associated with progression to CKD Stage 4 was calculated using the company approach to modelling health state utility in TA882. Where, in absence of LN-related CKD 3b-4 utility

data, a progression-related utility decrement was applied to the CKD 1-3a utility values based on a UK observational study (2016) (179).

A decrement of –0.055 is applied to CKD Stage 1-3b AD, PR and CR health states to give the utility value of the corresponding CKD Stage 4 response-based health states. The decrement is applied equally to each treatment included in the model. When the 'by treatment' utility values are used in scenario analysis, the decrement is applied to the midpoint of OBI+MMF and MMF arms to calculate the CKD Stage 4 utility values for all treatments.

3.4.5.3 CKD Stage 5: Dialysis and transplant

There were no data collected within the REGENCY study relevant to dialysis and transplant health states associated with CKD Stage 5 and ESRD. The trial did not observe any dialysis or transplant events, so the impact of these complications to patient quality of life could not be captured. So, consistent with TA882, the base case analysis used literature-sourced utility values for these health states. The base case analysis follows the precedent set in TA882, and uses utility values sourced from Lee et al., 2005 (180). Lee et al aimed to assess the health-related quality of life (HRQoL) in patients with kidney failure who had received renal transplants compared to those receiving haemodialysis, peritoneal dialysis or were waiting to start dialysis. Dialysis utility values were based on EQ-5D data presented in a UK survey of patients who received dialysis (peritoneal and haemo-dialysis) or renal transplant. The study presented a utility of 0.569 for peritoneal dialysis and 0.443 for haemodialysis.

In TA882, the company originally assumed that there was an equal distribution of patients receiving peritoneal and haemodialysis in the model, which returned a utility value of 0.485 associated with dialysis (82). In this analysis, the proportions of patients receiving peritoneal dialysis and haemodialysis was sourced from Table 3.7 the UKKA 26th Annual Report, in line detail presented in the EAG report in TA882 (82). The 2024 report highlighted that 12.2% are receiving peritoneal dialysis and 87.8% receiving haemodialysis (181). These proportions are applied to the utility values presented in Lee at al., 2005 to return a base case utility value for the CKD5 dialysis health state of 0.458 (180, 181).

Health state utility values for the CKD5 transplant health state were sourced directly from Lee et al., 2005. The base case analysis applies a utility value of 0.71 to account for the impact of receiving a kidney transplant. The SLR presented in Section 3.4.3 indicates alternative utility values for dialysis and transplant health states.

3.4.5.4 Adverse events

The base case analysis assumes that impacts to health-related quality of life from adverse reactions to treatment are captured in health state utility values. As base-case utility values in the cost-effectiveness model are sourced from TA882, the cost-effectiveness analysis considered the impact adverse events have on health-related quality of life in scenario analysis.

Table 57: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Ref	Justification
Base case: TA882 EAG approach				
CKD1-3b: Complete Response	0.814 (0.155)	(0.43, 0.99)	3.4.5.1	REGENCY utility values lacked face validity. EAG analysis in TA882 included in decision-making model.
CKD1-3b: Partial Response	0.800 (0.181)	(0.35, 1)	3.4.5.1	
CKD1-3b: Active disease	0.749 (0.192)	(0.3, 0.99)	3.4.5.1	
CKD4: Complete Response	0.759 (0.155)	(0.4, 0.98)	3.4.5.2	
CKD4: Partial Response	0.745 (0.149)	(0.41, 0.96)	3.4.5.2	
CKD4: Active Disease	0.694 (0.131)	(0.41, 0.91)	3.4.5.2	
CKD5: Dialysis	0.458 (0.330)	(0, 0.99)	3.4.5.3	
CKD5: Transplant	0.710 (0.270)	(0.1, 1)	3.4.5.3	
Scenario analysis: REGENCY per treatment arm				
CKD1-3b: Complete Response (OBI+MMF)	[redacted]	[redacted]	3.4.5.1	Test the impact of REGENCY utility values in scenario analysis
CKD1-3b: Partial Response (OBI+MMF)	[redacted]	[redacted]	3.4.5.1	
CKD1-3b: Active disease (OBI+MMF)	[redacted]	[redacted]	3.4.5.1	
CKD1-3b: Complete Response (MMF)	[redacted]	[redacted]	3.4.5.1	
CKD1-3b: Partial Response (MMF)	[redacted]	[redacted]	3.4.5.1	
CKD1-3b: Active disease (MMF)	[redacted]	[redacted]	3.4.5.1	
CKD4: Complete Response	[redacted]	[redacted]	3.4.5.2	
CKD4: Partial Response	[redacted]	[redacted]	3.4.5.2	
CKD4: Active Disease	0.734 (0.131)	(0.44, 0.94)	3.4.5.2	
CKD5: Dialysis	0.458 (0.330)	(0, 0.99)	3.4.5.3	
CKD5: Transplant	0.710 (0.270)	(0.1, 1)	3.4.5.3	
Scenario analysis: REGENCY pooled				
CKD1-3b: Complete Response	[redacted]	[redacted]	3.4.5.1	Test the impact of REGENCY utility values in scenario analysis
CKD1-3b: Partial Response	[redacted]	[redacted]	3.4.5.1	
CKD1-3b: Active disease	[redacted]	[redacted]	3.4.5.1	
CKD4: Complete Response	[redacted]	[redacted]	3.4.5.2	
CKD4: Partial Response	[redacted]	[redacted]	3.4.5.2	
CKD4: Active Disease	0.734 (0.131)	(0.44, 0.94)	3.4.5.2	
CKD5: Dialysis	0.458 (0.330)	(0, 0.99)	3.4.5.3	
CKD5: Transplant	0.710 (0.270)	(0.1, 1)	3.4.5.3	
Scenario analysis: TA882 company submitted				

CKD1-3b: Complete Response	0.830 (0.155)	(0.43, 1)	3.4.5.1	Test the impact of company approach in TA882 in scenario analysis
CKD1-3b: Partial Response	0.800 (0.181)	(0.35, 1)	3.4.5.1	
CKD1-3b: Active disease	0.710 (0.192)	(0.28, 0.98)	3.4.5.1	
CKD4: Complete Response	0.775 (0.155)	(0.41, 0.98)	3.4.5.2	
CKD4: Partial Response	0.745 (0.149)	(0.41, 0.96)	3.4.5.2	
CKD4: Active Disease	0.655 (0.131)	(0.38, 0.88)	3.4.5.2	
CKD5: Dialysis	0.458 (0.330)	(0, 0.99)	3.4.5.3	
CKD5: Transplant	0.710 (0.270)	(0.1, 1)	3.4.5.3	
Scenario analysis: Disutility values associated with adverse events				
Acute kidney injury	0.38	0.038	3.4.4	Test the impact of including additional decrements to quality of life associated with adverse events
COVID-19	0.31	0.031	3.4.4	
COVID-19 pneumonia	0.31	0.031	3.4.4	
Gastroenteritis	0.01	0.001	3.4.4	
Gastroenteritis viral	0.01	0.001	3.4.4	
Hypertension	0.15	0.015	3.4.4	
Infusion related reaction	0.2	0.02	3.4.4	
Intervertebral disc disorder	0.5	0.05	3.4.4	
Large intestinal stenosis	0.006	0.0006	3.4.4	
Nephrotic syndrome	0.5	0.05	3.4.4	
Neutropenia	0.09	0.009	3.4.4	
Pneumonia	0.31	0.031	3.4.4	
Small intestinal obstruction	0.006	0.0006	3.4.4	
Urinary tract infection	0.2	0.02	3.4.4	
Cholecystitis	0.2	0.02	3.4.4	
Pain in extremity	0.5	0.05	3.4.4	

3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify published studies reporting HRQoL data for patients with LN. A full description of the SLR, including detailed descriptions of the search strategy and extraction methods, as well as an overview of the identified studies, is provided in Appendix G.

A summary of the general search strategy is provided in Section 3.1.1 and presented in Figure 16. Of the included records (n=140), 93 reporting healthcare costs and/or resource use data. However, as stated previously (Section 3.1.1 and 3.4.3), the majority did not report the proportion of ISN/RPS Class III/IV ± V LN and just over half had a focus on LN patients.

Considering a further review, 16 records were identified as being of most relevance. Only three records were deemed relevant to the decision problem (82, 155, 156). Of which, only one study reported the population from which cost and/or resource use data were obtained (182): adults with SLE (with or without renal impairment). The population in the remaining two studies was unclear (82, 156). In the study that reported the patient population, the data

were sourced from SLE patients with 28.2% overall having renal involvement (6). All studies used a UK perspective for costs and reported on direct costs and resource use (82, 155, 156). No study reported on indirect costs. Cost drivers were reported in detail in one study, whilst the remaining two studies had limited data or did not report key cost drivers. A summary of the three studies, alongside a breakdown of direct cost and resource use is presented in Appendix G.

3.5.1.1 Intervention and comparators' costs and resource use

Treatment costs are calculated based on the recommended dosing regimen for each treatment included in the model, detailed in Section 1.3.2 and 3.2.3. The recommended dose per administration, administration schedule and list prices for relevant treatments are presented in Table 58. The total calculated drug acquisition costs per administration are also provided.

As previously described, OBI+MMF is implemented in the economic model according to the REGENCY study protocol and anticipated marketing authorisation (115). MMF is also implemented as per the REGENCY study protocol and its marketing authorisation. Other treatments included in the cost-effectiveness analysis, including VOC+MMF and RTX+MMF, were implemented in line with their marketing authorisations (62).

OBI is available to the NHS with a confidential patient access scheme (PAS). The current OBI PAS is [redacted]% which translates to a net price of £[redacted] per vial (Appendix I). There is also a confidential PAS for VOC and RTX is now available through biosimilars, the confidential prices of these treatments are unknown to the company. Cost-effectiveness results considering the confidential OBI PAS are provided in Section 3.10. Cost-effectiveness results at list price are presented in Appendix I.

Table 58: Drug formulation, dose, administration, proportion of doses received and total drug acquisition cost per week, intervention and active comparators – list prices

Drug	Cost per vial/pack	Vial size/tablets per pack	Dosing regimen	Vials/ tablets per admin	Total cost per admin	Source (Cost, regimen)
OBI	£3,312.00	1 x 1,000 mg	IV: 1000 mg on weeks 0, 2, 24, 26 and 52. Subsequent infusions every 6 months starting at Week 80	1	£3,312.00	Schedule & dosing: REGENCY(115) Price: BNF(183)
Mycophenolate mofetil	£6.45	50 x 500 mg	Oral: 2500 mg/day	5	£0.65 / day	Schedule & dosing: REGENCY study (patients could receive 2 to 2.5 g per day) (115) Price: eMIT National(184)
Voclosporin	£1,000.00	180 x 7.9 mg	Oral: 23.7 mg twice daily	6	£33.33 / day	Schedule & dosing: AURORA 1 study(124) Price: BNF(183)
Rituximab	£349.25	2 x 100 mg	IV: 1,000 mg on weeks 0, 2, 24, 26, and 52. Subsequent infusions every 6 months starting at Week 80 (assume same schedule as OBI)	5	£1,746.30	Schedule & dosing: Assumed same schedule as OBI, obtained from REGENCY(115); Dosing based on the LUNAR study Price: BNF(183)
	£873.15	1 x 500 mg		2		
Methylprednisolone	£4.77	1 x 125 mg	IV: 1 to 3 administrations of 500 to 1000 mg each. Assume average of 2 admins of 750 mg each.	6	£20.79	Schedule & dosing: REGENCY study(115) Price: eMIT National(184)
	£6.93	1 x 500 mg		1.5		
Prednisone	£1.20	150 mg	0.5 to 1.0 mg/kg/day; total daily dose ≤ 60 mg. Assume average dose of 0.75 mg/kg/day, maximum 60 mg. After week 24, 10 mg/day	5	£6.00	Schedule & dosing: REGENCY study (tapering from day 15 until week 24 is not considered, for simplicity)- (115) Price: eMIT National(184)
	£1.60	400 mg		2		
Key: BNF, British National Formulary; eMIT, electronic market information tool; g, gram; IV, intravenous; kg, kilogram; mg, milligram;						

3.5.1.2 Adherence

Drug acquisition costs were based on the full recommended dose, and does not account for dose interruptions, reductions and lack of adherence over the treatment period that may be expected in clinical practice. During a recent advisory board, a panel of nephrologists and rheumatologists explained that they often see better adherence in trials compared to the real world, due to good drug adherence, consistent regular follow-up and the provision of adequate adjunct therapy (68). They explained that this is often a reason for high placebo responses in clinical trials. Clinical experts indicated that adherence is a big issue in LN and explained that adherence is the most important factor in driving outcomes in LN.

The available clinical evidence for VOC is sourced from the AURORA-1 and AURORA-2 trials, in which the treatment was administered at the full recommended dose of 23.7 mg twice daily, i.e. 6 tablets daily (83, 124). Clinical experts at the advisory board commented that 6 tablets of VOC per day, added to 4 tablets of MMF per day, creates high 'pill burden' patients (68). Patients already complain about the number of tablets they are taking. Several advisors commented that improving adherence is very hard, it either requires a lot of extra support (e.g. phone calls, nursing visits) or prescribing an IV drug from the outset.

There are published studies on pill burden and studies on MMF adherence (185). Chauhan et al., 2022 investigated adherence with MMF treatment among patients attending UK rheumatology clinics with autoimmune inflammatory rheumatic diseases, including SLE. Retrospective data on 144 patients between January 2015 and December 2018 was collected and analysed. The study found that overall adherence with MMF was 62%, and the adherence rates were below 80% for all age groups. The study also found a significant difference between Asian patients (mean adherence 47%) and White patients (mean adherence 65%, $p < 0.001$). Finally, the study reported that poor adherence with MMF correlated with 3-fold increase in risk of flares compared to good adherence ($p = 0.002$). While the study focusses on MMF, it serves to highlight the extent of LN adherence issues. Increasing the pill burden with VOC in combination with MMF will only exacerbate potential low adherence. The study also highlights the importance of adherence on preventing progression of lupus, presenting the impact of low adherence on known predictive endpoints such as renal flare rates. The model cannot account for the anticipated loss of treatment benefit with missed doses, so the model applies the full recommended dose in line with the VOC marketing authorisation. Therefore, outcomes associated with VOC calculated in the cost-effectiveness analysis are likely not reflective of expected outcomes seen in the real world, due to adherence issues, their relationship with other clinical outcomes such as renal flares, and progression to ESRD.

After Year 1, OBI is administered via IV infusion every 6 months. Clinical experts indicated that the six-monthly IV dosing of OBI would improve compliance issues associated with high pill burden (68). So, as VOC outcomes are potentially overestimated in the cost-effectiveness model, any expected improvement in efficacy due to the improved adherence of OBI compared with VOC is not accounted for, so any results are likely conservative.

3.5.1.3 Administration costs

In the economic model, drug administration costs are accrued for the duration of treatment. OBI, RTX and some background corticosteroids are applied intravenously. A summary of administration costs is presented in Table 59.

Table 59: Drug administration costs

	Cost	Source
Initial IV administration	£418.29	National Schedule of NHS cost 2023–24; SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance - Daycase(186)
Subsequent IV administration	£426.15	National Schedule of NHS cost 2023–24; SB15Z - Deliver Subsequent Elements of a Chemotherapy Cycle - Daycase(186)
Oral administration	£0	Assumption

Key: IV, intravenous; NHS, National Health Service.
Notes: It is assumed there is no cost for oral administration

3.5.1.4 Subsequent treatment

Following discontinuation of initial treatment, patients go on to receive rescue or subsequent therapy. Base-case values in the model are determined by data from REGENCY for OBI+MMF and MMF (115). For other treatments, the same distribution of rescue therapy as for OBI+MMF is assumed. Treatment sequencing rules are specified where patients cannot go on to receive the same treatment they receive in the initial line i.e. people treated with OBI+MMF cannot get OBI as a subsequent treatment.

In total, [redacted] patients ([redacted]%) in the OBI+MMF arm [redacted] patients ([redacted]%) in the MMF arm received rescue therapy excluding corticosteroid-only rescue in the 76-week REGENCY data cut. The proportion of subsequent treatments included in the cost-effectiveness model are presented in Table 60. The proportion of patients captured in Table 60 as treated in the MMF arm is higher than [redacted]% as some patients received more than one subsequent therapy.

Clinical experts believed that the proportions for subsequent therapy seemed reasonable for the short trial period, noting that MMF led to more subsequent treatments which would be expected, if not more so, in clinical practice. Clinical experts suggested including a scenario where proportions are doubled on each treatment arm, to account for the greater likelihood of subsequent treatments over the model time horizon. Nevertheless, the conclusion remained that it is likely that subsequent treatment use is much higher for those people treated with MMF. So, as higher levels of subsequent treatment incur higher costs, cost-effectiveness results in the base case analysis can be considered conservative.

A scenario tests the impact of increasing the overall proportion of subsequent treatment on cost-effectiveness outcomes.

Where subsequent treatments are already included as comparators in the cost-effectiveness model, the total costs of the subsequent treatment regimens are taken from the total drug and administration costs. Where not, costs are calculated using list prices and expected treatment duration, detailed in Table 60.

Table 60: Proportion of subsequent treatment and associated treatment costs

Treatment regimen	Total costs per treatment (£)			Proportion of patients				Source
	Total drug costs	Total admin costs	Total	OBI	MMF	VOC	RTX	
ANIFROLUMAB	0.00	0.00	0	[redacted]	[redacted]	[redacted]	[redacted]	Assumed no reimbursement
BELIMUMAB	0.00	0.00	0	[redacted]	[redacted]	[redacted]	[redacted]	Assumed no reimbursement
CYCLOSPORIN	139.83		140	[redacted]	[redacted]	[redacted]	[redacted]	BNF Cyclosporin 100 mg x 30 capsules; assumed maximum treatment duration of 3 months (BNF Nephrotic Syndrome)(183)
CYCLOPHOSPHAMIDE	78.64	2,556.90	2,636	[redacted]	[redacted]	[redacted]	[redacted]	eMIT National cyclophosphamide 1g powder for solution for injection vials; dose per month assumed per maximum 6 months (184, 187)
OBI			13,813	[redacted]	[redacted]	[redacted]	[redacted]	Assumed consistent with treatment duration at first line
RTX			8,191	[redacted]	[redacted]	[redacted]	[redacted]	Assumed consistent with treatment duration at first line
TACROLIMUS	2,878.17		2,878	[redacted]	[redacted]	[redacted]	[redacted]	BNF Envarsus 4 mg modified release x 30 tablets; 4mg daily for a maximum of 1 year (183)
VOC			17,294	[redacted]	[redacted]	[redacted]	[redacted]	Assumed consistent with treatment duration at first line
TOTAL				[redacted]	[redacted]	[redacted]	[redacted]	

Key: BNF, British National Formulary; eMIT, electronic market information tool; mg, milligram; MMF, mycophenolate mofetil; OBI, OBI; RTX, rituximab; VOC, voclosporin.

3.5.2 Health-state unit costs and resource use

Supportive care costs in the model are considered health state dependent and apply consistently to all treatments. In the base case, the resource use and costs are informed by values used and validated as part of the TA882 NICE appraisal (82). Resource use costs are presented in Table 61, and are predominantly informed by the current NHS reference costs and the Personal Social Services Research Unit (PSSRU) report on the unit costs for health and social care (186, 188). Resource use frequencies are presented in Table 62. Frequencies are in line with those used in TA882, which were originally informed by clinical guidelines and clinical expert feedback (82). These values have been validated again for this submission and were deemed to be reflective of clinical practice.

Health state resource use costs combining unit costs and resource use frequencies are presented in Table 63.

Table 61: Resource use costs

Procedure	Cost per unit (£)	Source
Nurse visit	34.67	PSSRU 2024 Band 6 hospital-based nurse cost per working hour; TA882 KOL expert feedback (40 minutes of nurse time is required per visit)(82, 188)
Specialist visit	36.33	PSSRU 2024 Band 6 hospital-based Consultant: medical cost per working hour; KOL expert feedback (20 minute of specialist time is required per visit)(82, 188)
Psychologist	71.17	PSSRU 2024 Band 7 hospital-based clinical psychologist cost per working hour; TA882 average session time of length of 70 minutes(82, 188)
Kidney biopsy	1,044.53	National Schedule of NHS Costs 2023–2024. YL20A – Percutaneous Needle Biopsy of Lesion of Kidney, 19 years and over - Daycase(186)
Urinalysis (includes eGFR, serum albumin, proteinuria and urinary sediment)	1.46	National Schedule of NHS cost 2023–24. PATHS04 – Clinical biochemistry, Chemical Pathology Service(186)
Complete blood count	4.43	National Schedule of NHS cost 2023–24. DAPS05 – Haematology, Chemical Pathology Service(186)
Serum immunoglobulin measurement	7.29	National Schedule of NHS cost 2023–24. DAPS06 – Immunology, Chemical Pathology Service(186)
Antibody tests	7.29	National Schedule of NHS cost 2023–24. DAPS06 – Immunology, Chemical Pathology Service(186)
Chronic infection screening	2.39	Assumption. National Schedule of NHS Cost 2023–24. DAPS09 - Other, Chemical Pathology Service(186)
Cholesterol and lipid monitoring	2.39	Assumption. National Schedule of NHS Cost 2023–24. DAPS09 - Other, Chemical Pathology Service(186)
Anti-dsDNA and C3 and C4 level monitoring	2.39	Assumption. National Schedule of NHS Cost 2023–24. DAPS09 - Other, Chemical Pathology Service(186)
Dialysis	36,279.75	NICE 2018 (NG107: RRT and conservative management - Modalities of RRT. K.1): Adults dialysis via vascular access £23,643 weighted cost per year using 2016/17 NHS reference costs, inflated to 2024 cost-year using ONS CPI for health (189).
Initial assessment for kidney transplant	3,994.81	Kerr 2012 (£2,537 in 2009 inflated to 2024 cost-year using ONS CPI for health)(189, 190)
Waiting list clinic attendance (pre-transplant)	4,678.19	Kerr 2012 (£2,971 in 2009 inflated to 2024 cost-year using ONS CPI for health)(189, 190)

Kidney transplantation	19,286.13	National Schedule of NHS cost 2023–24. Weighted average of (LA01A, LA02A, LA03A plus LA10Z, LA11Z, LA14Z), plus LA12A and LA13A (186).
Post-kidney transplantation, year 1	25,097.38	Kerr 2012 (£12,884 in 2009 inflated to 2024 cost-year using ONS CPI for health, with immunosuppressive costs [£4,810] not inflated)(189, 190)
Post-kidney transplantation, year 2+	11,523.06	Kerr 2012 (£7,318 in 2009 inflated to 2024 cost-year using ONS CPI for health)(189, 190)
Vitamin D supplements	0.00	Assumed no cost to provider
ESAs and EPO	199.11	BNF 2024; Eprex 30,000units/0.75ml solution for injection pre-filled syringes(183)
Phosphate binders	116.07	eMIT National Database 2023/24; Lanthanum carbonate 1g chewable tablets sugar free / Packsize 90(184)
ACEI or ARB	0.30	eMIT National Database 2023/24; Lisinopril 10mg tablets / Packsize 28(184)
Anti-hypertensive medication	34.59	eMIT National Database 2023/24; Ambrisentan 10mg tablets / Packsize 30(184)
Ultrasound	67.25	National Schedule of NHS Cost 2023–24. RD40Z – Ultrasound Scan with duration of less than 20 minutes, without Contrast; Diagnostic Imaging Service (812)(186)
Echocardiogram	137.49	National Schedule of NHS Cost 2023–24. RD51A – Simple Echocardiogram, 19 years and over; Diagnostic Imaging Service (812)(186)

*, includes eGFR, serum albumin, proteinuria and urinary sediment.

Key: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; BNF, British National Formulary; C, complement; CPI, consumer price index; dsDNA, double-stranded DNA; eMIT, electronic market information tool; EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; KOL, key opinion leader; mg, milligram; ml, millilitre; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; ONS, Office for National Statistics; PSSRU, personal social services research unit; RRT, renal replacement therapy

Table 62: Resource use frequencies

	CKD_1_3b_CR		CKD_1_3b_PR		CKD_4_PR		CKD_4_AD		CKD_5_D		CKD_5_T	
Procedure	**One off cost**	**Rec. cost**	**One off cost**	**Rec. cost**	**One off cost**	**Rec. cost**	**One off cost**	**Rec. cost**	**One off cost**	**Rec. cost**	**Cost of first plus second cycle**	**Cost of third and following cycles**
Nurse visit	1	1	3.5	2	4	2.5	6	3				
Specialist visit	1	1	3.5	2	4	2.5	6	3	6	3		
Psychologist									6	1.5		
Kidney biopsy							1					
Urinalysis*	2	2	7	4	8	5	12	6				
Complete blood count	2	2	7	4	8	5	12	6				
Serum immunoglobulin measurement	0.5	0.5	6.25	3.25	6.25	3.25	12	6				
Antibody tests	0.5	0.5	6.25	3.25	6.25	3.25	12	6				
Chronic infection screening	0.5	0.5	6.25	3.25	6.25	3.25	12	6				
Cholesterol and lipid monitoring	0.5	0.5	6.25	3.25	6.25	3.25	12	6				
Anti-dsDNA and C3 and C4 level monitoring	2	2	7	4	8	5	12	6				
Dialysis									0.5	0.5		
Initial assessment for kidney transplant									1			
Waiting list clinic attendance (pre-transplant)									2	2		
Kidney transplantation											1	
Post-kidney transplantation, year 1											1	
Post-kidney transplantation, year 2+												0.5
Vitamin D supplements					0.5	0.5	0.5	0.5	0.5	0.5	1	0.5
ESAs and EPO					0.5	0.5	0.5	0.5	0.5	0.5	1	0.5

Phosphate binders					0.5	0.5	0.5	0.5	0.5	0.5	1	0.5
ACEI or ARB	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	1	0.5
Anti-hypertensive medication	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	1	0.5
Ultrasound							1					
Echocardiogram	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	1	0.5
Notes: *, includes eGFR, serum albumin, proteinuria and urinary sediment. **Key:** ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; C, complement; dsDNA, double-stranded DNA; EPO, erythropoietin; ESA, erythropoiesis-stimulating agents.												

*, includes eGFR, serum albumin, proteinuria and urinary sediment.
Key: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; C, complement; dsDNA, double-stranded DNA; EPO, erythropoietin; ESA, erythropoiesis-stimulating agents.

Table 63: Health state costs

Health state	One-off cost (£)	Recurrent cost per 6-monthly model cycle (£)
CKD Stage 1-3b AD	843.80	465.00
CKD Stage 1-3b PR	513.61	324.21
CKD Stage 1-3b CR	183.42	183.42
CKD Stage 4 AD	2,113.17	622.59
CKD Stage 4 PR	714.98	525.58
CKD Stage 4 CR	428.57	428.57
CKD Stage 5 D	32,379.84	27,955.78
CKD Stage 5 T	39,109.54	6,005.31

AD, active disease; CKD, chronic kidney disease; CR, complete response; D, dialysis; PR, partial response; T, transplant

3.5.3 Adverse reaction unit costs and resource use

The impact of adverse events was included in the base case analysis. The costs of adverse events while on treatment were calculated separately for OBI and MMF treatment arms based on the average number of treatment emergent adverse events per patient in the REGENCY trial and the unit costs of these adverse events (115). Treatment emergent adverse events are any adverse events that occur after a patient starts a treatment, regardless of whether the events are directly caused by the treatment. This includes all new adverse events or exacerbations of pre-existing conditions that occur from the beginning of the treatment up until the point of rescue. Only treatment emergent adverse events with a severity grade of 3 and higher were considered in the model.

Due to unavailability of data related to Grade 3+ adverse events for non-trial comparators, it was assumed that all treatments regimens which include MMF are assumed to have the same incidence of AEs as the MMF arm in REGENCY. All other treatments not including MMF are assumed to have no incidence of AEs. This assumption was also applied in TA882. This assumption is conservative as the cost of any adverse reactions associated with add-on treatments (i.e. VOC and RTX) are ignored.

Total lifetime costs of AE in each treatment arm were calculated by multiplying the average adverse event costs per patient week by the rate of events (number of events divided by number at risk) occurred in that treatment arm. The incidence of adverse events for OBI+MMF and MMF, sourced from REGENCY, and associated costs, sourced from NHS reference costs, are presented in Table 64.

The total cost associated with adverse events for each patient that enters the model and receives was calculated to be £239.09 for OBI+MMF and £109.43 for MMF (and VOC+MMF and RTX+MMF). The total costs associated with adverse reaction to each treatment arm included in the analysis are applied up front at Cycle 1.

Table 64: Grade 3+ adverse event cost and frequency

	Cost (£)	OBI+ MMF N=136	MMF N=132	Source
Acute kidney injury	670.65	[redacted]	[redacted]	NHS National Cost Collection data 2023/24; LA07L-P - Acute Kidney Injury without Interventions, weighted by CC Score - Non-Elective Inpatient - Short Stay(186)
COVID-19	654.52	[redacted]	[redacted]	NHS National Cost Collection data 2023/24; DX21A - COVID-19 Infection, 19 years and over - Non-Elective Inpatient - Short Stay(186)
COVID-19 pneumonia	742.95	[redacted]	[redacted]	NHS National Cost Collection data 2023/24; DX11A - COVID-19 Infection, with Pneumonia, 19 years and over - Non-Elective Inpatient - Short Stay(186)
Gastroenteritis	1,451.94	[redacted]	[redacted]	NICE TA882; NHS National Cost Collection data 2023/24; FD01C - Gastrointestinal Infections with Single Intervention, with CC Score 5+ - Non-Elective Inpatient - Short Stay(82, 186)
Gastroenteritis viral	1,451.94	[redacted]	[redacted]	NICE TA882; NHS National Cost Collection data 2023/24; FD01C - Gastrointestinal Infections with Single Intervention, with CC Score 5+ - Non-Elective Inpatient - Short Stay(82, 186)
Hypertension	404.67	[redacted]	[redacted]	NICE TA882; NHS National Cost Collection data 2023/24; EB04Z - Hypertension - Day Case(82, 186)
Infusion related reaction	1.16	[redacted]	[redacted]	NICE TA809; infusion-related reactions determined to be allergies and treated with an antihistaminic (fexofenadine); eMIT National Database 2023/24(186)
Intervertebral disc disorder	752.11	[redacted]	[redacted]	NHS National Cost Collection data 2023/24; HC20J-M - Vertebral Column Injury without Interventions, weighted by CC score - Non-Elective Inpatient - Short Stay(186, 191)
Large intestinal stenosis	436.65	[redacted]	[redacted]	NHS National Cost Collection data 2023/24; FD05B - Abdominal Pain without Interventions - Non-Elective Inpatient - Short Stay(186)
Nephrotic syndrome	196.88	[redacted]	[redacted]	NHS National Cost Collection data 2023/24; Nephrologist visits: – NHS trust and NHS foundation trusts. Total Outpatient Attendance – Service code 361
Neutropenia	618.04	[redacted]	[redacted]	NICE TA882; NHS National Cost Collection data 2023/24; WJ11Z - Other Disorders of Immunity - Regular Day or Night Admissions(82, 186)
Pneumonia	1,452.50	[redacted]	[redacted]	NICE TA882; NHS National Cost Collection data 2023/24; DZ11P - Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 8-12 - Day Case(82, 186)
Small intestinal obstruction	436.65	[redacted]	[redacted]	NHS National Cost Collection data 2023/24; FD05B - Abdominal Pain without Interventions - Non-Elective Inpatient - Short Stay(186)
Urinary tract infection	578.98	[redacted]	[redacted]	NHS National Cost Collection data 2023/24; LA04N-S - Kidney or Urinary Tract Infections, without Interventions, weighted by CC Score - Non-Elective Inpatient - Short Stay(186)
Cholecystitis	593.80	[redacted]	[redacted]	NHS National Cost Collection data 2023/24; FD01F-J - Gastrointestinal Infections without Interventions, with CC Score 0-1 - Non-Elective Inpatient - Short Stay(186)
Pain in extremity	0.26	[redacted]	[redacted]	eMIT National Database 2023/24; Paracetamol 500mg tablets / Packsize 16(186)

Key: BNF, British National Formulary; CC, complication/comorbidity; COVID, coronavirus disease; eMIT, electronic market information tool; MMF, mycophenolate mofetil; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OBI, OBI; TA, technology appraisal; PSSRU, personal social services research unit.

3.5.4 Miscellaneous unit costs and resource use

3.5.4.1 End-of-life costs

All mortality in the model incurs an end-of-life cost. The cost-effectiveness model includes two options to capture the increased resource cost associated with treatment at the end of life. The analysis captures the cost of death related to LN (assumed to relate to transitions to death from CKD 5 health states) and the cost of death not related to disease (assumed to relate to transitions to death from any other health state). This approach was applied in TA882, where deaths related to LN were based on hospital care costs associated with renal failure and non-disease related end of life costs were based on costs of hospital care for any diagnosis.

The cost of a background mortality-related death was £9,287, which is the cost of hospital care for any diagnosis from Table 7.2.2 of the latest PSSRU 2024 report (192), inflated to the 2025 cost-year using Consumer Prices Index (CPI) inflation indices for health (188, 189). The cost of an LN-related death was £14,922, based on hospital care costs associated with renal failure sourced from PSSRU 2024, inflated to the 2025 cost-year.

3.6 Severity

The population under consideration does not meet the criteria for a severity weight. No calculation of QALY shortfall is provided with this submission.

3.7 Uncertainty

The economic analysis is informed by efficacy and safety data from the phase III REGENCY study for OBI+MMF and MMF, and via an ITC for comparisons to other LN treatments. The phase III study is of sufficient quality to determine the clinical efficacy of OBI+MMF and support the use of OBI for LN (115).

However, underlying uncertainties relating to interstudy variability potentially limits the generalisability of ITC results. Uncertainties relating to heterogeneity between studies were noted by the EAG in TA882 and remain in this analysis. Another uncertainty listed in TA882 related to the long-term transition to ESRD and how long-term outcomes are impacted by differences in short-term endpoints. This is an uncertainty common to chronic conditions where short-term trials are used to inform decision-making for life-long conditions. To attempt to capture expected long-term differences between treatments and better reflect the true progression to ESRD, the cost-effectiveness analysis adjusts transitions to CKD Stage 4 using key predicted secondary endpoints such as renal flares. However, these adjustments themselves are inherently associated with uncertainty, but ignoring expected differences would not resolve this. The company also flagged uncertainties relating to the chronic, progressive nature of LN resulting in long-term treatment durations limited knowledge of treatment effect waning. This analysis attempts to leverage understanding relating to the impact of B-cell depletion on long-term maintenance of response to inform differences in treatment waning. Again, these assumptions inherently bring uncertainty, but equal uncertainty would be observed if expected differences in the duration of treatment effects were ignored.

The company sought extensive clinical input into key modelling assumptions. First at an advisory board with 11 UK nephrologists, rheumatologists, nurses and pharmacists with experience managing LN, where experts indicated evidence gaps and expected differences between treatments included in the analysis (68). Then, subsequent teleconferences with 3 clinical experts were undertaken to validate model changes following feedback at the original advisory board (68).

The cost-effectiveness analysis provides extensive scenario analyses (Section 3.11.3) to quantify the impact of structural uncertainty in the cost-effectiveness model.

3.8 Managed access proposal

REGENCY has an ongoing five-year open-label extension period where additional evidence will be collected on enrolled patients. However, this additional data is unlikely to resolve uncertainties associated with the long-term impacts related to CKD and ESRD such as the impact to dialysis and transplant rates. However, the company remains open to all possible routes to access so patients can benefit from OBI.

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base-case analysis inputs

A summary of the variables applied in the economic model, their base case values and the uncertainty distribution and uncertainty for each variable, is provided in Appendix H.

3.9.2 Assumptions

Key assumptions in the economic analysis are summarised in Table 65. The approach to economic modelling has been designed to make the best use of available data to inform the decision problem. In the absence of available data, assumptions are designed to minimise potential bias in the analysis. These two statements are illustrated by the likely direction of bias and justification for base case analysis assumptions, summarised in Table 65.

Table 65: Summary of key assumptions of the economic analysis

#	Assumption	Likely direction of bias	Justification
Model structure			
1	Six-monthly cycle deemed sufficiently granular to accurately capture the clinical and cost outcomes for patients with LN.	No bias expected	Section 3.2.2
2	All patients enter the model in the CKD_1_3b_AD health state.	No bias expected	Section 3.2.2
3	Progression along CKD health states can only occur in the proportion of patients with active LN.	No bias expected	Section 3.2.2 and 3.3.2.3
4	Transitions from CRR or PRR to CKD within Stage 4 are not possible. So 100% of patients in CKD Stage 4 are assumed to have active disease.	No bias expected	Section 3.2.2 and 3.3.2.3
5	Patients cannot regain kidney function and transition to lower CKD stages once progressed (i.e. from CKD 4 to CKD 3).	No bias expected	Section 3.2.2 and 3.3.2.3
6	All patients enter CKD 5 in the dialysis state.	No bias expected	Section 3.2.2 and 3.3.2.4
7	Post-kidney transplant remains as a standalone health state; patients to transition back to the start of the model.	No bias expected	Section 3.2.2 and 3.3.2.4
8	Possibility of transitioning to death from each health state is assumed equal for all treatments in the model.	No bias expected	Section 3.3.2.5
9	Transition probabilities from CKD Stage 4 AD, PR and CR to death are all the same in the absence of health state specific estimates.	No bias expected	Section 3.3.2.5
Indirect treatment comparison			
10	Assumed that the analysis time point of the ITC is 3 years.	No bias expected	Section 2.10
11	Despite trial differences, ITC assumes RCTs were sufficiently homogeneous for comparison.	In favour of VOC+MMF and RTX+MMF	Section 2.10.5 and 2.10.6
Transition probabilities			
12	Markovian assumption assumes transition probabilities are memoryless, i.e. time independent.	No bias expected	Section 3.2.2 and 3.3.2
13	VOC+MMF and RTX+MMF loss of response transitions equivalent to OBI+MMF transitions calculated from REGENCY.	In favour of VOC+MMF and RTX+MMF	Section 3.3.2.2
14	TA882 elicited probability for transition to CKD Stage 4 assumed to be relevant for standard of care at the time of the elicitation (i.e. MMF and RTX+MMF).	No bias expected	Section 3.3.2.3
15	Renal flare data can be used to account for the expected differences in long-term outcomes by adjusting single transition to CKD Stage 4.	No bias expected	Section 3.3.2.3

Treatment effect waning			
16	Applied 36-month stopping rules for all treatments included in the model.	No bias expected	Section 3.3.2.6
17	Treatment effect waning applied to all treatments following discontinuation.	No bias expected	Section 3.3.2.6
18	Following discontinuation of OBI+MMF, the treatment effect is maintained for 12 months before waning to MMF transitions over the next 12 months.	No bias expected	Section 3.3.2.6
19	Following discontinuation of VOC+MMF, the treatment effect wanes to equal MMF transition probabilities over 6 months.	In favour of VOC+MMF	Section 3.3.2.6
20	For RTX+MMF, the treatment effect is maintained for 6 months before waning to MMF transitions over the next 6 months.	In favour of RTX+MMF	Section 3.3.2.6
Health-related quality-of-life			
21	Health-state utility values applied consistently to all treatments.	No bias expected	Section 3.4.5
22	Utility health state utility estimates used in TA882 (i.e. AURORA trials) and literature estimates.	No bias expected	Section 3.4.5
23	Any impact to HRQoL associated with AEs are captured within health state utility estimates.	No bias expected	Section 3.4.4
24	In the absence of AE-specific values, extreme AE decrements and durations used.	Against OBI	Section 3.4.4
Cost and healthcare resource use			
25	No cost for oral administration	In favour of MMF and VOC+MMF	Section 3.5.1.3
26	Same subsequent treatment distribution of subsequent therapy as OBI+MMF assumed for VOC+MMF and RTX+MMF.	In favour of VOC+MMF and RTX+MMF	Section 3.5.1.4
27	Patients cannot go on to receive the same subsequent treatment they receive as initial treatment.	No bias expected	Section 3.5.1.4
28	All treatments regimens which include MMF are assumed to have the same incidence of AEs as the MMF arm in REGENCY.	In favour of VOC+MMF and RTX+MMF	Section 3.5.3

3.10 Base-case results

Considering the PAS price for OBI and list prices for all other treatments, the estimated ICER for OBI+MMF is £1,743 per QALY gained versus MMF, and dominant versus VOC+MMF and RTX+MMF. Appendix I presents ICERs at list prices for all treatments. Results show that OBI+MMF is highly likely be a cost-effective treatment option for people with active LN. These ICERS should also be considered in the context of OBI+MMF being an innovative technology that presents a step-change improvement for patients with LN and provides a real opportunity to relieve expenditure on the long-term management of ESRD.

- All relevant health outcomes and costs were included in line with the NICE reference case:
    - CRR and PRR were the main efficacy inputs used in the economic model. CRR and PRR from REGENCY were used for OBI+MMF and MMF and to inform the ITC. The ITC was used to facilitate comparisons against VOC+MMF and RTX+MMF and to model health outcomes over patients' lifetime
    - Cost categories included treatment acquisition and administration costs, health state resource use costs, AE costs, subsequent treatment costs and costs associated with end-of-life care
    - Health-related quality-of-life outcomes were captures using QALYs

3.10.1 Base-case incremental cost-effectiveness analysis results

All results presented in this section assume the PAS price for OBI and the list price for all other treatments. Pairwise cost-effectiveness results OBI+MMF versus MMF, OBIMMF versus VOC+MMF and OBI+MMF versus RTX+MMF are presented in Table 66 and disaggregated results are available in Appendix H.

The results show that OBI+MMF offers incremental health benefits compared with other treatments for LN, offering an additional [redacted], [redacted] and [redacted] QALYs compared with MMF, VOC+MMF and RTX+MMF, respectively. This benefit supports the importance of OBI as a treatment option for patients with LN who would otherwise face poor prognosis with current treatment options.

Considering the PAS price for OBI and list prices for all other treatments, treatment with OBI+MMF is associated with a cost difference of [redacted] compared with MMF, [redacted] compared with VOC+MMF and [redacted] compared with RTX+MMF, primarily driven by differences in treatment costs. The resulting ICER in the base case analysis is £1,743 versus MMF.

Base case cost-effectiveness results suggest that OBI+MMF dominates VOC+MMF and RTX+MMF. As some ICERs are dominant, it is appropriate to consider net monetary benefit (NMB) and net health benefit (NHB). The incremental NMB is shown to be £18,419 and £28,508 versus MMF, £31,132 and £35,407 versus VOC+MMF, and £42,981 and £50,349 versus RTX+MMF at £20,000 and £30,000 per QALY willingness to pay thresholds, respectively, as presented in Table 66. The incremental NHB is shown to be 0.921 and 0.950 versus MMF, 1.557 and 1.180 versus VOC+MMF, and 2.149 and 1.678 versus

RTX+MMF at £20,000 and £30,000 per QALY willingness to pay thresholds, respectively, as presented in Table 66. Appendix I presents ICERs, NMB and NHB at list price for OBI.

Table 66: Base case results versus OBI – OBI PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	NMB at £20,000	NMB at £30,000	NHB at £20,000	NHB at £30,000
OBI+MMF	[redacted]	[redacted]	[redacted]								
MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,743	18,419	28,508	0.921	0.950
VOC+MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	31,132	35,407	1.557	1.180
RTX+MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	42,981	50,349	2.149	1.678

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; MMF, mycophenolate mofetil; NHB, net health benefit; NMB, net monetary benefit; OBI, obinutuzumab; PAS, patient access scheme; QALYs, quality-adjusted life years; RTX, rituximab; VOC, voclosporin.

3.11 Exploring uncertainty

Sensitivity and scenario analysis results showed results to be robust to uncertainty around most input parameters. However, deterministic sensitivity results show that transition probabilities, particularly transitions to later CKD stages, as well as the cost of managing ESRD complications impact cost-effectiveness results. This highlights the importance of early intervention to prevent disease progression. While there is inherent uncertainty around the cost effectiveness of OBI+MMF, care has been taken to inform uncertain assumptions with the best data available, representing clinical practice to generate expected outcomes, and to be transparent in illustrating the uncertainty around results.

3.11.1 Probabilistic sensitivity analysis

The deterministic base case result represents the model result at the expected values of all input variables. When input variables are uncertain decision making about the adoption of a new health technology must also consider the uncertainty around the expected model results.

Probabilistic sensitivity analysis (PSA) was performed to account for joint uncertainties in the key model inputs, in which multiple input parameters were varied simultaneously over a number of iterations by sampling their values from uncertainty distributions. In the absence of data on the variability around health state cost values, variability (i.e. standard error) was assumed to be 10% of the mean value. The appropriate probability distributions were used, presented in Table 67. As explained in Section 3.9.1, a summary of the variables applied in the economic model, their base case values and the uncertainty distribution and uncertainty for each variable, is provided in Appendix H.

Table 67: Distributions used in the probabilistic sensitivity analysis

Type	Parameter	Distribution
Efficacy	Transition Probabilities	Dirichlet
	Adverse event rates	Log normal
Costs	Supportive care cost	Log normal
	Administration cost	Log normal
	Adverse event cost	Log normal
	Drug cost	No distribution was applied
	Rescue Therapy	No distribution was applied
Utilities	Health state	Beta
	Disutility due to adverse events	Log normal
Safety	Number of adverse events observed in the trial	Log normal

The results of the PSA based on 1,000 simulations are presented in Table 68, along with the results illustrated in a scatterplot in Figure 20 and Figure 21. The mean total outcomes from the PSA are fairly consistent with the base case results presented in Table 66. Total costs increase and QALYs decrease for all treatments when considering probabilistic results, but overall conclusions remain the same. So, outcomes from the cost-effectiveness model are considered robust to uncertainty from parameter distributions.

As in base case deterministic results some ICERs are dominant and, as confidence intervals in incremental costs or QALYs cross 0, it is appropriate to consider NMB and NHB. Mean

incremental NMB and NHB outcomes from the PSA are consistent with the base case results presented in Table 66. Again, outcomes from the cost-effectiveness model can be considered robust to uncertainty from parameter distributions, and as NMB and NHB increases when varied probabilistically, outcomes get more favourable when considering overarching uncertainty.

Based on cost-effectiveness acceptability curve results, OBI+MMF had [redacted]% and [redacted]% of being the most cost-effective treatment option at willingness-to-pay thresholds of £20,000 and £30,000 (Figure 22).

Table 68: Probabilistic sensitivity analysis results, ICER – OBI PAS price

	Total Costs (£)	Total LYGs	Total QALYs	Inc Costs (£)	Inc LYGs	Inc QALYs	ICER (£/QALY)	NMB at £30,000	NHB at £30,000
OBI+ MMF	[redacted]								
MMF	[redacted]						1,791	29,242	0.975
VOC+ MMF	[redacted]						Dominant	36,849	1.228
RTX+ MMF	[redacted]						Dominant	58,136	1.938

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; MMF, mycophenolate mofetil; NHB, net health benefit; NMB, net monetary benefit; OBI, obinutuzumab; PAS, patient access scheme; QALYs, quality-adjusted life years; RTX, rituximab; VOC, voclosporin.

Figure 20: Cost-effectiveness plane – OBI PAS price

[redacted]

Key: MMF, mycophenolate mofetil; OBI, obinutuzumab; PAS, patient access scheme; QALYs, quality-adjusted life years; RTX, rituximab; VOC, voclosporin.

Figure 21: Incremental cost-effectiveness plane – OBI PAS price

[redacted]

Key: MMF, mycophenolate mofetil; OBI, obinutuzumab; PAS, patient access scheme; QALYs, quality-adjusted life years; RTX, rituximab; VOC, voclosporin.

Figure 22: Cost-effectiveness acceptability curve – OBI PAS price

Key: GBP, Pounds, MMF, mycophenolate mofetil; OBI, obinutuzumab; PAS, patient access scheme; QALYs, quality-adjusted life years; RTX, rituximab; VOC, voclosporin; WTP, willingness-to-pay.

3.11.2 Deterministic sensitivity analysis

In the one-way sensitivity analysis (OWSA), values for all parameters with univariate uncertainty distributions were set to their upper and lower limits of the confidence intervals.

Figure 23 shows tornado diagrams depicting the 10 parameters that have the greatest influence on the NMB for OBI+MMF versus MMF. Figure 24 and Figure 25 show the impact of key parameters for OBI+MMF versus VOC+MMF and RTX+MMF, respectively.

As expected, the key drivers of the deterministic sensitivity analyses include transition probabilities, particularly those associated with the transition to later CKD stages. This highlights the importance of early intervention with targeted therapy to prevent disease progression and mirrors clinical understanding that preserving kidney function as early as possible is the most important outcome for people with LN. Other model drivers include health state utility values and supportive care costs associated with the ESRD complications dialysis and transplant, again highlighting the importance of early intervention to avoid later line complications.

Figure 23: Tornado diagram showing OWSA results, OBI versus MMF – NMB at WTP threshold of £30,000 – OBI PAS price

Figure 24: Tornado diagram showing OWSA results, OBI versus VOC+MMF – NMB at WTP threshold of £30,000 – OBI PAS price

Figure 25: Tornado diagram showing OWSA results, OBI versus RTX+MMF – NMB at WTP threshold of £30,000 – OBI PAS price

3.11.3 Scenario analysis

To provide a complete understanding of the impact of changing key model inputs and assumptions (i.e. related to methodological, parameter-specific or structural assumptions), an extensive list of scenarios was tested.

As demonstrated in Table 69, scenario results are generally robust to changes, indicating a relatively small impact of uncertainty on the base-case results.

Key scenarios include the consideration of a simplified cost-comparison analysis for add-on triplet therapies. In this scenario, assuming equivalence in transition probabilities between treatments, OBI+MMF was cost saving versus VOC+MMF and RTX+MMF. While results in Table 69 don’t include the confidential discounts for VOC and RTX, the same conclusion is reached when considering OBI at list price (Appendix I). This scenario ignores all key efficacy differences expected with OBI+MMF, including response, renal flares and their expected impact to long-term outcomes, steroid tapering and a dosing schedule with improved adherence, so can be considered the conservative estimate of the cost-effectiveness of OBI+MMF versus other add-on therapies. Even when ignoring these benefits, OBI+MMF is cost saving.

Other scenarios show that, despite the extensive investigation of structural uncertainty, results remain robust to changes and the overarching conclusion is that OBI+MMF can be considered a cost-effective treatment for LN. There is only one scenario that shows a negative NMB and NHB versus VOC+MMF. This scenario is implausible as it relates to an extrapolation of the VOC+MMF treatment effect for the duration of the time horizon, despite stopping treatment at 3 years. All other scenarios show OBI+MMF is a cost-effective treatment option.

Table 69: Scenario analysis results – OBI PAS price

		ICER			NMB			NHB		
Base case assumption	**Scenario**	**vs MMF**	**vs VOC+MMF**	**vs RTX+MMF**	**vs MMF**	**vs VOC+MMF**	**vs RTX+MMF**	**vs MMF**	**vs VOC+MMF**	**vs RTX+MMF**
Base case		1,743	Dominant	Dominant	£28,508	£35,407	£50,349	0.95	1.18	1.68
Treatment duration – 6 cycles	12	4,237	Dominant	Dominant	£35,139	£60,045	£61,534	1.17	2.00	2.05
	18	5,655	Dominant	Dominant	£40,405	£81,428	£70,597	1.35	2.71	2.35
Equivalence – FALSE	TRUE	NA	-52,825	NA	£28,508	£35,407	£50,349	0.95	1.18	1.68
Response transitions – ITC	REGENCY	3,935	Dominant	Dominant	£20,220	£44,860	£59,177	0.67	1.50	1.97
Loss of response transitions – by treatment	Pooled	2,431	Dominant	Dominant	£25,966	£34,883	£50,770	0.87	1.16	1.69
Loss of response transitions (other comparators) – Equal to OBI+MMF	Midpoint of OBI+MMF and MMF	1,743	Dominant	Dominant	£28,508	£36,586	£52,422	0.95	1.22	1.75
	Equal to MMF	1,743	Dominant	Dominant	£28,508	£37,811	£54,520	0.95	1.26	1.82
Impact of renal flares – applied to transition to CKD Stage 4	No	12,706	SW 1,536,062	Dominant	£8,387	£18,520	£30,228	0.28	0.62	1.01
	Response to active disease	6,165	Dominant	Dominant	£17,253	£27,953	£39,094	0.58	0.93	1.30
	Active disease and CKD stage 4	329	Dominant	Dominant	£35,768	£43,224	£57,608	1.19	1.44	1.92
Duration of effect wanes to MMF transition probabilities	OBI+MMF effect is maintained over time	Dominant	Dominant	Dominant	£99,226	£106,125	£121,067	3.31	3.54	4.04
	VOC+MMF effect is maintained over time	1,743	SW 16,543	Dominant	£28,508	-£11,311	£50,349	0.95	-0.38	1.68
	RTX+MMF effect is maintained over time	1,743	Dominant	SW 593,817	£28,508	£35,407	£28,528	0.95	1.18	0.95
	REGENCY - Mixed Model - per treatment arm	1,539	Dominant	Dominant	£32,502	£35,464	£49,746	1.08	1.18	1.66

Utility source – TA882 EAG approach	REGENCY - Mixed Model - pooled	1,866	Dominant	Dominant	£26,498	£35,284	£49,469	0.88	1.18	1.65
	NICE TA882 - company submitted	1,684	Dominant	Dominant	£29,564	£35,302	£50,635	0.99	1.18	1.69
AE disutility – FALSE	TRUE	1,743	Dominant	Dominant	£28,533	£35,432	£50,373	0.95	1.18	1.68
Exclude COVID AEs – FALSE	TRUE	1,691	Dominant	Dominant	£28,560	£35,460	£50,401	0.95	1.18	1.68
Include oral administration cost – FALSE	TRUE	1,403	Dominant	Dominant	£28,850	£81,937	£50,236	0.96	2.73	1.67
REGENCY subsequent treatment proportions	Multiplier: x 2	708	Dominant	Dominant	£29,552	£35,086	£50,212	0.99	1.17	1.67
	Multiplier: x 3	-327	Dominant	Dominant	£30,596	£34,766	£50,075	1.02	1.16	1.67
Time horizon – 70 years	60	1,670	Dominant	Dominant	£28,391	£35,353	£50,157	0.95	1.18	1.67
	80	1,756	Dominant	Dominant	£28,518	£35,412	£50,369	0.95	1.18	1.68
Discount rate costs – 3.5%	0	2,463	Dominant	Dominant	£28,654	£35,979	£58,770	0.96	1.20	1.96
	0.015	1,598	Dominant	Dominant	£64,037	£51,718	£76,378	2.13	1.72	2.55
Discount rate outcomes – 3.5%	0	802	Dominant	Dominant	£43,851	£42,427	£61,580	1.46	1.41	2.05
	0.015	1,156	Dominant	Dominant	£28,508	£35,407	£50,349	0.95	1.18	1.68

3.11.4 Threshold analysis

As VOC is available to the NHS with a confidential PAS discount and RTX is available through biosimilars, a threshold analysis has been provided to present base case cost-effectiveness outcomes for OBI+MMF versus VOC+MMF and RTX+MMF at a range of simulated discount rates. Cost-effectiveness outcomes for OBI+MMF versus VOC+MMF and RTX+MMF including the OBI PAS with varying levels of VOC and RTX discounts are presented in Table 70. The discount level for VOC and RTX are varied independently, i.e. cost-effectiveness outcomes for OBI+MMF versus VOC+MMF are presented when VOC discount level is varied and cost-effectiveness outcomes for OBI+MMF versus RTX+MMF are presented when RTX discount level is varied. Results show that the cost-effectiveness of OBI+MMF is robust to comparator pricing when considering base case assumptions.

Table 70: Threshold analysis at varying discount levels for VOC and RTX – NMB at WTP threshold of £30,000 – OBI PAS price

Discount rate	versus VOC+MMF			versus RTX+MMF		
	ICER	NMB	NHB	ICER	NMB	NHB
0%	Dominant	£35,407	1.18	Dominant	£50,349	1.68
10%	Dominant	£32,251	1.08	Dominant	£49,095	1.64
20%	Dominant	£29,095	0.97	Dominant	£47,842	1.59
30%	Dominant	£25,940	0.86	Dominant	£46,588	1.55
40%	Dominant	£22,784	0.76	Dominant	£45,335	1.51
50%	Dominant	£19,628	0.65	Dominant	£44,081	1.47
60%	Dominant	£16,472	0.55	Dominant	£42,828	1.43
70%	Dominant	£13,316	0.44	Dominant	£41,575	1.39
80%	6,235	£10,160	0.34	Dominant	£40,321	1.34
90%	13,617	£7,004	0.23	Dominant	£39,068	1.30
100%	20,999	£3,848	0.13	Dominant	£37,814	1.26

Key: ICER, incremental cost-effectiveness ratio; MMF, mycophenolate mofetil; NHB, net health benefit; NMB, net monetary benefit; OBI, obinutuzumab; PAS, patient access scheme; RTX, rituximab; VOC, voclosporin.

3.12 Subgroup analysis

No subgroup analyses were explored.

3.13 Benefits not captured in the QALY calculation

As explained in Section 3.4.1, the inclusion of OBI represents a step-change improvement in the treatment pathway for patients with LN. OBI+MMF will provide patients with a disease-modifying treatment option that has the potential to treat the underlying mechanism of the disease, while allowing patients to live with freedom from the burden of additional daily medication.

As explained in Section 1.3.1.7.2, as people with LN progress to ESRD there is a significant need for carers. The caregiver burden is associated with managing ESRD is not captured in this cost-effectiveness analysis. When considering the impact to caregivers, incremental QALY outcomes are likely to improve. This is due to OBI+MMF's potential for delaying

progression to ESRD, and avoiding decrements associated with caregiving, compared with other treatment options for LN.

The superior response-based efficacy associated with OBI+MMF will improve lifetime quality of life for patients with LN by delaying progression to more-burdensome CKD stages. In addition, the avoidance of renal flares and any short-term impacts to quality of life caused by flares, the tapering of corticosteroids and any avoidance of adverse reactions to corticosteroids, and a more infrequent, manageable dosing regimen is likely to further enhance the quality of life for patients treated with OBI. However, these factors are uncaptured in this analysis.

Clinical experts highlighted that preventing long-term complications like end-stage kidney failure, which significantly impacts quality of life, is a key benefit not fully captured in short-term trials. The analysis attempts to capture this in the application of CKD-relevant health state utilities from the literature. However, the impact to LN patients is uncertain.

As explained in Section 1.3.4, the prevalence of LN is greater in ethnic minority populations, including Chinese, Afro-Caribbean and Indo-Asian populations, relative to the Caucasian population. Health inequalities among ethnic minority populations in the UK are well documented, with several studies reporting poorer health outcomes versus the Caucasian population. Prevalence is also greater among women (female-to-male ratio of 5:1) and the median age at diagnosis was 35 for women and 65 for men. The cost-effectiveness analysis does not capture any impact OBI has on addressing underlying health inequalities and their impact to health-related quality of life.

LN is typically diagnosed most commonly diagnosed in women between the ages of 20 and 40. The burden of disease and associated treatment burdens are especially significant given that most patients are of working and childbearing age, where the complexity of managing medications can impact daily functioning, adherence and quality-of-life to a greater extent. The cost-effectiveness analysis doesn’t account for any societal impact to productivity to in the working age population.

3.14 Validation

3.14.1 Validation of cost-effectiveness analysis

The cost-effectiveness model was developed in line with the NICE reference case and guidance from the NICE DSU TSDs where appropriate. The cost-effectiveness model itself is quality-assured by external economists not involved in the construction of the economic model. Model validation methods included black-box and white-box testing of the economic model. The external health-economist reviewed the technical implementation of calculations and coding for correctness, reviewing and testing inputs and checking for implementation and/or logical inconsistencies.

This is the first economic evaluation assessing the cost-effectiveness of OBI+MMF for patients LN in the UK. No study assessing the UK cost-effectiveness of OBI+MMF for the target population specified above was identified from the SLR; therefore, it was not possible to compare the results of the economic model developed in this appraisal with a previous

study. There was only one economic analysis relevant to this target population, that of VOC+MMF for LN assessed in TA882. Model inputs and assumptions were consistent with this analysis, where appropriate and changes in assumptions were validated by clinical experts experienced in the management of LN in the UK.

3.14.2 Clinical validation

Roche conducted an advisory board in which eleven UK clinical experts operating in the NHS (nephrologists, rhematologists, nurses and pharmacists) were asked to comment on aspects of the clinical data and economic model specific to this appraisal. A confidential, anonymised advisory board report is provided with this submission and is referenced throughout this document (68). Follow-up consultations were conducted with a number of clinical experts who attended the advisory board (85).

3.15 Interpretation and conclusions of economic evidence

The key evidence presented in this submission are based directly on data from the REGENCY study, a phase III RCT investigating the efficacy of OBI+MMF versus MMF for patients with LN, and supported by NOBILITY, a phase II RCT investigating the efficacy of OBI+MMF versus MMF for patients with LN. OBI+MMF demonstrated statistically significant benefits to response compared with MMF. To compare to other treatments relevant to the UK clinical pathway, an ITC was conducted. The ITC showed non-significant differences between response outcomes.

In line with the NICE reference case and final NICE scope, a cost-effectiveness model was developed to compare OBI+MMF with MMF, VOC+MMF and RTX+MMF. This is aligned to UK practice, where clinicians typically treat patients with these treatment options. The base case analysis uses an ITC to calculate transition probabilities used to extrapolate short-term trial data. The analysis attempts to capture expected differences in long-term outcomes associated with the progression to ESRD. The model utilises renal flares – a known and accepted predictor of long-term prognosis – to adjust the transition probability associated with progression to CKD Stage 4 to account for expected differences between treatments.

Results show that OBI+MMF offers incremental health benefits compared with other treatments for LN, offering an additional [redacted], [redacted] and [redacted] QALYs compared with MMF, VOC+MMF and RTX+MMF, respectively. Considering the PAS price for OBI and list prices for all treatments, treatment with OBI+MMF is associated with a cost difference of [redacted] compared with MMF, [redacted] compared with VOC+MMF and [redacted] compared with RTX+MMF, primarily driven by differences in treatment costs. Base case cost-effectiveness results suggest that the resulting ICER in the base case analysis is £1,743 versus MMF and that OBI+MMF dominates VOC+MMF and RTX+MMF. The base case results are wholly supported by the sensitivity and scenario analysis, which demonstrate a high degree of consistency. This highlights the small level of uncertainty associated with cost-effectiveness outcomes.

Cost-effectiveness results can be considered a conservative estimate of the true value the addition of OBI is likely to bring patients with LN and the NHS. While attempts have been made to account for long-term differences in prognosis expected with alternative treatments,

it is highly likely the model does not fully capture the full impact. To allow an ITC to be investigated, an assumption of homogeneity between trials was required. Section 2.10.6 outlines the uncertainties associated with the ITC which are likely to underestimate the relative effect of OBI versus other treatments. Due to strict monitoring and high patient engagement, adherence is higher in LN clinical trials than is expected in real-world clinical practice. Low adherence is known to be a consistent issue for patients treated with MMF and VOC, and any reduction in adherence is likely associated with a reduction in efficacy. This analysis cannot account for this impact. The model also makes a number of conservative assumptions in the absence of alternative data. For example, the model assumes that both VOC+MMF and RTX+MMF loss of response transitions are equivalent to OBI+MMF, experience a longer degree of treatment effect waning than is expected in clinical practice and are assumed to be associated with no treatment-specific AEs; and the model assumes no cost for oral administration – favouring MMF and VOC+MMF.

Despite inherent uncertainties associated with modelling in LN, the company submission attempts to present a broad, holistic assessment of the cost-effectiveness of OBI for LN.

OBI+MMF is shown to be a cost-effective treatment option in all clinically plausible scenarios, even with a number of conservative assumptions.

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Company submitted results - renal flare surrogacy scenarios

Surrogacy relationship	ICER versus				NMB versus				NHB versus			
	MMF	VOC	RTX	BEL	MMF	VOC	RTX	BEL	MMF	VOC	RTX	BEL
0%	12,097	SW 2,100,748	Dominant	Dominant	£8,687	£18,780	£29,886	£29,186	0.29	0.63	1.00	0.97
10%	10,181	Dominant	Dominant	Dominant	£10,610	£20,381	£31,809	£29,548	0.35	0.68	1.06	0.98
20%	8,577	Dominant	Dominant	Dominant	£12,552	£22,001	£33,751	£29,916	0.42	0.73	1.13	1.00
30%	7,216	Dominant	Dominant	Dominant	£14,514	£23,640	£35,712	£30,292	0.48	0.79	1.19	1.01
40%	6,046	Dominant	Dominant	Dominant	£16,495	£25,298	£37,693	£30,674	0.55	0.84	1.26	1.02
50%	5,030	Dominant	Dominant	Dominant	£18,496	£26,975	£39,694	£31,064	0.62	0.90	1.32	1.04
60%	4,139	Dominant	Dominant	Dominant	£20,516	£28,672	£41,715	£31,461	0.68	0.96	1.39	1.05
70%	3,351	Dominant	Dominant	Dominant	£22,557	£30,388	£43,756	£31,865	0.75	1.01	1.46	1.06
80%	2,649	Dominant	Dominant	Dominant	£24,619	£32,125	£45,817	£32,277	0.82	1.07	1.53	1.08
90%	2,020	Dominant	Dominant	Dominant	£26,701	£33,881	£47,899	£32,696	0.89	1.13	1.60	1.09
Company base case: 100%	**1,454**	**Dominant**	**Dominant**	**Dominant**	**£28,804**	**£35,658**	**£50,002**	**£33,123**	**0.96**	**1.19**	**1.67**	**1.10**

EAG results - renal flare surrogacy scenarios (Apply HR to CKD 4 risk, REGENCY for all combinations)

Surrogacy relationship	ICER versus				NMB versus				NHB versus			
	MMF	VOC	RTX	BEL	MMF	VOC	RTX	BEL	MMF	VOC	RTX	BEL
EAG base case: 0%	**23,791**	**659,384**	**Dominant**	**Dominant**	**£2,460**	**£17,661**	**£11,223**	**£23,479**	**0.08**	**0.59**	**0.37**	**23,791**
10%	20,409	941,782	Dominant	Dominant	£4,249	£17,976	£11,212	£23,561	0.14	0.60	0.37	20,409
20%	17,650	1,659,537	Dominant	Dominant	£6,053	£18,296	£11,201	£23,645	0.20	0.61	0.37	17,650
30%	15,356	7,200,716	Dominant	Dominant	£7,873	£18,622	£11,190	£23,731	0.26	0.62	0.37	15,356
40%	13,419	Dominant	Dominant	Dominant	£9,710	£18,954	£11,178	£23,818	0.32	0.63	0.37	13,419
50%	11,762	Dominant	Dominant	Dominant	£11,563	£19,291	£11,167	£23,906	0.39	0.64	0.37	11,762
60%	10,327	Dominant	Dominant	Dominant	£13,433	£19,634	£11,156	£23,996	0.45	0.65	0.37	10,327
70%	9,073	Dominant	Dominant	Dominant	£15,320	£19,983	£11,144	£24,088	0.51	0.67	0.37	9,073
80%	7,968	Dominant	Dominant	Dominant	£17,224	£20,337	£11,133	£24,182	0.57	0.68	0.37	7,968
90%	6,987	Dominant	Dominant	Dominant	£19,145	£20,698	£11,122	£24,278	0.64	0.69	0.37	6,987
100%	6,109	Dominant	Dominant	Dominant	£21,084	£21,065	£11,110	£24,375	0.70	0.70	0.37	6,109

EAG results - renal flare surrogacy scenarios (Apply HR to CKD 4 risk, CS base case)

Surrogacy relationship	ICER versus				NMB versus				NHB versus			
	MMF	VOC	RTX	BEL	MMF	VOC	RTX	BEL	MMF	VOC	RTX	BEL
0%	23,791	659,384	Dominant	Dominant	£2,460	£17,661	£11,223	£23,479	0.08	0.59	0.37	23,791
10%	20,409	Dominant	Dominant	Dominant	£4,249	£19,146	£13,011	£23,775	0.14	0.64	0.43	20,409
20%	17,650	Dominant	Dominant	Dominant	£6,053	£20,647	£14,815	£24,077	0.20	0.69	0.49	17,650
30%	15,357	Dominant	Dominant	Dominant	£7,873	£22,163	£16,636	£24,383	0.26	0.74	0.55	15,357
40%	13,420	Dominant	Dominant	Dominant	£9,710	£23,695	£18,472	£24,694	0.32	0.79	0.62	13,420
50%	11,762	Dominant	Dominant	Dominant	£11,563	£25,244	£20,326	£25,011	0.39	0.84	0.68	11,762
60%	10,328	Dominant	Dominant	Dominant	£13,433	£26,808	£22,195	£25,333	0.45	0.89	0.74	10,328
70%	9,074	Dominant	Dominant	Dominant	£15,320	£28,390	£24,082	£25,660	0.51	0.95	0.80	9,074
80%	7,969	Dominant	Dominant	Dominant	£17,224	£29,987	£25,986	£25,992	0.57	1.00	0.87	7,969
90%	6,988	Dominant	Dominant	Dominant	£19,145	£31,602	£27,907	£26,330	0.64	1.05	0.93	6,988
100%	6,110	Dominant	Dominant	Dominant	£21,083	£33,233	£29,846	£26,674	0.70	1.11	0.99	6,110

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Obinutuzumab for treating lupus nephritis [ID6420]

Summary of Information for Patients (SIP)

July 2025

File name	Version	Contains confidential information	Date
ID6420_Obinutuzumab_LN_SIP_[CON]	1.0	Yes	23 July 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

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

Brand name: GAZYVARO® (obinutuzumab)

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

GAZYVARO® (obinutuzumab) with immunosuppressive therapies for treating adult patients with lupus nephritis (LN).

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.

The marketing authorisation for obinutuzumab in lupus nephritis is pending. Please refer to Table 2 in Section 1.2 of the company submission for the anticipated date of approval. Obinutuzumab already has UK marketing authorisation for the treatment of chronic lymphocytic leukaemia and follicular lymphoma.

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:

Roche is in touch with the following patient groups: Lupus UK, Kidney Care UK, Kidney Research UK and the National Kidney Federation. Roche has not provided any donations, grants or sponsorships to any of these groups over the last year (2024-25).

Roche is involved with Kidney Research UK's Kidney Policy Forum which comprises patient groups, healthcare professionals and industry. Participation is by invitation and voluntary. Collaboration focuses on the development of national health policy that improves NHS patient care across the pathway.

SECTION 2: Current landscape

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.

Main condition that the medicine plans to treat

LN is a serious complication of systemic lupus erythematosus (SLE), often just called lupus. Lupus is a chronic autoimmune disease, meaning the body's immune system mistakenly attacks its own healthy tissues and organs (1). In LN, the immune system specifically attacks the kidneys, leading to inflammation and damage. Over time, this damage can reduce the kidneys' ability to filter waste from the blood, potentially leading to kidney failure (1).

Main symptoms of disease

LN often does not have obvious symptoms in its early stages (1). When symptoms do appear, they can include:

- Swelling (oedema): this is common in the legs, ankles, feet and sometimes the face or hands, due to fluid retention.
- Foamy urine: this can be a sign of too much protein in the urine.
- High blood pressure.
- Blood in the urine (haematuria): this may be visible or only detectable with a lab test.
- Less frequent urination or reduced urine output in severe cases.

General symptoms of lupus can include fatigue, joint pain, muscle aches, fever and a butterfly-shaped rash on the face (2).

How many people have the condition

SLE affects approximately 97 per 100,000 people in the UK, based on 2012 data, with a trend of increasing prevalence (3). It is estimated that the prevalence of SLE in England and Wales is around 60,000 people (3). Of those with SLE, up to 60% will develop LN at some point during their illness (4). This means tens of thousands of people in the UK are affected by LN. LN is more common in women than men, and it is mostly diagnosed in individuals between the ages of 20 and 40 (5). It is also more prevalent and often more severe in people of African, Hispanic, and Asian descent (6).

Burden of disease

LN can range from mild to severe. If not treated effectively, it can lead to chronic kidney disease (CKD) and, in about 10-30% of cases, progress to end-stage renal disease (ESRD), requiring dialysis or a kidney transplant (1). Even with treatment, many patients experience flares (periods of increased disease activity) or ongoing kidney damage (1).

Managing LN often involves long-term treatment with potent medications that suppress the immune system. These treatments can have side effects, and patients often need regular monitoring of their kidney function. The unpredictable nature of flares and the potential for serious complications can significantly impact a patient's daily life, work and social activities, leading to considerable clinical and economic burdens (8, 9).

Emotional effects

Living with LN can have a profound emotional impact. The chronic nature of the disease, the unpredictable flares and the potential for serious health complications like kidney failure can lead to significant anxiety, stress and depression. Studies show that anxiety and depression are very common in patients with LN, with a recent study reporting anxiety in 38% and depression in 50% of LN patients (7). Patients may experience feelings of helplessness, frustration and worry about their future health. The side effects of medications, such as weight gain or hair loss, can also affect self-esteem and body image. Regular doctor visits and treatments can disrupt routines, leading to feelings of isolation (8). Support from family, friends and patient groups are important in managing the emotional burden of the disease.

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?

If LN is suspected, a doctor will first order blood and urine tests (9).

Urine tests look for:

- Protein in urine: a key sign of kidney damage.
- Blood in urine: even if not visible by eye.
- Red blood cell casts: clumps of cells indicating kidney inflammation.

Blood tests check:

- Kidney function: levels of waste products like creatinine.
- Autoantibodies: antibodies that attack the kidneys.
- Complement levels: low levels of C3 and C4 are suggestive of LN.

If results from the urine and blood tests suggest that a patient may have LN, a diagnosis is confirmed with a kidney biopsy (9). This where a piece of tissue is taken from the kidneys and examined under a microscope by a specialist. The specialist then classifies the type of LN (e.g., Class I-VI) (9). Classification of LN is important because it guides treatment

decisions; Roche intends for obinutuzumab to be used in patients with Class III or Class IV LN, who may or may not also have some features of Class V LN.

After diagnosis and starting treatment, blood and urine tests are used to monitor kidney function and see if the treatment is working (9).

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.

1. 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.

There is currently no cure for LN. The main goal of treatment is to protect the kidneys and keep them working well for as long as possible. Generally, patients with Class III or Class IV LN benefit most from treatment.

Treatment happens in two stages:

- Induction treatment aims to get kidney inflammation under control and put the disease into remission (a period where the disease is not active).
- Maintenance treatment aims to keep the disease in remission.

Induction treatment

When a patient is first diagnosed with active LN, doctors usually start with a combination of a steroid and an immunosuppressant. Sometimes, a third drug is added; this is known as "triple therapy":

- Steroids (such as prednisolone): these powerful anti-inflammatory drugs reduce inflammation and calm the immune system. The starting dose is typically high and it is slowly reduced as the patient gets better. Keeping the dose low helps reduce side effects such as weight gain, mood changes and a higher risk of infections.
- Immunosuppressants: these drugs specifically dampen the overactive immune system. MMF is usually the first choice. Cyclophosphamide (CYC) is often used for more severe cases but can have more serious side effects, including affecting fertility. Azathioprine (AZA) is a safer option than MMF or CYC if a patient is planning to get pregnant.
- Targeted drugs: these medications specifically interfere with the immune system processes that cause lupus to attack the kidneys. Examples include voclosporin/tacrolimus (calcineurin inhibitors) and belimumab (BAFF inhibitor).

If the induction treatment does not fully control the disease, or if the disease comes back (relapses), doctors will consider other options. This decision is often made by a team of

specialists, including kidney doctors (nephrologists) and lupus specialists (rheumatologists). They might switch the immunosuppressant or targeted drug.

Maintenance treatment

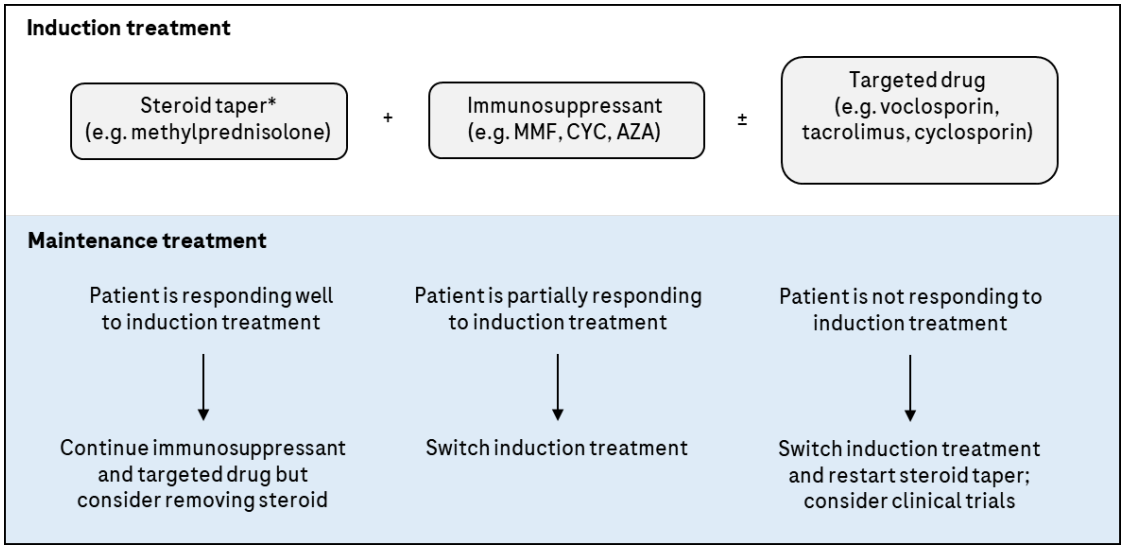
Once a patient responds well to induction treatment, they will continue to receive the immunosuppressant and targeted drug. Some patients will eventually stop steroids completely, while others will continue taking low doses long-term.

How obinutuzumab fits in

Obinutuzumab is a drug designed to target and remove specific immune cells called CD20-positive B-cells. These B-cells are key drivers of the inflammation and kidney damage seen in LN. Because of this, obinutuzumab is intended to be used as another targeted drug in combination with steroids and MMF. Medical experts in the UK agree with this approach (10), and upcoming guidelines from the British Society for Rheumatology (BSR) recommend use of obinutuzumab in combination with MMF and steroids as part of the triple therapy (11).

UK clinicians treat patients with LN according to published guidelines and local guidelines. The current treatment pathway for Class III/IV ± V LN in the UK is summarised below (Figure 1).

Figure 1: UK treatment pathway for Class III/IV ± V LN



Key: *the initial dose of steroid is based on body weight and is reduced gradually.

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.

Many studies have looked at the experiences of patients with SLE, but less research has been done on how LN affects the quality of life of patients and their caregivers. This section discusses data from several sources, including a European study from 2020 of 4,375 SLE patients (782 with LN) (12), a UK online survey of SLE patients (13), and a review of literature on quality-of-life, fatigue, and health issues in LN patients (14).

- **Physical symptoms**: Patients with LN often experience many physical symptoms, with fatigue being the most troubling (12-14). Other common symptoms include joint pain, muscle pain, stiffness and trouble sleeping (14). On average, patients with LN report more symptoms than SLE patients who do not have LN (12). Additional symptoms more common in LN patients include kidney issues, high blood pressure, haematological problems, shortness of breath, osteoporosis and hair loss (12).These symptoms can be unpredictable and hard to distinguish from those caused by SLE or its medications (15).
- **Psychosocial and emotional impact**: LN greatly affects patients' emotional health and social life. Many struggle with their diagnosis, sometimes facing delays from weeks to years (15). Patients often lack understanding of LN before diagnosis, making it hard for them to grasp the illness (15). Social exclusion and misunderstandings from friends and family may lead some to hide their condition to avoid stigma. Unpredictable symptoms can worsen their mental health (15). A recent study found higher rates of anxiety and depression in LN patients (38% and 50%, respectively) compared to those with non-LN SLE (28% and 30%, respectively) (7).
- **Impact on health-related quality-of-life (HRQoL)**: LN negatively impacts HRQoL, with LN patients showing worse HRQoL and more fatigue compared to healthy people (14). It affects all aspects of the 36-item SF-36 health survey, especially general health, physical functioning, and physical roles (14). Patients with severe or long-term LN, active disease, or particularly poor kidney function typically experience worse HRQoL (14).
- **Treatment burden and preferences**: Managing LN requires adjusting to new medications and dealing with often debilitating side effects (15). These side effects are the main factor in choosing medications. Frequent healthcare appointments and tests are time-consuming. Patients wish for more awareness and understanding of LN (15). In addition, patients with LN may have to take a high number of pills every day, which is an inconvenience that can lead to patients not taking their medicines as prescribed (16-18).
- **Caregiver burden**: LN also significantly impacts caregivers, who often neglect their social activities due to caregiving responsibilities (13). Many report reduced household income and extra expenses from the patient's illness, along with missed work (13). Caregivers provide emotional support and help with daily tasks (13).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

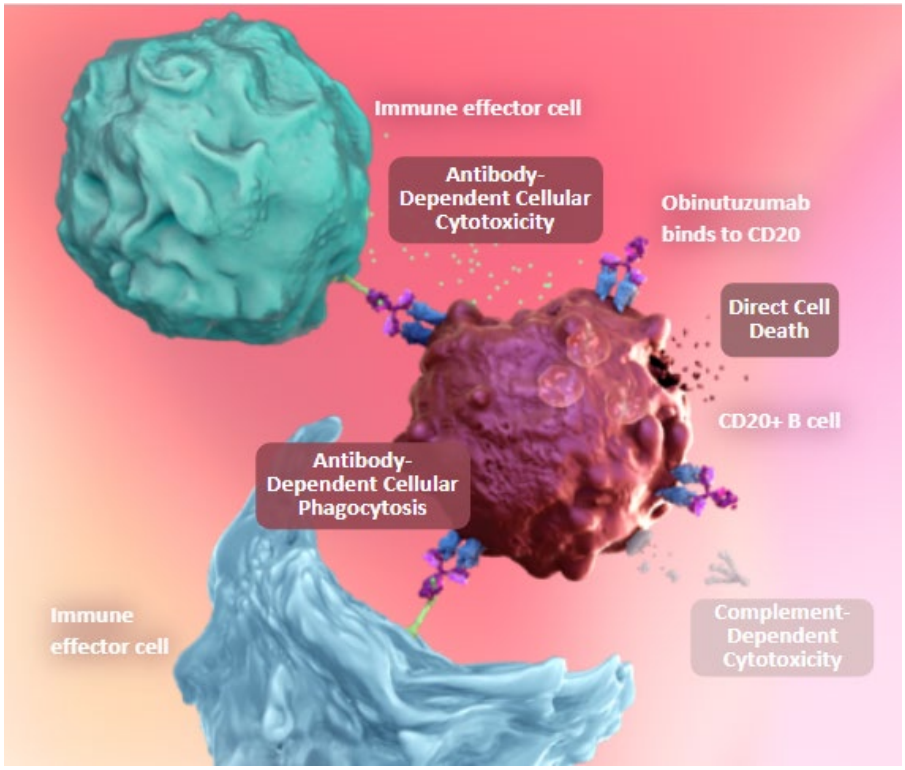
Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

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.

Obinutuzumab is a monoclonal antibody designed to target a protein called CD20 on the surface of B-cells. B-cells are a type of white blood cell. As part of the immune system, they produce antibodies. When you have an autoimmune condition, these antibodies mistakenly attack your own body. By binding to CD20 on B-cells, obinutuzumab prompts the destruction of B-cells, which is beneficial in treating LN. This mechanism helps reduce the immune system's attack on the kidneys, which is a characteristic of LN. The action of obinutuzumab is crucial in managing LN, especially when conventional treatments are not effective. See Figure 2 for an illustrated diagram showing how obinutuzumab works on B-cells.

Figure 2: How obinutuzumab works



Source: (19)

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes

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.

Obinutuzumab is to be used alongside standard therapy in patients with LN to enhance treatment effectiveness. By targeting and reducing B-cells, obinutuzumab helps decrease the immune attack on the kidneys, improving disease control and preventing further damage (19).

Standard LN therapy includes immunosuppressants and steroids to suppress the immune response and reduce inflammation. Obinutuzumab complements these treatments by specifically destroying B-cells, thereby reducing autoimmune activity.

Combining obinutuzumab with standard therapy has been shown in clinical trials to improve patient outcomes and reduced disease activity (20). Common side effects include infusion-related reactions, low blood cell counts (neutropenia) and infections, which are managed through careful monitoring and supportive care (20).

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?

Patients will receive obinutuzumab alongside standard therapy for LN under the supervision of a doctor experienced in treating autoimmune conditions, typically in a hospital setting.

Pre-medication

Shortly before obinutuzumab is given, patients will be given other medicines (pre-medication) to reduce the chance of having a reaction to obinutuzumab:

- Methylprednisolone (a steroid)
- Paracetamol (to reduce fever and relieve pain)
- Diphenhydramine (an antihistamine)

How much and how often obinutuzumab will be given

Patients will receive a fixed dose of 1000 mg obinutuzumab on Day 1 and at Weeks 2, 24, 26 and 52. Obinutuzumab is given as a drip into a vein (intravenous [IV] infusion). The time required for infusion will depend on how the patient responds to the treatment. After Week 52, obinutuzumab will be given at intervals of six months.

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.

NOBILITY (NCT02550652):
In the phase II NOBILITY study, the effectiveness and safety of obinutuzumab plus MMF were first tested in patients with LN. The study found that the combination was effective in reducing disease activity and was generally well tolerated. It established the dosing schedule of obinutuzumab used in the subsequent phase III study. The data were published in a peer-reviewed medical journal (21).

REGENCY (NCT04221477):
The phase III REGENCY study is a global study testing the effectiveness and safety of obinutuzumab in combination with MMF, compared to a placebo in combination with MMF, in patients with active LN. A total of 271 patients participated in the study, with 135 patients receiving obinutuzumab plus MMF and 136 patients receiving placebo plus MMF. The main objective (primary endpoint) of the study was the proportion of patients achieving a complete renal response (CRR) at Week 76. Data collected in August 2024 showed that patients receiving obinutuzumab plus MMF in the REGENCY study had higher rates of CRR compared to those receiving placebo plus MMF. These data were recently published in a peer-reviewed medical journal (22).

Further information on the REGENCY study is available on the ClinicalTrials.gov website: https://www.clinicaltrials.gov/study/NCT04221477.

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.

The REGENCY and NOBILITY studies assessed whether the obinutuzumab combined with standard therapy works better than a placebo with standard therapy for patients with active LN (21, 22). The main goal of the studies was to measure CRR, which is a marker of improved kidney health, such as better kidney function and less protein leakage into the urine (proteinuria). Both studies showed that obinutuzumab was more effective than the placebo.

- In the REGENCY study, by Week 76, 46% of the patients who received obinutuzumab achieved CRR, compared to 33% of patients who received the placebo.
- In the NOBILITY study, by Week 52, 35% of the obinutuzumab group achieved CRR, compared to 23% of the placebo group.

These results were statistically significant.

Both studies also confirmed that obinutuzumab significantly reduces the number of CD19+ B-cells in the blood (20, 23). For example, in the REGENCY study:

- By Week 4, 99% of patients on obinutuzumab had nearly no detectable B-cells left.
- Even at Week 76, 95% of patients on obinutuzumab still had long-term depletion of these B-cells.

This deep and lasting reduction in B-cells is consistent with prior studies in non-human primates and humans (20, 24, 25). B-cell depletion is believed to improve kidney health and may help protect kidney function in the long term for patients with LN.

In summary, these studies highlight the potential of obinutuzumab, when added to standard therapy, to provide significant benefits for patients with active LN.

To allow comparisons versus treatments not included in REGENCY, such as voclosporin and rituximab, an indirect treatment comparison was conducted. The indirect treatment comparison showed numerically higher response rates compared with MMF, but largely showed no statistically significant differences between treatments.

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.

The Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale is a 13-item measure used to assess patient-reported fatigue and its impact on daily activities and functioning. The scale is specifically designed to evaluate fatigue related to chronic illness.

The items on the FACIT-F scale cover various aspects of fatigue, including its severity, how it affects physical, social and emotional well-being, and its impact on the ability to carry out everyday tasks. Each item is scored, and the scores are added to give a total score. Higher scores indicate less fatigue, while lower scores indicate greater fatigue.

In the REGENCY study, patients were asked to complete the FACIT-F questionnaire at the beginning of treatment and after 76 weeks. Because of the statistical methods used in the study, it was not possible to say there was a statistically significant difference in levels of fatigue between obinutuzumab and placebo at week 76 (22).

Patients were also asked to complete the EQ-5D-5L health status questionnaire. Data from this questionnaire was used for economic modelling purposes.

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.

Each medicine has its own side effects, and the same medicine can produce different reactions in different people.

The REGENCY study evaluated the safety in patients who received at least one dose of obinutuzumab or placebo. The data can be summarised as follows:

- More patients who received obinutuzumab experienced side effects compared with those who received placebo.
- The most common side effects (≥ 30% of patients in either group) included a high percentage of non-serious adverse events such as infections and events related to COVID-19.
- Serious adverse events occurred in 32.4% of patients treated with obinutuzumab, compared with 18.2% in the placebo group.
- Deaths occurred in 2.2% of patients treated with obinutuzumab and 0.8% of patients treated with placebo.
- No patients discontinued the study due to adverse events.

The high number of infections among patients receiving obinutuzumab in the REGENCY study is likely due to the study taking place during the COVID-19 pandemic. In contrast, the phase II NOBILITY study, conducted before the pandemic, showed that obinutuzumab had fewer serious side effects, serious infections, and deaths compared to placebo. It is important to note that the overall dose of obinutuzumab in the NOBILITY study was lower than in the REGENCY study.

Overall, the REGENCY study concluded that while more serious adverse events were identified with obinutuzumab compared to placebo, the safety profile of obinutuzumab was considered manageable with no unexpected safety signals reported (22).

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

Obinutuzumab is a disease-modifying treatment that is designed to be administered alongside standard therapy. Obinutuzumab is expected to be positioned alongside current treatments for LN.

Obinutuzumab is effective and well tolerated in patients

The REGENCY study confirmed that obinutuzumab is effective and well tolerated in patients with active LN. The study demonstrated that obinutuzumab combined with standard therapy significantly increased renal response rates in the overall patient population compared to standard therapy alone. The effectiveness of obinutuzumab is thought to be linked to its strong and lasting ability to deplete B-cells. The safety profile of obinutuzumab in the whole patient population was manageable and consistent with the known risks of the individual study drugs.

Obinutuzumab has a convenient mode and frequency of administration

Non-adherence is a significant obstacle in achieving favourable clinical outcomes for patients with LN. Obinutuzumab is given intravenously, so it does not contribute to the pill burden already faced by patients. After the initial doses, obinutuzumab needs to be administered only every six months. This convenience is expected to enhance adherence and result in improved clinical outcomes for patients.

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

Clinical studies show that roughly 50% to 60% of patients respond to the treatment, and about 40% to 50% experience a complete response. Unfortunately, it is not possible to predict whether a patient will respond to obinutuzumab when their doctor decides to use it (20).

Most side effects of obinutuzumab are mild. A small number of patients may have a reaction to the infusion, but these reactions are usually mild, tend to happen after the first infusion, and can be managed effectively by doctors (20). Obinutuzumab also carries a risk of neutropenia (a low level of white blood cells). Proper monitoring and management by doctors are essential to address this risk (20).

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.

How the model reflects the condition

- The economic base case presented in this submission is based on an analysis assessing the use of obinutuzumab with standard therapy compared with standard therapy alone for the treatment of adult patients with LN.
- The approach taken to model costs and health benefits is done by splitting patients into nine different health states relating to CKD stages and response outcomes: CKD Stage 1-3b active disease, partial response and complete response, CKD Stage 4 active disease, partial response and complete response, CKD Stage 5 Dialysis and CKD Stage 5 Transplant, and death. This is consistent with the approach used in the previous NICE TA882 appraisal.
- The data used to predict how long patients receiving each treatment would remain in each health state, which informs the amount of costs and health benefits they would accrue, is based on data from the REGENCY study for obinutuzumab and MMF and an indirect treatment comparison to compare against treatments not included in the REGENCY study, including voclosporin and rituximab.

Modelling how much a treatment extends life

- Based on the economic modelling, it is predicted that people with LN treated with obinutuzumab will live longer than those treated with MMF. These gains mostly occur from delaying disease progression through CKD stages towards end-stage renal disease.

Modelling how much a treatment improves quality of life

- Quality of life in the economic model is determined by the health state a patient is in. The quality-of-life values assigned to each health state are based on the values previously used in the TA882 NICE submission, ultimately informed by AURORA-2 and the literature.
- EQ-5D data collected in REGENCY was deemed to lack face validity, as worse active disease health states were associated with better quality-of-life scores and better response health states were associated with worse quality-of-life scores.
- With TA882 utility values, quality of life improvements are achieved if a patient with LN continues to respond to treatment and patients avoid progression to CKD Stages 4 and 5.
- TA882 health-state utility values are applied consistently to all treatments included in the economic analysis.
- The majority of benefits come from the Stage 1-3b health states for all treatments, particularly complete response and active disease health states.

Modelling how the costs of treatment differ with the new treatment

- Overall, the total costs of treatment related to obinutuzumab are expected to be greater than that of MMF alone. This is driven by increased treatment costs

associated with triple therapy. However, the total costs of treatment related to obinutuzumab are expected to be lower than that of MMF alone, voclosporin and rituximab treatments.

- A benefit of obinutuzumab is that, due to better short-term clinical outcomes compared with MMF alone, obinutuzumab is likely to reduce healthcare spending on treatments associated with downstream CKD stages and end-stage renal disease such as dialysis and transplant.
- Most costs for triple therapy regimens are associated with the add-on treatment. For all treatment regimens included in the model, resource use costs associated with dialysis and transplants contribute to a large amount of the total costs.

Uncertainty

- Due to limited trial follow-up, there is some uncertainty regarding the efficacy estimates included within the economic model, although this is a common obstacle with clinical trial evidence.
- The economic analysis included assumptions that attempted to capture the difference in short-term endpoints on long-term outcomes for each treatment. There remains uncertainty regarding the true impact, but scenario analyses assess the potential differences to give a range of possible outcomes that attempt to capture and quantify uncertainty. Generally, adjusting these assumptions in the economic analysis does not change the overall cost-effectiveness conclusion.

Cost-effectiveness results

- In the company's base-case analysis, obinutuzumab with MMF is predicted to provide more QALYs for more cost when compared with MMF alone. Company cost-effectiveness results suggest that obinutuzumab would be a cost-effective treatment option compared with MMF alone. When compared with voclosporin with MMF and rituximab with MMF at list prices, company base case results suggest that obinutuzumab with MMF provides more QALYs for less costs, suggesting obinutuzumab with MMF is the dominant triple therapy regimen. These results do not take into account any confidential commercial discounts for the comparator treatments, or the committee's preferred assumptions which may differ to those applied in the company base-case analysis.

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)

Obinutuzumab has some advantages over another anti-CD20 antibody that is sometimes used to treat LN, known as rituximab. Both treatments target B-cells, but they work in different ways:

- **Killing of B-cells**: obinutuzumab is designed to kill B-cells more effectively. This means it can more directly and powerfully target the cells that contribute to the disease.
- **Independent Mechanism**: obinutuzumab does not rely as much on other parts of the immune system to kill B-cells. It can induce cell death on its own, making it potentially more efficient.

The unique features of obinutuzumab make it a novel and promising treatment option for LN, offering potential advantages in clinical effectiveness and patient outcomes.

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

There should be no equality issues in accessing this treatment. Obinutuzumab should be available in any rheumatology or nephrology treatment unit if it is recommended by NICE and the centre in question is commissioned by the NHS to prescribe it.

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.

Patient groups and charities:

- Lupus UK
- Kidney Care UK
- Kidney Research UK
- National Kidney Federation

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

Term	Acronym	Description
Adverse event		An unexpected medical problem that arises during treatment with a drug or other therapy. They may be mild, moderate or severe.
Antibody	-	A protein that plays an important role in the immune system. Each antibody is unique and recognises a specific part of a germ or other invader. Antibodies can be custom designed for use as drugs.
Biopsy	-	A process in which a very small part of tissue in the body is removed to look for signs of disease.
B-cells/B-lymphocytes	-	A type of white blood cell that plays a key role in the immune system. B-lymphocytes are responsible for producing antibodies, which are proteins that help the body identify and neutralise foreign substances such as bacteria and viruses.
CD20	-	A protein on the surface of B-cells that is the target of obinutuzumab.
Chronic kidney disease	CKD	A long-term condition where the kidneys are damaged and cannot filter blood as well as they should, leading to a build-up of waste and extra fluid in the body.
Clinical trial	-	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention,

		diagnosis, or treatment of a disease. Also called clinical study.
Complete renal response	CRR	A complete disappearance of all signs and symptoms of cancer after treatment. It indicates that no cancer cells can be detected by any of the tests used for the diagnosis of the specific type of cancer that the patient had.
End-stage renal disease	ESRD	A serious condition where the kidneys have permanently lost the ability to function properly, meaning they can no longer filter waste and excess fluid from the blood.
Fatigue		Tiredness or exhaustion
Flare	-	A worsening of lupus nephritis activity, particularly affecting the kidneys, leading to increased inflammation and damage.
Immune system	-	A complex network of cells, tissues, organs, and the substances they make that helps the body fight infections and other diseases.
Immunosuppressive therapy	-	A medicine that reduces the activity of the immune system
Medicines and Healthcare products Regulatory Agency	MHRA	A UK government agency responsible for ensuring that medicines, medical devices and blood components for transfusion meet applicable standards of safety, quality and efficacy.
Mycophenolate mofetil	MMF	A drug that is used to treat lupus nephritis by suppressing the activity of the immune system.
Monoclonal antibody	-	Man-made molecules that mimic the immune system's ability to fight off harmful pathogens, such as viruses or cancer cells. They are designed to target specific proteins on the surface of cells and act as a "lock and key" mechanism to bind to these proteins and trigger an immune response to destroy the cells. Monoclonal antibodies are used in the treatment of various medical conditions, including cancer, autoimmune disorders, and infectious diseases.
Overall response rate	ORR	A measure of the proportion of patients in a clinical trial or other study who experience a significant reduction in the size of their tumour or other disease.
Prognosis	-	A medical term that refers to the likely course or outcome of a disease or condition. It is an estimate of how the disease will progress in an individual patient, based on factors such as the patient's age,

		medical history, severity of the disease, and response to treatment.
Quality of life	QoL	The overall enjoyment of life. Many clinical trials assess the effects of cancer and its treatment on the quality of life. These studies measure aspects of an individual's sense of well-being and ability to carry out activities of daily living.
Steroids	-	Powerful drugs that reduce the activity of the immune system by affecting the function of white blood cells. They help to reduce damage to the kidneys in patients with lupus nephritis.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Obinutuzumab with immunosuppressive therapies for treating lupus nephritis [ID6420]

Company response to clarification questions

September 2025

File name	Version	Contains confidential information	Date
ID6420_Obinutuzumab_Clarification_Response_[noCON]_01092025	V1.0	Yes	01/09/2025

Section A: Clarification on effectiveness data

A1. PRIORITY: Can the company please provide further rationale on why cyclophosphamide, tacrolimus, cyclosporin, and belimumab + MMF were not included in the decision problem as comparators to obinutuzumab despite being included as comparators in the NICE scope.

a) **Specifically, could the company please provide any real-world UK evidence to support the company's medical expert opinion as reported in section 3.2.3 of the company submission (CS) that these comparators are not relevant in current NHS practice?**

The most relevant comparators for this appraisal were discussed at length with UK clinical experts. As detailed in Section 3.2.3 of the CS (1), several comparators within the NICE scope were identified as having limited relevance to UK clinical practice. This was based on three key reasons:

- Limited clinical use: Medical experts advised that these treatments are rarely used in the UK.
- UK-specific data: Their exclusion was based on limited publicly available UK data.
- Comparative effectiveness data: Lack of sufficient comparative data or a connected network for cost-effectiveness analysis against some comparators.

To supplement this rationale, the Company provides further detail on each of the mentioned comparators below.

The decision not to compare against tacrolimus or cyclosporin (with or without MMF) based on advice given by medical experts is further substantiated by recent UK clinical practice data. In a published survey of UK rheumatologists and nephrologists, zero respondents (from n=77) used these calcineurin inhibitors (CNIs) as first-line therapy for LN (either alone or in combination), reserving use for non-responding patients only (2). This also aligns with the information included in the resource impact report for voclosporin (VOC) (TA882), which estimates tacrolimus usage at 1%, and does not include cyclosporin (3). Thus, given VOC is the most relevant CNI, with a more favourable side-effect profile than tacrolimus, the Company maintains

that comparisons against either tacrolimus or cyclosporin would offer no additional value.

The decision not to compare with cyclophosphamide was based on several contributing factors outlined in CS Section 3.2.3. To further support this, real-world evidence of its clinical use in the UK is markedly lower than the immediate alternative of MMF (2, 3). Significantly, the updated BSR guidelines recommend it as a 'second choice' behind combination regimens with MMF. It is also widely published in head-to-head studies and meta-analyses that cyclophosphamide has an equivalent efficacy to MMF, but with a poorer adverse event profile (4-6). Given that MMF is used more widely in UK clinical practice, equivalent in efficacy with a better safety profile, and provides a more robust, less uncertain network for comparison, the Company maintains that a comparison with cyclophosphamide would be of limited relevance.

Finally, the decision not to include belimumab (BEL) as a comparator can be substantiated by its limited use in the UK for the treatment of LN (2), lack of NICE recommendation in this indication and absence from the decision problem of other relevant appraisals (TA882). The Company argues that the proportion of patients treated with BEL for LN were initiated treatment for SLE prior to renal involvement. However, in response to question B1, and in the interest of completeness and to reduce uncertainty, the Company has provided an updated cost-effective analysis comparing OBI+MMF with BEL+MMF (see response to question B1). However, the Company still questions the relevance of a comparison to a treatment not recommended for reimbursement for the target indication.

b) **Could the company please provide any further details on the process by which these medical experts were identified and selected, their clinical speciality, their role within the NHS (if applicable) and any conflicts of interest? Given the known variations in practice across the UK, regional locations would also be useful.**

The medical experts consulted by the Company were carefully selected to provide a comprehensive view of LN management in the UK. The selection process focused on clinical and academic leadership, professional diversity and national representation.

The Company prioritised individuals with deep expertise in either nephrology or rheumatology, reflecting the multifaceted nature of LN. The selected experts hold senior positions at top UK institutions and are widely recognised as national or international leaders in their fields. Their extensive experience is demonstrated through their roles in major clinical trials including REGENCY, contributions to clinical guidelines, and leadership positions in renal or rheumatology societies.

In addition to four consultant nephrologists and five consultant rheumatologists (of which two-thirds are contributors to the British Isles Lupus Assessment Group Biologics Register [BILAG-BR], which is a UK-based prospective register of patients on biologic or biosimilar treatment for SLE), the Company consulted a renal clinical nurse specialist and a specialist rheumatology pharmacist. These individuals provided valuable insights into patient care from the perspectives of everyday management and practical drug implementation within the NHS. Furthermore, the Company ensured a broad geographical spread, with experts from major centres across England (Birmingham, Cambridge, Leeds, London, Manchester, Newcastle and Southampton), Wales and Scotland, to account for regional variations in clinical practice.

All medical experts consulted by the Company confirmed they had no conflicts of interest that would prevent their participation.

A2. PRIORITY: Please could the company provide baseline characteristics, efficacy and safety outcomes for the EU patients in REGENCY and NOBILITY and for the UK patients in REGENCY.

Baseline characteristics, including demographics, primary efficacy (complete renal response; CRR), and safety outcome data for the UK and EU patient subpopulations in REGENCY are provided as separate attachments to this response (*ID6420_CQ A2_Baseline Disease Characteristics_EU and UK Subpopulation_REGENCY_[CON], ID6420_CQ A2_Demographics_EU and UK Subpopulation_REGENCY_[CON], ID6420_CQ A2_Primary Efficacy CRR_EU and UK Subpopulation_REGENCY_[CON], ID6420_CQ A2_Safety Outcomes_EU and UK Subpopulation_REGENCY_[CON]*). The Company notes that the study was not powered for this patient subpopulation, and therefore any results being reported, including p-values, are descriptive only.

The Company has focussed on providing the UK/EU data from REGENCY as this is the pivotal data used within the submission. The similarity of population baseline characteristics and demographics between REGENCY and NOBILITY is high, as are efficacy results and safety profiles in general. Therefore, outcomes from the smaller EU subgroup within NOBILITY are unlikely to provide further insight here.

Baseline characteristics between the obinutuzumab (OBI) and placebo arms of the UK/EU subpopulation are generally comparable, and resemble the overall REGENCY patient group. The UK/EU subpopulation is predominantly female, with a White or Asian race background. For the primary endpoint of CRR, the proportion of patients achieving this at Week 76 was numerically greater in the OBI arm ([redacted]% [95% CI: [redacted]]) compared with the placebo arm ([redacted]% [95% CI: [redacted]), with an adjusted difference of [redacted]% (95% CI: [redacted]; nominal p-value=[redacted]). The safety outcomes from the EU/UK subpopulation were generally in-line with the full REGENCY safety-evaluable population, with similar numbers experiencing at least one AE in the OBI and placebo arms. There were also comparable numbers of infectious AEs between the 2 arms, whereas the OBI arm showed higher numbers of serious AEs, as seen in the full safety-evaluable population.

Based on this, the Company believes that the REGENCY study outcomes are relevant for the EU/UK patient subpopulation.

A3. PRIORITY: CS, Section 2.6.1.2 Primary efficacy endpoint: For the primary endpoint of CRR at 76 weeks, and additional endpoints of PRR the analysis provided by the company focused on absolute risk differences. Please could the company present ratio-based estimates alongside mean risk differences for CRR and PRR (along with confidence intervals in alignment with the CONSORT 2025 statement).

As requested, the Company has re-analysed the primary efficacy endpoint of CRR at 76 Weeks, altering the summary measure from difference in proportions to odds ratio. We have also provided an odds ratio outcome for the additional requested endpoint of PRR (with no CRR [a definition of PRR can be found in the REGENCY CSR Section 5.1.3.5 (7)]) at Week 76. These analyses are provided with this response (*ID6420_CQ A3_Odds Ratio CRR_Week 76_REGENCY_[CON*] and

ID6420_CQ A3_Odds Ratio PRR_Week 76_REGENCY_[CON]). Odds ratio is an appropriate method for analysing proportions in two treatment groups at a given time point. The Cochran-Mantel-Haenszel model using odds ratios allowed consistency with the primary analysis and adjustment for stratification factors, race and region, to calculate an adjusted odds ratio to compare the treatment effect of OBI versus placebo. Missing data was handled as done in the primary analyses (SAP Section 4.2.2) (8).

The outcomes from this ratio-based analysis of the REGENCY study are consistent with the conclusions from the primary analyses of CRR at Week 76, which showed a significant improvement in the OBI arm compared with the placebo arm (CS, Section 2.6.1.2 (1)). The adjusted odds ratio for patients in CRR at Week 76 was [redacted] (95% CI: [redacted]), with a nominal p-value of [redacted], suggesting patients receiving OBI + standard of care are [redacted] times more likely to achieve a CRR compared with patients receiving placebo + standard of care.

PRR (without CRR) was not analysed independently in REGENCY, but as part of a composite secondary endpoint of ORR at Week 50 (CS, Section 2.6.1.3.5 (1)). This showed a numerical improvement in ORR in the OBI arm compared with the placebo arm, without statistical significance. [redacted], for the requested ratio-based analysis of PRR (without CRR) at Week 76, the adjusted odds ratio was [redacted] (95% CI: [redacted]), with a nominal p-value of [redacted].

The Company acknowledges that presentation of the primary endpoint of CRR at Week 76 as both as absolute measure (such as adjusted risk difference) and as a relative measure (such as odds ratio) better aligns with the CONSORT 2025 guidance, providing a more comprehensive understanding of the REGENCY primary efficacy outcome.

A4. Both the REGENCY and NOBILITY trials excluded paediatric patients under 18 years. However, the population described in the NICE scope is ‘people with lupus nephritis’ with no age restriction. We are aware that the scope presented by the company aligns with the proposed indication for marketing authorisation. However, could the company please comment on the implications of excluding the paediatric

population, specifically adolescents (12 years to less than 18 years), from the submission?

The EAG is correct in their observation that neither NOBILITY nor REGENCY included paediatric patients (under 18 years of age). Therefore, it would be inappropriate for the Company to make a submission including that patient population without supporting data, irrespective of the final NICE scope.

Nevertheless, the Company has not excluded the paediatric population from the OBI investigation plan and is currently conducting a phase 2 study of OBI in LN, namely the POSTERITY study (NCT05039619), which includes UK sites.

The objective is to evaluate the safety, efficacy and pharmacokinetics (PK) of OBI in adolescent participants aged 12 to less than 18 years old with biopsy-confirmed proliferative LN. It will also evaluate open label safety and PK of OBI in paediatric participants, aged 5 to <12 with LN.

A5. Could the company please comment on the implications of excluding people with Class V lupus nephritis alone from the submission?

The REGENCY study was undertaken to confirm the results observed in NOBILITY and provide long-term data to inform the use of OBI in proliferative LN. In NOBILITY, the population studied was patients with ISN/RPS Class III or IV LN with active inflammatory processes as evidenced by a renal biopsy. Class III and IV LN was selected because these patients have proliferative disease, which has a poor prognosis and requires significant immunosuppressive therapy. Patients with Class V LN were allowed protocol entry if the Class V membranous nephritis was detected on a renal biopsy and concurrent with Class III or IV disease.

The rationale for exclusion of pure Class V LN from NOBILITY, and hence REGENCY, was based on the clinical distinctions of the different classes of LN. Pure class V (or membranous) LN is characterised by significant proteinuria, often in the nephrotic range, with normal or only slightly elevated kidney function, and is caused by subepithelial immune complex deposits on thickened glomerular basement membranes. In contrast, class III or IV LN involves proliferative lesions such as endocapillary hypercellularity and subendothelial deposits, leading to more active urine sediments, likely kidney impairment, and a more severe prognosis requiring

prompt immunosuppressive treatment (9). This distinction between classes (III and IV or V) is also represented in treatment guidelines (KDIGO and BSR) where independent recommendations are made for treating active or proliferative class III or IV LNs compared with non-proliferative class V LN which can often be treated more conservatively (or specifically in cases with severe proteinuria where there is a preference for CNIs) (10, 11).

Given this distinction between classes, the differences in guideline treatment recommendations, and particularly the exclusion of patients with pure class V LN from REGENCY and NOBILITY, it would be inappropriate to include people with Class V LN alone in the submission. This was confirmed to be clinically appropriate with medical experts (12) and aligns with our proposed MA which was recommended to follow the REGENCY study population by regulatory authorities.

A6. CS, Section 2.6.1.2 Primary efficacy endpoint: What was the mean follow-up time for the primary efficacy analysis of REGENCY?

The primary efficacy endpoint of CRR in REGENCY, was performed at week 76 utilising the efficacy-evaluable patient population and corresponds to a landmark analysis. Of the 271 patients within this group, 242 completed their Week 76 visit and had similar follow-up (within the confines of the Week 76 visit window [detailed in the response to question A7]). CRR is a composite endpoint derived using multiple sources of information, with any missing data imputed as outlined in Section 4.2.2 of the REGENCY SAP (8); this was only required for 5 patients completing the Week 76 visit. Those patients who withdrew early from the study (13 in the OBI arm and 16 in the placebo arm) were classified as non-responders at Week 76 using a composite strategy to handle the intercurrent event of early withdrawal (SAP section 4.2.1.1 (8)). As these patients would never achieve a response, complete knowledge of their response status was therefore assumed, and they were assigned 76 weeks of follow-up. Given this, calculating the mean follow-up time for this analysis provides no additional value or information.

A7. CS, Section 2.6.1.3.10 Time to onset of CRR over the course of 76 weeks: What population was used for this analysis? What was the mean follow-up time of the population used for this analysis considering [redacted]?

As per the REGENCY CSR, section 5.1.4.4; including Table 33 and Figure 6 (8), the endpoint of Time to onset of CRR over the course of 76 weeks was evaluated using the 'efficacy-evaluable population'. Time to onset of CRR is defined as the time from randomisation to the achievement of CRR, however, this is tied to scheduled assessments. It can therefore only be recorded at Week 24, 50, or within the Week 76 window as per protocol analysis. For reference the Week 76 visit window (SAP, section 4) has an upper limit of 3 days prior to the next OBI or placebo infusion or 30 days beyond Week 76 whichever is shorter. As outlined in SAP Section 4.3.2.4, if CRR is not achieved by a patient within 76 weeks, or an intercurrent event occurs before achieving CRR, the data are censored at Week 76.

For the analysis of time to onset of CRR, the Kaplan-Meier method was used (see REGENCY CSR, section 5.1.4.4 Figure 6 (7)), allowing the median (but not mean) time to event to be estimated. The parameters of the Week 76 window and the limited data time points involved likely lead to the [redacted]. In reality, the median time to onset of CRR may be [redacted]; however, the scheduling of data collection does not allow exploration of this possibility.

A8. CS, Section 2.8 Subgroup analysis; Figure 7: Can the company please comment on the presence of large and statistically significant differences in the gender subgroups for CRR risk differences?

Gender (male or female) was a pre-specified subgroup analysis of the primary endpoint of CRR in REGENCY (detailed in Section 5.1.2.3 of the CSR) (7). As such, all analyses are exploratory in nature and must be interpreted with caution. Particularly when there is a small sample size (as seen in the male subgroup), and thus no statistical significance can be attributed.

The observed difference in CRR between the male and female subgroups was driven by a [redacted] proportion of responders in the [redacted] arm of the [redacted]([redacted]% [n =21]), resulting in an overall [redacted] adjusted difference

for CRR ([redacted]% [95% CI: [redacted]], n=42). This is [redacted] the adjusted difference for CRR observed in the [redacted] of [redacted]% (95% CI: [redacted], n=229). It is important to note that the proportion of responders in the OBI arms of the male and female subgroups were [redacted] ([redacted]% [n=21] and [redacted]% [n=114], respectively). While the CRR rate in the [redacted] was [redacted], it is difficult to account for this; it may be a chance finding due to the [redacted] in the study. Given this, the Company considers it inappropriate to segment these data any further as no meaningful conclusions may be drawn.

A9. CS, Section 2.4.1 REGENCY, Table 8: Can the company please clarify the difference between the “Randomised population” and the “Efficacy evaluable population”? Can the “Efficacy evaluable population” be considered equivalent to an intention-to-treat (ITT) population?

As per the REGENCY CSR (7), Section 3.7.2, Table 2, the analysis populations for REGENCY are defined as:

- Randomised population: Includes all patients randomised into the study
- Efficacy-evaluable population: Includes all randomised patients regardless of whether they received the study drug. Patients are grouped according to randomised (assigned) treatment, rather than treatment received. Patients who received an incorrect therapy are reported under the treatment arm to which they were randomised

As stated in Section 4.5, the 271 patients randomised in the study (135 in the OBI arm and 136 in the placebo arm) comprise the efficacy-evaluable population. Based on these definitions, the efficacy-evaluable population in REGENCY could be considered equivalent to an ITT population (where participants are analysed based on the group they were initially assigned to, regardless of whether they actually received that treatment or adhered to the protocol).

A10. CS, Section 2.6.1.1 Study population and disposition for REGENCY: Please can the company clarify why 3 patients in the placebo group in the randomised

population were not treated and dropped from the analysis at baseline? How was this addressed in the statistical analysis plan?

As per the REGENCY CSR (7), Section 4.5, a total of 271 patients were randomised in the study (135 in the OBI arm and 136 in the placebo arm); these patients comprised the efficacy-evaluable population. From the placebo arm, three patients did not receive any study treatment after randomisation and were therefore excluded from the placebo safety-evaluable population (but were included within the placebo efficacy-evaluable population). The reasons captured as to why these three patients did not receive treatment are:

- One was lost to follow-up; never returned on Day 1 or for any other visits
- One was found to have tuberculosis on Day 1 and was never dosed
- One had a light cough on Day 1; an X-ray confirmed pneumonia, so the patient was never dosed

In terms of how this was addressed, the REGENCY SAP (8), Sections 3.1.2, and 3.1.3 detail how each evaluable population (efficacy or safety) are composed and analysed. For the efficacy-evaluable populations, patients are grouped here based on their 'assigned' treatment, rather than the treatment they received (or did not in the case of these three patients). The 3 patients here were therefore classified as non-responders due to their early withdrawal from the study following the defined composite strategy to handle this intercurrent event (SAP section 4.2.1.1) (8).

The safety-evaluable population does not include patients who did not receive any part of blinded infusion of OBI or placebo, and hence the three patients were excluded from these analyses.

Section B: Clarification on cost-effectiveness data

In response to Section B questions, the Company cost-effectiveness model has been updated. Therefore, the base case cost-effectiveness analysis has changed. Changes to base case assumptions that impact base case cost-effectiveness results include:

- The inclusion of belimumab as a comparator (affects subsequent treatment costs)

- The analysis now includes 3000 CODA samples, and the base case deterministic analysis takes the mean of these 3000

The Company also fixed an error in the estimation of base case probabilistic utility values. Utilities for OBI+MMF and MMF were being varied separately for each treatment arm when using the EAG approach from TA882 used in the base case. In some model runs this caused implausible results, so the values are varied once by health state then applied consistently to OBI+MMF and MMF.

B1. PRIORITY: CS Section 3.2.3: Clinical advisors to the EAG have highlighted the role of belimumab and MMF in the clinical pathway. We recognise that belimumab does not have an indication for LN and is therefore being used off-label; however, its use has been featured in the updated BSR 2025 guidelines which are expected to influence clinical practice (based on feedback from BSR, UKKA, and the clinicians consulted by the EAG). We wish to request that the company include belimumab + MMF as a comparator in the economic analysis using the evidence presented in the NMA as appropriate. In the absence of this comparator could the company further justify its absence from the economic analysis, especially compared to rituximab + MMF which is also used off-label in clinical practice?

As discussed in CS Section 3.2.3 (1), and as recognised in this question, BEL is not recommended for LN by NICE. BEL only has reimbursement in England in the SLE indication. It is the Company's understanding that the small proportion of patients expected to be receiving BEL for LN will have been initiated treatment prior to renal involvement when their condition could be classed as SLE. It is unlikely that patients are being treated with BEL once renal involvement has been confirmed and classed as LN.

However, for completeness and in the interest of reducing outstanding uncertainty, the Company has provided an updated cost-effectiveness analysis considering the cost-effectiveness of OBI versus BEL using the available published clinical evidence and ITC (CS Sections 2.9 and 2.10 (1)).

This comparison suggests that OBI+MMF offers incremental health benefits compared with BEL+MMF as the model predicts an additional [redacted] QALYs.

Considering the PAS price for OBI and list prices for BEL, treatment with OBI+MMF is associated with a cost-difference of [redacted] compared with BEL+MMF. So, cost-effectiveness results for this comparison suggest OBI+MMF dominates BEL+MMF. The incremental NMB and NHB at a willingness-to-pay threshold of £30,000 are shown to be £33,123 and 1.104, respectively, suggesting OBI+MMF is a cost-effective treatment option when compared with BEL+MMF for LN.

With the addition of BEL into the cost-effectiveness model, cost-effectiveness outcomes for OBI+MMF versus other comparators have also changed slightly. This is due to the inclusion of BEL as a subsequent therapy using consistent methodology as with other first-line therapies (OBI, MMF, VOC and RTX). Cost-effectiveness results in the updated cost-effectiveness model for OBI+MMF versus other treatments are presented below in Table 2 alongside originally submitted results for comparison in Table 1. The inclusion of BEL has reduced ICERs for OBI+MMF versus MMF, VOC+MMF and RTX+MMF as the proportion of subsequent BEL observed in REGENCY is higher in the MMF arm of REGENCY. The Company have also provided an updated threshold analysis in Table 3 varying the discount of VOC, RTX and now BEL.

However, as explained in response to question A1, the Company still question the relevance of a comparison to a treatment not recommended for reimbursement for the target indication. The Company argue that the proportion of patients treated with BEL for LN were initiated treatment for SLE prior to renal involvement. So, the decision not to include belimumab (BEL) as a comparator can be substantiated by its limited use in the UK for the treatment of LN specifically, a lack of a NICE recommendation and therefore reimbursement in this indication, and its absence from the decision problem of other relevant appraisals (i.e. TA882). In the interest of completeness and to reduce uncertainty, the Company has provided an updated cost-effective analysis comparing OBI+MMF with BEL+MMF, but the company believe the relevance of this comparison should be considered first.

Table 1: Originally submitted deterministic cost-effectiveness results – OBI+MMF versus comparators– OBI PAS price; comparators list price

	Tot Costs (£)	Tot LYs	Tot QALYs	Inc Costs (£)	Inc QALYs	ICER (£)	NMB 20k	NMB 30k	NHB 20k	NHB 30k
OBI + MMF	[redacted]	[redacted]	[redacted]							
MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,743	18,419	28,508	0.921	0.950
VOC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	31,132	35,407	1.557	1.180
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	42,981	50,349	2.149	1.678

Table 2: Updated deterministic cost-effectiveness results – OBI+MMF versus comparators (including BEL) – OBI PAS price; comparators list price

	Tot Costs (£)	Tot LYs	Tot QALYs	Inc Costs (£)	Inc QALYs	ICER (£)	NMB 20k	NMB 30k	NHB 20k	NHB 30k
OBI + MMF	[redacted]	[redacted]	[redacted]							
MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,454	18,714	28,804	0.936	0.960
VOC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	31,353	35,658	1.568	1.189
BEL_IV + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	31,147	33,123	1.557	1.104
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	42,777	50,002	2.139	1.667

Table 3: Threshold analysis at varying discount levels for VOC, RTX and BEL – NMB at WTP threshold of £30,000 – OBI PAS price

Discount rate	versus VOC+MMF			versus RTX+MMF			versus BEL+MMF		
	ICER	NMB	NHB	ICER	NMB	NHB	ICER	NMB	NHB
0%	Dominant	£35,658	1.19	Dominant	£50,002	1.67	Dominant	£33,123	1.10
10%	Dominant	£32,502	1.08	Dominant	£48,749	1.62	Dominant	£30,717	1.02
20%	Dominant	£29,346	0.98	Dominant	£47,495	1.58	Dominant	£28,311	0.94
30%	Dominant	£26,190	0.87	Dominant	£46,242	1.54	Dominant	£25,906	0.86
40%	Dominant	£23,034	0.77	Dominant	£44,988	1.50	Dominant	£23,500	0.78
50%	Dominant	£19,878	0.66	Dominant	£43,734	1.46	Dominant	£21,094	0.70

60%	Dominant	£16,722	0.56	Dominant	£42,481	1.42	Dominant	£18,689	0.62
70%	Dominant	£13,566	0.45	Dominant	£41,227	1.37	Dominant	£16,283	0.54
80%	5,817	£10,410	0.35	Dominant	£39,974	1.33	Dominant	£13,877	0.46
90%	13,148	£7,254	0.24	Dominant	£38,720	1.29	Dominant	£11,472	0.38
100%	20,479	£4,098	0.14	Dominant	£37,467	1.25	Dominant	£9,066	0.30
Key: BEL, belimumab; ICER, incremental cost-effectiveness ratio; MMF, mycophenolate mofetil; NHB, net health benefit; NMB, net monetary benefit; OBI, obinutuzumab; PAS, patient access scheme; RTX, rituximab; VOC, voclosporin.									

B2. PRIORITY: Economic model executable file: For the purposes of enhancing transparency could the company please add a “Parameters” sheet to the economic model executable file listing the risk, relative effectiveness, quality of life and cost parameters going into each Markov trace, along with the confidence intervals used in the deterministic analysis and the distributions used for the probabilistic analysis where applicable?

Please see the addition of the "*Parameters*" sheet in the updated version of the cost-effectiveness model.

B3. PRIORITY: CS Section 3.3.2 Health state transition probabilities: Besides the main assumption of the risk of progression to CKD stage 4, could the company please provide information on any other approaches to capturing the impact of renal flares in the economic model?

As described in CS Section 3.2, in the only previous NICE appraisal for LN (TA882) (3) it was concluded that the committee-accepted analysis model still had uncertainties relating to the long-term effects of early intervention with VOC. Particularly, in CS Section 3.3 for this appraisal, Roche highlights that in TA882 the committee and EAG described the uncertainty associated with transitions and relative-effectiveness estimates used to model long-term progression to ESRD.

Section 3.10 of the TA882 final guidance states that "*Submissions from stakeholders highlighted that a long-term treatment effect is an unproven assumption, but that short-term benefits can be predictive of improved longer-term outcomes*" (3). TA882 CS Section 3.2 explains how "*a key limitation of previous LN models is that the cumulative impact of renal flares was not adequately captured*".(3) This analysis attempts to account for this by utilising the available frequency of renal flare evidence. As duration and frequency of renal flares are well accepted to be a predictor of long-term outcomes and impact progression to later CKD stages, this analysis uses renal flare data to adjust the transition probability to CKD Stage 4. This allows the model to test the impact of observed differences in renal flare rates on cost effectiveness.

The cost-effectiveness model has the option to apply the renal flare HR to adjust the loss of response transitions, progression to CKD Stage 5 transitions or both. Roche

believes the base case approach is the most appropriate mechanism to capture the full impact of renal flares on cost effectiveness. If the analysis had only attempted to capture the short-term cost and quality-of-life impact of renal flares, it would miss the important implications persistent flares have on progression to ESRD and associated high-cost treatments for dialysis and transplant. These implications were missed in TA882 and flagged as an uncertainty (3); this analysis aims to address this uncertainty.

B4. PRIORITY: CS Section 3.3.2.1 CKD stages 1-3b response: "It is assumed that the analysis time point of the ITC is 3 years, which is the likely treatment duration for targeted therapies before clinical review". Does this assumption imply that relative risk estimates (i.e. Odds Ratios) from the ITC are assumed to correspond to a 3-year time-point? This assumption seems to be at odds with the efficacy estimates from the NMA corresponding to timepoints around 48 weeks, and REGENCY estimates corresponding to 76 weeks. Please could the company present formulas and estimates for the economic model that are consistent with the clinical evidence used.

Estimates of transition probabilities from "CKD_1_3b_AD" to "CKD_1_3b_PR" and "CKD_1_3b_CR" for each treatment were obtained from the ITC. As explained in Section 3.3.2.1 (1) and noted in this question, it was assumed that the analysis time point of the ITC was 3 years. This assumption was made to align with expected treatment duration for the majority of treatments in clinical practice, as detailed in the various recent clinical guidelines (10, 13, 14) (15). These guidelines recommend a response assessment and treatment decision at 3 years, so the 3-year time point was selected to match this.

The Company cost-effectiveness model submitted to NICE in TA882 (3) also assumed a 3-year treatment duration which was accepted by the committee and included in the decision-making analysis.

The base-case time point was also selected to account for the wide variety of follow-up durations observed in LN clinical trial readouts. Three years was sufficiently long enough to capture all trial read-outs (76 weeks for REGENCY, 104 weeks for NOBILITY, 52 weeks for AURORA 1, 104 weeks for BLISS-LN and 52 weeks for LUNAR), meaning no adjustment would be needed. This means that the responses

observed at the read-out time of each trial would remain unchanged at 3 years if the treatment is continued. This is a strong assumption, as it is likely that some of the patients in each study could stop responding; however, a “common” point had to be set in order to perform the indirect comparison.

The updated cost-effectiveness model submitted as part of the Company response to clarification includes an amendable cell (*itc_effect*) to investigate alternative time points. The Company still recommends using a 3-year time point to align with treatment decisions in clinical practice but have run an analysis using a 1.5-year time point, to correspond to the 76w REGENCY data cut.

Using a 1.5-year timepoint improves the cost-effectiveness outcomes for OBI+MMF compared to all treatments. Considering OBI+MMF versus MMF using the PAS price for OBI and the list price for all other treatments, the ICER in the updated base case model reduces from £1,454 to £201. ICERs versus all other treatments remain dominant (Table 4). NMB and NHB results improve for all comparisons, presented in Table 5.

A further scenario investigates the impact of a 1.5-year time-point and using an exponential distribution to transform transition probabilities, described and presented in the response to CQ B16.

Table 4: Scenario analysis – ITC time point (ICERs) – OBI PAS price; comparators list price

Scenario	ICER			
	vs MMF	vs VOC+MMF	vs BEL+MMF	vs RTX+MMF
Original base case (3 years)	1,743	Dominant	N/A	Dominant
Updated base case (3 years)	1,454	Dominant	Dominant	Dominant
Scenario analysis (1.5 years)	201	Dominant	Dominant	Dominant

Table 5: Scenario analysis – ITC time point (NMB and NHB) – OBI PAS price; comparators list price

Scenario	NMB				NHB			
	vs MMF	vs VOC+MMF	vs BEL+MMF	vs RTX+MMF	vs MMF	vs VOC+MMF	vs BEL+MMF	vs RTX+MMF
Original base case (3 years)	28,508	35,407	N/A	50,349	0.950	1.180	N/A	1.678
Updated base case (3 years)	28,804	35,658	33,123	50,002	0.960	1.189	1.104	1.667
Scenario analysis (1.5 years)	38,160	34,962	33,297	46,428	1.272	1.165	1.110	1.548

B5. Appendix J says that people in the REGENCY study who had an adequate response at Week 76 without a need for intensification of therapy or unmanageable TEAEs continued to receive a single blinded OBI 1000 mg or placebo infusion every 6 months. The company model assumes that all treatments are administered for 3 years in the base case analysis. Treatment costs appear to be applied to all patients alive across all health states in each model cycle.

a) Please could the company comment on the modelling of treatment costs for all patients alive across all health states in each model cycle.

Costs associated with treatment are applied to the proportion of patients who are alive and on treatment up to a 3-year time point in the base case analysis. These costs include intervention acquisition costs, administration costs and costs associated with corticosteroids. Adverse event costs are applied in Cycle 1 and are assumed to capture the costs associated with full treatment duration. Health state supportive care costs are applied in every model cycle and summed dependent on the proportion in health state. Finally, end-of-life costs are captured informed by the proportion of patients transitioning to the death state each cycle.

Subsequent treatment costs are applied up front, and CS Section 3.5.1.4 (1) acknowledges that this is likely an underestimation of the true cost associated with subsequent therapy in UK clinical practice. However, Roche believes that this will ultimately bias against OBI as the proportion of subsequent therapy received is expected to be greater for other treatment regimens included in the model.

The Company response to question B5b discusses the Company approach to treatment discontinuation and an alternative scenario provided in response to questions.

b) Can the company please provide further rationale on why time-to-treatment discontinuation data from the REGENCY and NOBILITY trials were not included in the company model.

The cost-effectiveness analysis assumes that all treatments are administered in line with their SmPC or pivotal clinical trial protocol, i.e. assumes the treatments are administered in full, up to a 3-year treatment duration in line with recent clinical guidelines (10, 13, 14) (15).

There were a proportion of patients who discontinued OBI+MMF in REGENCY, however, as noted in the question, the model does not explicitly model those discontinuations.

Currently total drug costs included in the base case model can be considered the upper bound, given there is no discontinuation included. Roche does not have access to time-to-discontinuation data for other treatments included in the analysis (VOC, RTX and BEL). Any discontinuation assumptions for OBI calculated from REGENCY would likely bias results in favour of OBI+MMF by removing costs associated with OBI treatment. If the Company model included discontinuation data from REGENCY, the model would capture a proportion of patients discontinuing OBI treatment every model cycle. This would reduce the total costs of OBI without adjusting the efficacy and ICERs would improve. So, results are conservative, and cost-effectiveness results would only improve if discontinuation was included for OBI.

Alternatively, any discontinuation assumptions could be extended to the other treatments for consistency. However, this is not without its own associated uncertainty, as Roche does not have the data to validate whether the proportion discontinuing OBI is appropriate for other treatments.

It is clear that neither of these approaches would be ideal. So, for consistency and to ensure a conservative estimate of the true cost of OBI+MMF treatment on NHS resources, the base case analysis assumed all treatments are administered in full up to the 3-year time point.

In response to this question, Roche investigated the impact of including OBI treatment discontinuation on model cost-effectiveness results. Time-to-OBI infusion discontinuation through Week 76 in the safety-evaluable patients is provided with this response (*ID6420_CQ B5b_Time-to-OBI Discontinuation_Median_95%CI_ [CON]*). This shows that [redacted]% of patients had a discontinuation event by 76 weeks. The time-to-OBI discontinuation Kaplan-Meier plot is also provided with this response (*ID6420_CQ B5b_Time-to-OBI Discontinuation_KM_[CON]*).

For simplicity in this scenario, if we assume a constant rate of discontinuation over this time point using an exponential distribution, we calculate the rate to be -[ln(1-[redacted])]/76 = [redacted]. Then, as the readout of the study was 76 weeks and the cost-

effectiveness model consider 6-month cycles. So, from this “Instantaneous rate” we calculate the half-yearly probability using an exponential function, 6-monthly probability of discontinuation: 1 - exp (-[redacted] x 26) = [redacted].

The cost-effectiveness analysis has been updated to including the option to investigate the impact of this exponential discontinuation rate on cost-effectiveness results. Calculations for the transition probability (*TTD_rate*) have been included on the *Model Inputs* sheet. This probability can be included for OBI only or assumed to apply to all triplet therapy add-on treatments (VOC, RTX and BEL), as described in the two scenario options above. Cost-effectiveness results for these two scenarios are presented below in Table 6 and Table 7.

As expected, cost-effectiveness outcomes improve when discontinuation is applied to the proportion of patients receiving OBI in the model. ICERs versus MMF reduce from £1,460 in the updated base case to £826 and £880 when applying discontinuation to OBI only and all treatments, respectively. ICERs considering the PAS price for OBI and the list price for all other treatments remain dominant compared with other triplet therapies.

When considering NMB and NHB, outcomes in both scenarios are consistent with the updated base case. As expected, incremental NMB and NHB improve when applying treatment OBI discontinuation sourced from REGENCY to OBI only. When applying the probability of discontinuation calculated from REGENCY OBI data to all other add-on therapies, incremental NMB and NHB results are very similar but slightly reduced compared with the updated base case.

Table 6: Scenario analysis – OBI time to discontinuation rate calculated from REGENCY (ICERs) – OBI PAS price; comparators list price

Scenario	ICER			
	vs MMF	vs VOC+MMF	vs BEL+MMF	vs RTX+MMF
Original base case	1,743	Dominant	N/A	Dominant
Updated base case	1,454	Dominant	Dominant	Dominant
Scenario analysis (probability applied to OBI only)	826	Dominant	Dominant	Dominant
Scenario analysis (probability applied to all add-on treatments)	880	Dominant	Dominant	Dominant

Table 7: Scenario analysis – time to discontinuation (NMB and NHB) – OBI PAS price; comparators list price

Scenario	NMB				NHB			
	vs MMF	vs VOC+MMF	vs BEL+MMF	vs RTX+MMF	vs MMF	vs VOC+MMF	vs BEL+MMF	vs RTX+MMF
Original base case	28,508	35,407	N/A	50,349	0.950	1.180	N/A	1.678
Updated base case	28,804	35,658	33,123	50,002	0.960	1.189	1.104	1.667
Scenario analysis (probability applied to OBI only)	29,437	36,293	50,637	33,758	0.98	1.21	1.69	1.13
Scenario analysis (probability applied to all add-on treatments)	29,383	34,246	49,911	31,349	0.98	1.14	1.66	1.04

c) **Can the company please provide further rationale on why a 3-year stopping rule is applied for initial treatments in the base case, and how this assumption relates to study treatment discontinuation in the REGENCY and NOBILITY trials, the expected summary of product characteristics for obinutuzumab and the anticipated use of obinutuzumab in NHS clinical practice.**

As explained in CS Section 1.3.3 (1) and response to question B5a, there is a defined clinical decision following induction therapy at around 3 years. It is expected that these guidelines will be followed in UK clinical practice. Additionally, as detailed in CS Section 3.3.2.6 and response to question B5a, the Company model was programmed to follow precedent with the only recent NICE appraisal for LN (TA882), where appropriate. In TA882, the Company used a 3-year treatment duration for all treatments, which was accepted by the committee and included in the decision-making analysis (3). A 3-year treatment duration was used for all treatments to ensure consistency with the most recent (and only) NICE appraisal and the most-recent clinical guidelines.

NOBILITY considered a fixed study duration of 2 years with a final analysis at that time point. Within NOBILITY, OBI was administered at Week 0, 2, 24 and 26 only, then patients were followed up until the end of the study period (2 years) with no further treatment.

REGENCY has a less fixed study endpoint to the open-label extension. Within REGENCY, OBI administration was at Week 0, 2, 24, 26, (50), and 52 within the primary treatment period of 76 weeks. Patients could be randomised to either receive 1 or 2 doses of OBI at the third treatment phase i.e. (50) and 52 or 52 alone. After 76 Weeks, patients can continue OBI treatment at 6 monthly intervals beginning at Week 80 (blinded follow-up). Alternatively, they can go into the 'open-label' phase where they start at Week 0 and receive OBI at Week 0, 2, 24, 26, 52 etc. and then every 6 months thereafter. Once a patient reaches the “6-monthly thereafter” schedule they can receive treatment every 6 months until study close out (assuming benefit and no AEs).

Roche do not expect an explicit stopping rule to be included in the updated OBI SmPC. The expectation is that the label will

[redacted]. However, it is unclear what the final summary of product characteristics will state.

B6. PRIORITY: CS Section 3.3.2.1 CKD stages 1-3b response: "The CRR estimates for OBI+MMF were obtained using the formula:

$$CRR\_OBI_{3y} = \frac{CRR\_OR\_OBI \ \frac{CRR\_MMF_{3y}}{1 - CRR\_MMF_{3y}}}{CRR\_OR\_OBI \ \frac{CRR\_MMF_{3y}}{1 - CRR\_MMF_{3y}} + 1}$$

Where CRR_OBI_3y denotes the CRR estimate at 3 years for OBI+MMF".

a) Could the company please clarify the type of estimate that this formula is trying to capture for CRR_OBI_3y (i.e. probability, rate, odds ratio, risk ratio)?

The formula calculates the predicted CRR for OBI+MMF at the three-year time point, based on the CRR observed in the REGENCY trial for MMF (Cell *ITC!K45* - 33.1% response rate at the primary endpoint) and the odds ratios calculated in the NMA (Cell *ITC!J49*). This represents the probability of reaching CRR. Then the model converts this 3-year probability into a 6-monthly transition probability used in the model transition matrices. The same formula is applied to all other treatments included in the cost-effectiveness analysis. These estimates then inform the calculation of the rates for the subsequent transition probabilities.

b) Could the company please clarify the definitions for CRR_OBI_3y, CRR_MMF_3y, and CRR_OR_OBI?

- CRR_OBI_3y denotes the CRR estimate at three years for the OBI+MMF regimen
    - The CRR for Obi as calculated by the NMA, based on the REGENCY MMF arm and anchor to the NMA, which is 33.1% for MMF, and odds ratio calculated by the NMA (*ITC!G49*). The regency study reported outcomes at 76 weeks; however, an assumption was made to use an 3-year time point for all interventions in the model.
- CRR_MMF_3y denotes the CRR estimate at three years for the MMF regimen

- CRR_OR_OBI denotes the average CRR odds ratio estimate for OBI+MMF vs. MMF, obtained from the NMA. An average of 3,000 CODA samples (mean or median, discussed in response to question B6c) was used for the deterministic analysis, found in *ITC!G49*.

The CRR estimates at three years for the other regimens are calculated in a similar way. The CRR_OBI_3y, CRR_VOC_3y, CRR_BEL_3y and CRR_RTX_3y estimates can be found in the model in cells *ITC!K49:K52*.

c) Could the company please confirm that the inputs in this formula are based on mean rather than median values, and report the timepoints of the estimates used?

In the updated Company cost-effectiveness model, we obtained the mean (over 3,000 CODA estimates) CRR odds ratios for each treatment (OBI+MMF, VOC+MMF, RTX+MMF [and now BEL+MMF]) compared to the reference treatment (MMF) from the ITC. The original model considered 1,000 CODA estimates, but the updated model has been updated to include 3,000 CODA estimates to reduce uncertainty. As with other responses to questions B6, the ITC assumed a treatment time point of 3 years. These mean CRR odds ratio estimates are presented in the model in cells *ITC!J49:J52*.

The updated Company cost-effectiveness model also has the option to consider the median values. Median values can be used to account for skewed distributions as the median is a more stable measurement of the distribution. We have provided a scenario using the median values as part of the response to this question. Using the median yielded a closer result to the ITC point estimates, but cost-effectiveness outcomes were very similar, indicating this was not a key assumption. Cost-effectiveness results for this scenario are presented in Table 8 and Table 9.

Table 8: Scenario analysis – average CODA sample selection (ICERs) – OBI PAS price; comparators list price

Scenario	ICER			
	vs MMF	vs VOC+MMF	vs BEL+MMF	vs RTX+MMF
Original base case	1,743	Dominant	N/A	Dominant
Updated base case (mean)	1,454	Dominant	Dominant	Dominant
Scenario analysis (median)	1,649	Dominant	Dominant	Dominant

Table 9: Scenario analysis – average CODA sample selection – OBI PAS price; comparators list price

Scenario	NMB				NHB			
	vs MMF	vs VOC+MMF	vs BEL+MMF	vs RTX+MMF	vs MMF	vs VOC+MMF	vs BEL+MMF	vs RTX+MMF
Original base case	28,508	35,407	N/A	50,349	0.950	1.180	N/A	1.678
Updated base case (mean)	28,804	35,658	33,123	50,002	0.960	1.189	1.104	1.667
Scenario analysis (median)	27,637	35,516	33,449	52,833	0.921	1.184	1.115	1.761

d) Could the company report the estimates that are being used as inputs for this formula in the economic model.

Please refer to the responses to B6b and B6c. The values used in the formula are present in the ITC sheet of the cost-effectiveness model.

B7. CS Section 3.3.2.3 CKD stage 4: “In NOBILITY and REGENCY, treatment with OBI+MMF reduced the risk of renal flare by 57% and 56%, respectively when compared with MMF (…) When comparing the HRs associated with OBI versus MMF+MMF and VOC+MMF versus MMF in a standard her comparison, it is predicted that OBI+MMF [redacted] when compared with VOC+MMF ([redacted]).” Could the company provide further details of the methods and rationale for this ITC?

As explained in CS Section 3.2 and 3.3 (1) and in response to question B3, there were key uncertainties associated with the expected long-term prognosis driven by differences in short-term outcomes. It is widely supported that frequency and duration of renal flares are indicative of worse long-term outcomes, i.e. the more time spent experiencing a renal flare and the more frequently flares occur, the faster progression to later CKD Stages and greater likelihood of dialysis and transplant.(16) The previous TA882 analysis did not fully attempt to capture the impact of renal flares (3). Instead, the Company thought that the transition from a response health state back to the active disease health state could be considered to capture a renal flare. The Company argued that this partly captured the impact of renal flares, and the cumulative impact would be captured in the cumulative 'return' transitions to active disease. However, Roche argues that this fails to capture the full cost and health-related quality-of-life impacts associated with the downstream effects of cumulative renal flares, and won't fully reflect the expected long-term differences associated with the different drug classes included in the analysis.

So, for this submission, Roche used available renal flare evidence from the REGENCY and AURORA trials. As described in Section 3.3.2.3 (1), treatment with OBI+MMF investigated in NOBILITY and REGENCY was associated with a reduction in the risk of renal flare by 57% (HR: 0.43 [0.24, 0.82]) and 56% (HR 0.44 [0.49, 1.45]) when compared with MMF, respectively. However, in AURORA-2, VOC+MMF was only shown to reduce renal flares by 12% (HR: 0.88). So, when

comparing the two HRs for OBI+MMF vs MMF and VOC+MMF vs VOC in a standard Bucher comparison, it is predicted that OBI+MMF reduces renal flare rate by half when compared with VOC+MMF. Roche acknowledges the formula presented in CS Section 3.3.2.3 is incorrect. The correct values for the HRs are OBI vs VOC HR: [redacted] / 0.88 = [redacted] and VOC vs OBI HR: 0.88 / [redacted] = [redacted].

Following response to question B1, and in the interest of completeness, Roche has now included a cost-effectiveness comparison versus BEL+MMF. The updated model uses the same methodology considering available renal flare evidence for BEL+MMF from BLISS-LN. Treatment with BEL+MMF is associated with a 51% reduction in the risk of renal flare when compared with MMF (HR: 0.49). So, when comparing the two HRs for OBI+MMF vs MMF and BEL+MMF vs VOC in a standard Bucher comparison, it is predicted that OBI+MMF reduces renal flare rate by [redacted]% when compared with BEL+MMF (HR: [redacted]).

In the cost-effectiveness model, the probability of transitioning from CKD Stage 1-3b to CKD Stage 4 is informed by the expert elicited value from TA882 (3). This probability is used to capture the underlying risk of transitioning to CKD Stage 4 with treatments available at the time of TA882 (i.e. MMF and RTX+MMF). Then, this analysis utilises the reported HRs versus MMF to adjust the probability of transitioning from CKD Stage 1-3b to CKD Stage 4 for OBI+MMF, VOC+MMF and BEL+MMF to model the impact these advances in clinical practice will have on the long-term prognosis of LN and ESRD. Adjusted transition probabilities are found in the *Transition matrices* sheet in the cost-effectiveness model.

B8. PRIORITY: CS Section 3.3.2.3 CKD stage 4: "The base case analysis in this submission utilises hazard ratios (HRs) versus MMF associated with time to renal flare (Table 46) to adjust the probability of transitioning from CKD Stage 1-3b to CKD Stage 4." The changes in eGFR presented in Appendix H show a small proportion of patients moving to an eGFR score equivalent to CKD stage 4 compared to the proportion of patients experiencing flares in the trial. Could the company provide any further evidence to support the claim that the effect

on the risk of flares from therapy is equivalent to the effect on the risk of CKD progression in the base-case economic model?

As explained in CS Section 1.3.4 (1), renal flares in uncontrolled LN lead to progressive, irreversible loss of nephrons, causing a worsening of proteinuria and a decline in GFR (17). When added to age-related nephron loss and kidney injuries that occur over the course of a life, renal flares accelerate the time to ESRD and shorten the lifespan of the kidneys by decades (18). As few as two renal flares in the lifetime of a patient with LN can result in kidney failure. In addition to irreversible nephron loss, renal flares significantly impair treatment responses during future flares (19). Therefore, timely diagnosis of LN followed by prompt, aggressive treatment is critical to prevent further loss of nephrons and worsening of renal prognosis.

CS Section 2.13.1 goes on to detail the positive effects OBI has on reducing renal flares. At the recent advisory board referenced in the CS, UK clinical experts agreed that the flare data demonstrates the ability of OBI to delay flares and preserve nephrons earlier in the disease course. Thus, initiating treatment with OBI early would preserve nephrons and delay disease progression, reducing the need to cycle through other drugs and slow the progression to later CKS stages, ESRD and high-cost, high-burden dialysis and transplant procedures (12)

Finally, as explained in response to questions B3 and B7, the approach to account for frequency of renal flares and their impact on progression to CKD Stage 4 was used to address outstanding uncertainties from the TA882 analysis (3). Namely, differences in long-term outcomes and progression to ESRD expected between treatments based on short-term clinical effectiveness. As detailed in response to question B7, it is well supported that the frequency and duration of renal flares are indicative of worse long-term outcomes, i.e. the more time spent experiencing a renal flare and the more frequently flares occur, the faster progression to later CKD Stages and greater likelihood of dialysis and transplant.

At the advisory board (12), experts discussed the expected long-term impact of renal flares. They supported the Company's attempts to capture expected long-term differences between treatment classes, explained that renal flares were a good indicator of poorer prognosis, and highlighted that important differences had been

observed in the pivotal Phase III trials for treatments included in the NICE scope. Experts also referenced the Perez-Arias et al., 2023 study, which evaluated the influence of repeated flares on response to therapy and prognosis in LN (16). One outcome measure considered was time to persistent 30% decline in eGFR. Persistent decline is the important outcome measure when it comes to worsening CKD stage and progression of LN, as a reversal of an initial decline would mean a patient would not necessarily advance to a higher CKD stage. The study showed that patients in their 3rd flare were 69% more likely and patients in their 2nd flare were 50% more likely to have persistent decline than patients in their 1st flare. A persistent 30% decline in eGFR can push patients into a higher CKD stage, so whilst the risk of flare may not equal risk of CKD progression, the two strongly correlate. The study shows that it is clear the chance of worsening renal function gets greater with each flare. Finally, the study reports that the mortality risk was 285% greater after 3 flares compared with 1 flare, due to ESRD in most patients. The cost-effectiveness model does not account for increased mortality using a standardised mortality ratio but attempts to account for this risk using health state-dependent death transition probabilities informed by Sugrue et al., 2019. (20)

The changes in eGFR presented in Appendix H (21) shows the per-patient eGFR movements through REGENCY. The plot shows that there [redacted] instances of eGFR values below 30 ml/min/m^2 from a total [redacted] patients of [redacted] in the safety-evaluable population. As explained in Appendix H, the numbers are small and caution should be taken when interpreting results. However, there are numerically more observed instances of eGFR within the CKD Stage 4 threshold in the MMF arm compared with OBI, which indicates the potential benefit for OBI in avoiding transitions to later CKD stages. When considering the renal flare data specifically from REGENCY (CS Section 2.6.1.3.12 (1)), the proportion of patients with a LN flare between Weeks 24 and 76 was [redacted] in the OBI arm ([redacted] [redacted%]) than the placebo arm ([redacted] [redacted%]), with a hazard ratio of [redacted] (95% CI: [redacted], [redacted]; nominal p-value = [redacted]), supporting [redacted] of LN flares [redacted] OBI. Additionally, the Kaplan-Meier plot of time to LN flare through Week 76 showed separation [redacted] arm beginning at Week 24 through Week 76. So, the total instances of eGFR below 30 ml/min/m^2 presented in Appendix H does not completely correlate with the number of renal flare events, due to the definition of

renal flares in the trial covering not only eGFR decreases, but also UPCR increases or receipt of rescue therapy (CS Section 2.6.1.3.12).

Figure 10 and Figure 11 in Appendix H (21) present eGFR for patients in REGENCY. As explained in this response, and referenced in Perez-Arias et al 2023 (16), the important outcome when it comes to progression is persistent decline. Event numbers are small in Figure 10 and Figure 11, and caution should be taken when interpreting results, but there are more instances that could be interpreted to be persistent decline in the MMF arm compared with OBI. Perez-Arias also details the worsening prognosis when experiencing a second or third renal flare (16). More patients experienced flare in the MMF arm, so there are a greater proportion at greater risk of persistent decline if they experience another flare. The overall cost-effectiveness modelling approach to capture the impact of renal flares attempts to characterise and quantify the value associated with short-term response outcomes and reduction in renal flares and their expected reduction of long-term high-cost chronic LN complications and cost effectiveness. Roche argues that ignoring these important impacts would fail to capture the true value of early intervention with OBI triplet therapy for patients and the healthcare system.

B9. PRIORITY: CS Section 3.3.2.5 Death: "There were [redacted] deaths recorded in the REGENCY study over a total follow-up of [redacted] periods of 6-month cycles. In the base case, a multi-state model is used to estimate movements to the death health state." Considering that low event count can be an issue, can the company perform a survival analysis on the overall survival data from REGENCY using the guidance from TSD 14?

The original statement in CS Section 3.3.2.5 (1) referred to 10 deaths in the total follow-up period i.e. a follow up greater than the 76-week period. Only 4 deaths had occurred in the 76-week data cut.

Time-to-death was calculated from the date of randomisation to the date of death. Patients who did not die were censored at Week 76, except for those who withdrew early, who were censored at the time of withdrawal. Summary statistics of time-to-death (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the methods of Brookmeyer and Crowley and are provided with this response (ID6420_CQ B9_Time-to-Death_Median_95%CI_[CON]).

The time-to-death Kaplan-Meier plot is also provided with this response (ID6420_CQ B9_Time-to-Death_KM_[CON]). This plot shows the minimal impact these death events have on the time-to-event survival data. Roche argues that, due to the limited number of observed events and lack of maturity in the Kaplan-Meier, full survival analysis in line with methods set out in TSD 14 (22) would fail to tell a compelling story. Roche believes that the methods used to generate death transitions for the CKD Stage 1-3b health states is an appropriate and informative method of capturing survival for LN patients included in REGENCY.

B10. PRIORITY: CS Section 3.4.1 Health-related quality-of-life data from clinical trials: "The key endpoints considered were change from baseline in EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) index-based and Visual Analog Scale (VAS) scores at Weeks 0, 24, 50, and 76"

a) Can the company clarify why the patient health-related quality of life analyses from the trial presented in the submission were based in EQ-5D VAS rather than EQ-5D-5L index scores?

The EAG's interpretation is incorrect. Roche apologises if the description in the evidence submission was not clear enough to ease interpretation.

In line with the NICE reference case, and to incorporate important impacts to HRQoL, EQ-5D data collected from REGENCY were analysed and used in the economic model. REGENCY HRQoL data were collected using the EQ-5D-5L at the following time points:

- Baseline
- Week 24
- Week 50
- Week 76

Consistent with the current NICE methods on the use of EQ-5D in technology appraisals, EQ-5D-5L data from REGENCY was analysed and mapped to EQ-5D-3L index scores using the methodology developed by Hernández Alava et al. 2023 (23). So, the REGENCY utility values included in the model use UK EQ-5D-5L tariff

values. The utility values for each treatment arm over time are graphically depicted in CS Figure 18 (1).

Linear Mixed-Effects Models were used to account for within- and between-patient variation. First, a linear mixed-effects model was fitted to predict post-baseline utility values as a function of both health state and baseline utility value, incorporating random intercepts to account for subject-level variability. Based on this model, health states ("PRR independent of CRR" and "Active Disease") do not appear to have a statistically significant impact on post-baseline utility values relative to the reference state ("CRR"). However, baseline utility values significantly predict post-baseline utility, emphasising the importance of initial health status in determining subsequent utility outcomes.

However, as explained in Section 3.4 of the CS (1), the utility values observed in our analyses using REGENCY data did not follow the anticipated hierarchy; instead, the highest utility values were predicted in the Active Disease health state, while the lowest were associated with the CRR health state. However, the differences in utility values between the health states do not appear to be significant or clinically meaningful. So, in line with clinical expectations, consistency with TA882 (3) and to better reflect the expected disease course, the Company base case analysis utilises the EAG utilities accepted in TA882.

b) Can the company provide an analysis of EQ-5D-5L index scores using the UK scoring algorithm and the mapping algorithm to EQ-5D-3L scores in accordance with NICE guidelines?

Please refer to the response to question B10a.

B11. PRIORITY: Adverse Events in the cost-effectiveness analysis:

a) CS Section 3.4.4 Adverse reactions: "It is assumed that any impact to HRQoL associated with AEs are captured within health state utility estimates. So, additional decrements are not accounted for in the economic base case analysis." It is common practice in economic modelling for NICE TAs to include adverse events Grade 3 or above due to their impact on patients and health care costs. Please could the

company include the impact of adverse events in the base-case results using the best available evidence for each therapy arm?

The base-case analysis assumes that HRQoL impacts of adverse events are included in the health state utility values. This is a fairly common assumption used in cost-effectiveness analysis. However, as described in Section 3.4.4, the cost-effectiveness model does include the option to include the impact of standalone adverse events. This is investigated in a scenario analysis, originally presented in CS Section 3.11.3 Table 69, "*AE disutility – TRUE*" which showed a marginal impact to cost-effectiveness outcomes of <£1 difference to the ICER versus MMF and incremental NMB of £35,432 versus VOC and £50,373 versus RTX compared to £35,407 and £50,349 in the original base case.

Cost-effectiveness results for this scenario using the updated company base case model tell a similar story. ICERs versus MMF change from £1,454 in the base case to £1,452 when considering AE disutility. NMB versus other treatments change from £35,682 versus VOC, £33,147 versus BEL and £50,027 versus RTX when considering AE disutility compared to £35,658, £33,123 and £50,002 in the updated base case.

However, it should be noted that in line with assumptions made in TA882 and as described in CS Section 3.5.3, the analysis assumes the MMF incidence of AEs from REGENCY for all MMF containing regimens (e.g. VOC+MMF, RTX+MMF and BEL+MMF). Therefore, the scenario essentially assumes no adverse reactions to VOC, RTX and BEL treatment. This is a strong, conservative assumption.

b) **CS Section 3.5.3 Adverse reaction unit costs and resource use: "The impact of adverse events was included in the base case analysis. The costs of adverse events while on treatment were calculated separately for OBI and MMF treatment arms based on the average number of treatment emergent adverse events per patient in the REGENCY trial and the unit costs of these adverse events." Please ensure there is consistency in the assumptions around patient HRQoL and resource**

use related to the inclusion of adverse events, as these are inconsistent with Section 3.4.4 in the submission.

As explained in the Company response to question B11a, the methods for accounting for the cost and HRQoL impacts associated with adverse events were included in the originally submitted model. The original Company base case accounted for the increased cost of resolving adverse events, but assumed that the quality-of-life impact was captured in the health state utility values. The Company also presented a scenario investigating the impact of including additional impacts to quality-of-life associated with adverse events.

So, the Company disagrees that the methods were inconsistent as the model contained the functionality to consider both. As in response to question B11a, the Company notes that this is a conservative assumption when compared to other triplet therapy regimens.

c) **Use of corticosteroids is associated with serious adverse events. Did the company explore methods like Gibson et al., 2024 to capture the impact of these AEs and cumulative toxicity of corticosteroids on incurred cost and patients' HRQoL in the economic model?**

The Company did not consider explicitly modelling the cost and HRQoL impact of cumulative corticosteroid toxicity. In the base case analysis, all regimens include steroids in line with their clinical trial protocol dose. So, there are slight differences in the level of corticosteroids administered for OBI, VOC, RTX and BEL. However, the Company believes that starting corticosteroid levels would likely be similar for each treatment as they will be somewhat standardised in clinical practice. The current Company cost-effectiveness analysis also does not capture the tapering of steroids observed in REGENCY and expected for OBI in clinical practice. So, for simplicity, the Company base case did not consider the methods outlined in Gibson et al., 2024 (24), but the Company would welcome the consideration of any methods that allow the model to more accurately capture the impacts of LN and the full value of OBI.

B12. PRIORITY: CS Section 3.10.1 ‘‘Pairwise cost-effectiveness results OBI+MMF versus MMF, OBIMMF versus VOC+MMF and OBI+MMF versus RTX+MMF are presented in Table 66 and disaggregated results are available in

Appendix I.'' But the NICE reference case recommends a cost-utility analysis with fully incremental analysis for technological appraisal submissions. Hence, could the company provide the full incremental analysis for deterministic and probabilistic results in the CS model and the CS submission?

Please refer to the fully incremental analysis results in the updated cost-effectiveness model (Results Table sheet) and below in Table 10.

Table 10: Fully incremental deterministic cost-effectiveness results – OBI PAS price; comparators list price

	Tot Costs (£)	Tot LYs	Tot QALYs	Inc Costs (£)	Inc LYs	Inc QALYs	ICER
MMF	[redacted]	[redacted]	[redacted]				
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
VOC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
BEL_IV + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
OBI + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,454

B13. PRIORITY: In the CS the company does not mention the dosage assumptions around vial sharing and its implementation in the company submitted economic model. But the company model adopts a vial sharing approach for calculating the drug costs for the cost-effectiveness analysis.

a) **Could the company explain the assumptions made about vial sharing and the method in which it is captured in the company model.**

As the doses of some drugs included in the model are weight-dependent, wastage may occur and impact the cost per treatment cycle of the respective treatment regimen. Vial sharing assumptions only impact treatments administered by IV infusion. For all other treatments, whether oral or SC, perfect sharing (no wastage) is assumed.

In the Company cost-effectiveness analysis, the only treatment that vial sharing assumptions impact is IV methylprednisolone. So, for simplicity, the Company base case included "Planned dose with vial sharing". With this assumption, the costs of treatment assumes no wastage and the drug costs are calculated by mg and multiplied by the dose expected in clinical practice in line with each drug's SmPC. This is a simplifying assumption given the low cost of IV methylprednisolone.

The model also includes the option to account for drug wastage using the "Planned dose without vial sharing". With this option, the user can further select the proportion of the opened vials will actually be used in other patients (*vial_sharing*), i.e. physicians might dispose of vials with small quantities left after the use in one or more patients so might not re-use all open vials entirely, and the proportion of a new vial would be needed to justified its use (*prop_min*), i.e. a physician might not open a new vial if only 7% of its content is needed to administer the intended dose so the 7% would be wasted.

For completeness, and to satisfy the response to this question, the Company has conducted a scenario to investigate the impact of assuming no vial sharing (the extreme to the Company base case of full vial sharing). This scenario shows the minimal impact vial sharing assumptions has on cost-effectiveness results.

When considering no vial sharing, OBI+MMF versus MMF is associated with an ICER of £1,447 compared to £1,440 in the updated base case and remains dominant versus all other treatments. The scenario is associated with an incremental NMB of £35,637 versus VOC, £34,791 versus BEL and £50,005 versus RTX compared to £35,658, £33,123 and £50,002 in the updated base case, respectively.

b) **Assuming vial sharing in the base case might be a favourable assumption for Obinutuzumab; the position adopted by NICE pertaining to drug wastage is to consider no vial sharing in the base case. Hence, can the company change the base case in the economic model to no vial sharing among patients and provide the deterministic, probabilistic, sensitivity, scenario and threshold analyses results?**

The EAG view that vial sharing in the base case might be a favourable assumption for OBI is incorrect. As explained in CS Section 3.5.1.1 (1), OBI is supplied in vials of 1000 mg and administered at a dose of 1000 mg by IV infusion. Therefore, there is no wastage and vial sharing assumptions have no impact on the total drug costs of OBI. The company has not updated the base case accordingly.

B14. PRIORITY: The EAG have rerun the probabilistic sensitivity analysis of 1000 iterations several times in the company model. But the results showed high degree of variations (which was not within the acceptable range) from the deterministic and probabilistic results presented in the CS document. Can the company therefore please provide the sensitivity results with a higher number of iterations, (preferably 10,000 iterations)?

Please refer to the PSA results run over 5,000 iterations in the updated cost-effectiveness model, which are also provided below for completeness. Results are consistent with updated deterministic results presented in Table 2.

Table 11: Updated probabilistic sensitivity analysis results over 5,000 iterations, ICER – OBI PAS price; comparator list price

	Total Costs (£)	Total LYGs	Total QALYs	Inc Costs (£)	Inc LYGs	Inc QALYs	ICER (£/QALY)	NMB at £30,000	NHB at £30,000
OBI+ MMF	[redacted]								
MMF	[redacted]						1,368	29,039	0.968
VOC+ MMF	[redacted]						Dominant	37,775	1.259
BEL+ MMF	[redacted]						Dominant	40,491	1.350
RTX+ MMF	[redacted]						Dominant	57,463	1.915

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; MMF, mycophenolate mofetil; NHB, net health benefit; NMB, net monetary benefit; OBI, obinutuzumab; PAS, patient access scheme; QALYs, quality-adjusted life years; RTX, rituximab; VOC, voclosporin.

Figure 1: Cost-effectiveness plane – OBI PAS price; comparator list price

Key: MMF, mycophenolate mofetil; OBI, obinutuzumab; PAS, patient access scheme; QALYs, quality-adjusted life years; RTX, rituximab; VOC, voclosporin.

Figure 2: Incremental cost-effectiveness plane – OBI PAS price

Key: MMF, mycophenolate mofetil; OBI, obinutuzumab; PAS, patient access scheme; QALYs, quality-adjusted life years; RTX, rituximab; VOC, voclosporin.

Figure 3: Cost-effectiveness acceptability curve – OBI PAS price

Key: GBP, Pounds, MMF, mycophenolate mofetil; OBI, obinutuzumab; PAS, patient access scheme; QALYs, quality-adjusted life years; RTX, rituximab; VOC, voclosporin; WTP, willingness-to-pay.

Figure 4: Convergence plot (NMB) – OBI PAS price; comparator list price

B15. In the company submitted economic model, the convergence result chart for incremental NMB vs simulations in sheet 'Results Chart', shows divergence in graphs of incremental NMB values. Could the company please comment on this?

The convergence plot in the Results Chart sheet of the Company cost-effectiveness model only showed iterations up to 300. When the axis is updated to 1000 iterations the convergence is more stable and more stable still at the 5,000-iteration run in the updated cost-effectiveness model (Figure 4).

B16. CS Section 3.3.2.1 ''To calculate the CRR estimates at 6 months to match the cycle length used in the model, the CRR estimates at 3 years are extrapolated using a Weibull distribution. The same ITC methodology is used to generate the transition probabilities of partially responding (i.e. from AD to PR) for OBI+MMF, MMF, VOC+MMF and RTX+MMF.''

a) Could the company please clarify why the standard approach of estimating probabilities from rates, which is a common approach used in NICE TAs, was not used to calculate the CRR estimates in this submission? Could they provide their justification for the choice of the Weibull distribution to calculate CRR 6-month estimates?

The transition probabilities from CKD 1-3B AD to CR and PR are calculated in the *ITC* sheet of the cost-effectiveness model. In the base case, the transition probabilities derived from the trial results are transformed into 6-monthly probabilities using a Weibull distribution. It is the Company's understanding that the "standard approach" suggested here by the EAG refers to the estimation of probabilities from rates using the exponential distribution as described in Briggs et al., 2006 (25). Therefore, the Company's response to this question relies on this understanding being correct.

As transition probabilities are constant throughout the model, a reliable transition probability would be one that predicts a proportion of patients responding at three years which is close to the point estimate calculated by the ITC at three years. In order to verify how the transition probabilities perform, the square root of the sum of squared deviations for both endpoints and for all treatments is calculated in *Model Inputs!I159*. The lower this value, the better the prediction.

The Company base case considered a Weibull distribution to transform transition probabilities. As the Weibull distribution is a particular case of the exponential distribution, it has an added shape parameter (k in this model). The model user has the option to test alternative *k_weibull* parameters to test the model's prediction. The "standard exponential approach" cited above was first evaluated, i.e. if the *k_weibull* parameter is changed to 1, the distribution becomes exponential. When a value of 1 was tested, the Company argues this provided unrealistic results and there is a higher prediction value and higher error.

Please see below a worked example calculating the 6-monthly transition probabilities using both Weibull and exponential approaches for the MMF transition probabilities (*ITC!K46:L47*):

The CRR for each treatment, calculated as described in question B6, from which the rates can be derived using the below formula:

- Rate = -[ln(1-p)]/3
- Rate = -[ln(1-0.331)]/3
- Rate = 0.1339 (see cell K46 in ITC tab)

Where p is the probability as described in question B6 and 3 is the analysis time point for the calculation (e.g. 3 years).

From this "Instantaneous rate" we can calculate the transition probabilities. The standard approach would use an exponential distribution:

- 6-monthly probability: 1 - exp (-0.1339 x 0.5) = -0.0647 (see cell L46 in the ITC tab).

However, the use of a Weibull distribution was explored as follows:

- For the 3 year timepoint : p= $P(X \leq 3)=1-\exp[-(3/\lambda)^k]$
- For the ½ year timepoint: q= $P(X \leq 0.5)=1-\exp[-(0.5/\lambda)^k]$

After manipulating the equation, we arrive at the formula in cell *ITC!L49*, which calculates the 6-monthly transition probabilities:

6-monthly transition probability = 1 – exp (exp (k_weibull * (ln(0.5) - ln(3))) * ln (1 - p))

Where:

- p is the CRR probability derived from the NMA (*ITC!K49:K52*) for each treatment.
- The k_weibull parameter for the Weibull distribution found in Model Inputs (when k_weibull = 1, distribution becomes exponential)
- 0.5 represents 6-monthly model cycle
- 3 represents the 3-year analysis point for the NMA.

As part of the Company's response to this question, Roche investigated a scenario applying a Weibull k parameter or 1 and limiting the Weibull model to an exponential distribution. In this scenario, cost-effectiveness outcomes are very similar to the updated Company base case. Considering the PAS price for OBI and the list price for all other add-on treatments, ICERs slightly increase when compared to MMF (from £1,454 to £1,593). ICERs remain dominant and incremental NMB/NHB outcomes slightly improve versus all other treatments. The results of this scenario are presented below in Table 11 and Table 12.

b) Could the company please clarify whether other methods for calculating the CRR estimates at 6 months were explored.

As explained in the response to question B16a, the Company explored an exponential approach but opted to use the Weibull distribution as the prediction at 3 years improves. The Weibull k parameter was tested and selected using an iterative process where the prediction was best using a parameter k = [redacted].

In response to question B4, the Company included a user amendable cell (*itc_effect*) to investigate alternative time points used to calculate the prediction of transition probabilities. The Company has provided a scenario investigating a 1.5-year time point which improved cost-effectiveness outcomes (Table 11 and Table 12).

Finally, the model does have the option to use the MSM outputs from the REGENCY trials. As explained in CS Section 3.3.2.1 (1), for transitions from Active Disease (AD) to Partial and Complete Response (PR and CR) health states in the OBI and

MMF arms, the model as the option to use either transitions calculated directly from REGENCY (CS Table 44) or utilise the ITC outputs (CS Table 43). In the cost-effectiveness model, this can be selected using the *effect_fTP_source* switch. However, as explained in Section 3.3.2.1, the Company base case uses transition probabilities derived from the ITC, as this ensures consistency in methods between treatments included in the analysis.

When considering the two additional scenarios provided in response to questions B4 and B16a, the Company still believes that the most appropriate base case is a 3-year time point and a Weibull model with k parameter = [redacted]. However, these scenarios show the strength of OBI's cost-effectiveness story, suggests the Company base case was conservative and provides 'positive' uncertainty where results improve with alternative assumptions.

Table 12: Scenario analysis – CRR transition probabilities (ICERs) – OBI PAS price; comparators list price

Scenario	ICER			
	vs MMF	vs VOC+MMF	vs BEL+MMF	vs RTX+MMF
Original base case (Weibull)	1,743	Dominant	N/A	Dominant
Updated base case (Weibull)	1,454	Dominant	Dominant	Dominant
Scenario analysis (Exponential function)	1,593	Dominant	Dominant	Dominant
Scenario analysis (1.5-year time-point)	201	Dominant	Dominant	Dominant
Scenario analysis (Exponential and 1.5-year timepoint)	Dominant	Dominant	Dominant	Dominant

Table 13: Scenario analysis – CRR transition probabilities (NMB and NHB) – OBI PAS price; comparators list price

Scenario	NMB				NHB			
	vs MMF	vs VOC+MMF	vs BEL+MMF	vs RTX+MMF	vs MMF	vs VOC+MMF	vs BEL+MMF	vs RTX+MMF
Original base case (Weibull)	28,508	35,407	N/A	50,349	0.950	1.180	N/A	1.678
Updated base case (Weibull)	28,804	35,658	33,123	50,002	0.960	1.189	1.104	1.667
Scenario analysis (Exponential function)	27,212	37,159	33,391	53,656	0.907	1.239	1.113	1.789
Scenario analysis (1.5-year time-point)	38,160	34,962	33,297	46,428	1.272	1.165	1.110	1.548
Scenario analysis (Exponential and 1.5-year timepoint)	42,020	36,206	34,029	50,559	1.401	1.207	1.134	1.685

B17. CS Section 3.11.3, Table 69 in the company submission document, the ICER results for the scenario assuming equivalence in transition probabilities between treatments do not correspond to the company submitted economic model results. Could the company please clarify this?

In response to this question, Roche discovered an error in the application of the equivalence assumption in the cost-effectiveness model.

In the updated cost-effectiveness model, the *effect_equivalence* cell is used to assume equivalence in response outcomes across treatments. When *effect_equivalence* is TRUE the transition probabilities for VOC, RTX and BEL in the Transition matrices sheet are assumed equal to those of OBI. This was not the case in the final originally submitted model.

Roche have provided scenario results for this equivalence assumption below in Table 13 and Table 14. The scenario “transitions assumed equivalent to OBI” in Table 13 and Table 14 adjusts the transition matrices for VOC+MMF, RTX+MMF and BEL+MMF only and the MMF transitions remain unchanged. This is due to the clinical expectation that triplet therapy has efficacy benefit over MMF alone. The ICER value for OBI+MMF versus MMF alone changes slightly in this scenario due to the impact of downstream subsequent therapy costs informed by calculations changing to assume equivalence in first-line therapies. It should also be noted that, in the scenario, OBI+MMF versus other triplet therapy ICERs remain dominant at PAS price for OBI and list price for all other comparators (i.e. OBI+MMF is still estimated to return greater QALYs for less cost). This is due to the differing assumptions relating to treatment effect waning for each treatment, detailed extensively in CS Section 3.3.2.6.

For the interest of completeness, Roche has also investigated a scenario assuming equivalence in transition probabilities and assuming equivalent treatment waning assumptions. When transition probabilities and treatment effect waning assumptions for all other triplet therapies are set to be equal to OBI, there is no QALY difference between treatments and the model reverts to a cost-comparison analysis. At PAS price for OBI and list price for all other treatments, OBI+MMF is predicted to be cost saving against all triplet therapies. However, Roche strongly argues that this scenario does not fully capture the value of OBI.

Table 14: Scenario analysis – Equivalence assumptions (ICERs) – OBI PAS price; comparators list price

Scenario	ICER			
	vs MMF	vs VOC+MMF	vs BEL+MMF	vs RTX+MMF
Updated base case (transitions informed by ITC, REGENCY loss of response and renal flare HRs)	1,454	Dominant	Dominant	Dominant
Scenario analysis (transitions assumed equivalent to OBI)	1,452	Dominant	Dominant	Dominant
Scenario analysis (transitions and waning assumed equivalent to OBI)	1,452	Cost saving: -19,292	Cost saving: -25,931	Cost saving: -3,321

Table 15: Scenario analysis – Equivalence assumptions (NMB and NHB) – OBI PAS price; comparators list price

Scenario	NMB				NHB			
	vs MMF	vs VOC+MMF	vs BEL+MMF	vs RTX+MMF	vs MMF	vs VOC+MMF	vs BEL+MMF	vs RTX+MMF
Updated base case (transitions informed by ITC, REGENCY loss of response and renal flare HRs)	28,804	35,658	33,123	50,002	0.960	1.189	1.104	1.667
Scenario analysis (transitions assumed equivalent to OBI)	28,805	25,552	29,589	6,980	0.960	0.852	0.986	0.233
Scenario analysis (transitions and waning assumed equivalent to OBI)	28,805	19,292	25,931	3,321	0.960	0.643	0.864	0.111

Section C: Textual clarification and additional points

Clarification on literature searching

C1. Appendix B 2.1.1 Methods (Table 1): The company chose to limit the search of conference abstracts/proceedings to the last 3 years between 2021 – 2024 (2022-2025 for the update search). Could the company please provide a rationale for limiting by this date range?

The date range for searching conference proceedings in the clinical and economic SLRs was limited to the past 3 years to prioritise the inclusion of recent findings. This aligns with the Company's standard practice, recognising that older conference data is frequently superseded by subsequent peer-reviewed publications. These publications would have been captured through the broader bibliographic database searches, where no publication date restrictions were applied (26, 27).

C2. Appendix 2 7.2.1 and 7.2.2: Could the company please provide references to all third-party search filters applied to the searches conducted for the Economic SLR in MEDLINE, Embase and EBM Reviews and any other third-party filters used if applicable?

The following filters from Canada's Drug Agency Search Filters Database were used in the economic searches, and the web links are provided in the References list:

- Economic Evaluations & Models - Embase (28)
- Economic Evaluations & Models - MEDLINE (29)
- Economic - Health Utilities / Quality of Life - Broad - Embase (30)
- Economic - Health Utilities / Quality of Life - MEDLINE (31)

C3. It was stipulated that searches were conducted in conference proceedings, clinical trials registries and Global HTA and regulatory body websites for both the clinical effectiveness and economic SLR, however only example search terms were provided. Can the company please provide the exact terms used to search these

databases, detail whether they were basic or advanced searches and/or list any specific fields searched if applicable.

Hand-searching methodology for supplemental sources, including conference proceedings, is provided in Table 32 of the clinical effectiveness SLR report (26) and Table 32 of the economic SLR report (27). These tables list the actual terms searched (not example). The search type (basic or advanced) and the specific search fields were not recorded.

Minor editorial points

C4. Figure 2 (Page 21) of the Network meta-analysis report is illegible. Could the company please provide an image with higher resolution?

The Company acknowledges the low resolution of Figure 2 in the NMA report (32). A high-resolution version of this figure is provided with this response (ID6420_CQ C4_Figure_2_NMA_report [CON].pdf).

C5. CS Section 3.3.2.3 CKD stage 4: “In NOBILITY and REGENCY, treatment with OBI+MMF reduced the risk of renal flare by 57% and 56%, respectively when compared with MMF (…) When comparing the HRs associated with OBI versus MMF+MMF and VOC+MMF versus MMF in a standard her comparison, it is predicted that OBI+MMF [redacted] when compared with VOC+MMF ([redacted]).” Could the company clarify whether the HR estimate provided in this paragraph was a typo? The probabilities of the risk of renal flare presented in this section also do not match those presented in Table 27, can the company clarify whether this is a typo?

The Company acknowledges the incorrect formula for the standard Bucher comparison of HRs for renal flares with OBI versus MMF+MMF and VOC+MMF versus MMF. Please refer to the response to question B7 for the corrected formula.

The EAG are reminded that the risk of renal flare presented in Section 3.3.2.3 CKD stage 4 for OBI+MMF compared with MMF in NOBILITY and REGENCY was reduced by 57% and 56%, respectively. The 56% risk reduction for REGENCY corresponds to the HR of 0.44 presented in Table 27 (1).

C6. In Section 3.10.1 of the company submission document, ‘’All results presented in this section assume the PAS price for OBI and the list price for all other treatments. Pairwise cost-effectiveness results OBI+MMF versus MMF, OBIMMF versus VOC+MMF and OBI+MMF versus RTX+MMF are presented in Table 66 and disaggregated results are available in Appendix I’’. But the disaggregated results are presented in Appendix H. Could the company please correct this reference?

This cross-reference has been corrected to "Appendix H" in the updated CS provided with this response (33).

C7. CS Section 3.11.1, Table 68 gives the probabilistic sensitivity analysis results. The results in the 9th column of this table with the heading ‘’NMB at £20,000’’ gives the results corresponding to NMB at £30,000 in the CS model. Could the company please add the correct heading to this column since it is misleading to the reader?

This heading has been corrected to "NMB at £30,000" in the updated CS provided with this response (33).

C8. There are a small number of error notifications where a reference or cross-reference has not matched in the CS; can the company please provide the relevant references or cross-references.

The Company acknowledges that one study cited in the CS was incorrectly formatted in the bibliography (reference 182 on page 130, Khamashta et al., 2014). This issue, along with the incorrect cross-references, have been corrected in the updated CS provided with this response (33).

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Obinutuzumab with immunosuppressive therapies for treating lupus nephritis [ID6420]

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].

Information on completing this submission

- 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
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Lupus UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Lupus UK is the only national registered charity supporting people affected by lupus, with a vision for a world where people with lupus can live full and active lives. The charity offers practical, social, and emotional support services across all four nations. Lupus UK is no longer a membership organisation since becoming a CIO. We still currently have 1,600 active members; however, we are here for all people affected by lupus and therefore engage with many more people across the UK as membership is not a requirement of support or information. This includes those living with lupus and their carers, healthcare professionals, workplace & education providers, and the research community. We provide community & peer support, health information, and a helpline. We also fund medical research, run a Centre of Excellence programme, support PPIE in research & clinical care, and advocate for change in the healthcare system. Funding is received primarily through community fundraising, charitable trust & foundation grants, corporate sponsors, and individual giving.
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.**	LUPUS UK has received no funding from Roche, the company bringing the treatment to NICE, in the past 12 months. In the past 12 months, we have received funding from one manufacturer of a comparator product (Otsuka – March 2025). For transparency, we have listed all pharmaceutical funding received in the past 12 months, including amount and purpose of funding: • July 2025 - £341 from Biogen for consultancy services to source patient speakers and present a talk on lupus at an internal company event. • March 2025 - £220 from Otsuka Pharmaceuticals for consultancy services to support patient input for an internal company education event. • February 2025 - £450 from Autolus Ltd for consultancy services to source patient speaker and present a talk on the needs of people with lupus at an internal company event. • January 2025 - £33,600 from Autolus Ltd – restricted educational grant to Lupus UK & Cognitant Ltd for development of an animated video on CAR-T. Autolus had no editorial or content input or control.

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?	Experiences and views from the community have been collected through various recent surveys and reports, including:
	• An anonymous Lupus UK online survey conducted between 04/07–15/07/2025 (n=23), specifically designed to understand the experiences & treatment needs of people with lupus nephritis & carers for this submission. All quotes in this submission are taken from this survey.
	• An anonymous Lupus UK online/postal survey & series of focus groups conducted between 04/03/2025 – 25/05/2025 (n=548) about the experience & needs of the whole lupus community, including people with lupus nephritis and carers.
	• Previous Lupus UK surveys on experiences of lupus nephritis and its treatment in 2020 and 2023.
	• External reports on the experiences of people with lupus including:
	  ○ 2025 RAIRDA survey "Rare Care Matters"
	  ○ 2025 CEDAR NHS Wales Lupus Report
	  ○ Other research studies & reports are cited throughout & a reference list is given in an Appendix at the end of this form.

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?	Lupus nephritis (LN) represents a major source of morbidity and mortality among individuals with systemic lupus erythematosus (SLE), with an estimated 25–60% of SLE patients developing the condition. It occurs more frequently and with greater severity in those from Black, Hispanic, Asian, and Indigenous populations [1]. The day-to-day symptoms of lupus nephritis are similar to those of other kidney diseases and can include: • Changes to urine (including appearing dark, containing blood, or being foamy) • Increased frequency of urination, especially at night • Puffiness/swelling in the feet, ankles, and legs that worsens over the course of the day • Fatigue • High blood pressure As LN is a manifestation of SLE, people with LN will also experience a range of wider SLE symptoms such as skin rashes, joint pain, and

	mouth ulcers. The lived experience of LN can vary considerably. Some people may only experience mild symptoms with limited kidney damage, whereas as others will have more severe disease and progress to End-Stage Renal Disease (ESRD). Approximately 4–28% of patients with LN develop ESRD [2]. It is a flaring condition, and as such can be unpredictable and worsen even in those whose disease is currently well-controlled or mild. Respondents to our surveys shared that this unpredictability had a significant impact on their quality of life, mental health, and ability to engage with social and work life. *"More than anything, there's a constant awareness and anxiety about triggering a flare-up. When flares do happen, everything changes."* *"It's the unpredictability and constant vigilance that wears you down - never knowing which small indulgence or moment of overexertion might tip the balance."* The constant fear of disease progression was echoed by others, who described living in a state of *"worry that it will get worse"* and the toll that takes on their mental wellbeing, including among those whose disease was currently well-controlled: *"I'm not too bad. I work full time. It plays on my mind sometimes, as there's always the worry it will get worse and lead to kidney failure."* *"Since last year's flare, I'm down to an eGFR of 30. I'm actively dreading the next stage."* Fatigue is commonly reported as one of the most burdensome symptoms in our own surveys and in peer-reviewed research [3], which has an impact on all areas of life. There are also significant impacts of other symptoms such as pain, swelling, and loss of mobility: *"Relapsing from a renal point of view is tricky. I end up being so oedematous that I can't wear footwear and then wake up every morning with a swollen puffy face… it's scary because I'm already on lots of medication and hard to see a way out."* *"When I flared I could not go to the toilet by myself or get out of bed or walk."* Prevalence of poor mental health is high amongst patients living with LN. In one study, the majority of patients reported both moderate anxiety and depression (60% and 61% respectively), causing a significant deterioration in quality of life and disease outcomes. Emotional health, burden to others, body image, intimate relationships, pain, planning and physical health were all reported as quality of life domains impacted [4]. In our surveys, people described feeling socially isolated, anxious, and depressed, especially

	when their ability to participate in life was limited. *"It prevents me from participating in many activities out of fear of running out of battery."* *"I'm on long-term sick which is affecting my mental health… my flares seem to be every day."* SLE, and LN specifically, can impact a person's ability to maintain employment. In RAIRDA's 2025 survey, 31% of respondents with lupus were unable to work at all due to their health. Of all respondents, 66% of working individuals said their condition affects their ability to perform their job effectively, and 40% had made changes to their working hours due to their condition [5]. Responses to our LN survey included some people who are *"able to hold down a full time job and continue with [my] life with some modifications"* and others who had to leave employment entirely, with serious financial and housing implications: *"When I was first diagnosed with LN and had to spend time in hospital - it led swiftly to the end of an academic career. This led to my having to claim benefits, and eventually to the loss of my home."* They also described how the condition affected their sleep, diet, energy, and hobbies ultimately leading to social isolation and loss of joy. The impact of caring for someone with lupus can be significant. This may be especially true for those whose lupus hasn't responded well to standard therapy – those who could potentially benefit most from obinutuzumab. Fatigue, pain and weakness can be limiting factors in mobility and capacity for activities. This often means a partner/carer will need to provide additional assistance with transport for medical appointments and essential personal and household care. Caring can also have an impact on mental health. The unpredictable nature of the disease, frequent flares, and long-term uncertainty can cause ongoing anxiety and feelings of helplessness. In responses on our surveys, carers described significant impacts, including anxiety and reduced time for work or social life, especially when symptoms worsened. Although the impacts described here are often shared by those with SLE without LN, individuals with active LN experience greater impairments in physical and emotional functioning, poorer mental health outcomes, and reduced health-related and non-health-related quality of life compared to those with SLE without LN [6]. Patients with LN experience substantial QoL impairment across all domains measured by the SF-36. Importantly, QoL appeared worse in those with active disease or class III/IV LN. [3]. The lived experience of lupus nephritis is consistently marked by unpredictability, fatigue, physical limitations, and emotional stress. Whether in remission or facing ongoing flares, people with LN often have to adjust their lives significantly, both practically and psychologically.

7. What do patients or carers think of current treatments and care available on the NHS?	Some people with lupus nephritis (LN) are satisfied with their current treatment, feeling it controls their symptoms well. However, most people in our recent surveys expressed a desire for more effective treatments, less side effects, and more treatment options. Although current treatments can be effective for some, as a heterogenous condition they are not effective for all, or may not be well-tolerated by all. Flares often necessitate an increase in treatment to control the inflammation; many people with lupus will have been prescribed several different medications to try and manage their condition. It is often the case that a treatment does not sufficiently control symptoms or causes adverse effects that cannot be tolerated. Many lupus treatments can take months before the full benefit may be experienced, meaning a significant period with a lower quality of life. In our survey, the effectiveness of treatments across different facets of life varied considerably, even among those who felt their treatment mostly met their needs. For example, around 35% of respondents said their treatment completely meets their needs when it comes to moving around and caring for themselves. However, only 23% felt that their treatment completely supports them in managing daily responsibilities such as work, study, parenting, or housework. Similarly, 28% of people said their treatment somewhat enables them to enjoy socialising and hobbies, but satisfaction drops further in the area of intimacy and relationships, where 19% said treatment does not help at all. Many people with LN expressed concern that they were running out of options as their treatment was no longer, or had never, controlled their disease. “Effectiveness” was the common wish for future treatments. *“I just want something that works. I feel like I’ve exhausted options and now just waiting for my renal function to deteriorate to the point of dialysis/transplant.”* The side effects from current treatments were also a significant concern. Side effects were sometimes reported to be felt to have as a great an impact on quality of life and ability to engage in work/social life as LN itself. Common side effects that people find difficult to manage include insomnia, nausea, and hair loss. *“One of the biggest challenges is the side effects. Over time, the cumulative impact of things like hair loss, hyperpigmentation, and chronic fatigue adds up, not just physically, but emotionally too. So having a treatment that is effective without such a high cost to my*

	quality of life is important to me." *"It is frustrating to live with the disease and the treatment side effects simultaneously, without a clearer path toward improvement."* Steroids are often highlighted as having particularly challenging side effects to tolerate, alongside associated risks of long-term use such as osteoporosis. Some people also have concerns about the impact of immunosuppressants and the risk of infection. Many treatments for lupus suppress the immune system, and consequently increase the risk of infection and can reduce the efficacy of some vaccines. Approximately 19-35% of people with LN develop serious infections partly owing to immunosuppressive therapies and steroid use [7]. *"I worry about the risk of infection vs taking immunosuppressants, especially as [I'm] taking an unusual cocktail."* The provision of care for people with lupus in England and Wales is inconsistent. A recent UK-based study suggested that there is geographical variation in treatment protocols and access to specialist management [8]. Many patients living closer to larger cities and able to access a specialist centre with multidisciplinary clinics report a much higher level of satisfaction with the care they receive. Most LN patients without access to specialist MDT services will be required to attend additional consultations split between nephrology, rheumatology and possibly multiple other specialties. This is often accompanied by poor communication between clinicians, a lack of a coordinated care plan, and barriers to accessing some treatments, such as biologic therapies. For example, two recent reports from Wales highlighted difficulties in access to care and services, particularly for those living rurally [9] [10]. *"I often have to drive for more than an hour and a half to get to appointments. I worry about what will happen when I am too old or too poor to do this."*

8. Is there an unmet need for patients with this condition?	Despite advances, lupus nephritis (LN) remains associated with considerable unmet medical needs. It is linked to significant morbidity and increased risk of end stage renal disease (ESRD). There is a significant need for effective treatments which work quickly, and are sustained. Despite improvements in therapeutic strategies, decreased mortality rate, and an improvement in the disease prognosis, the percentage of patients progressing into ESRD remains steady [11]. The risk of ESRD in lupus nephritis improved between the 1970s and the mid-1990s and then plateaued, with an increase in the late 2000s [12]. This pattern suggests limitations in the effectiveness of, or access to, current treatments. There is a critical need for those patients who are refractory to all current treatments. *"I can't help but worry that there will come a point when there is nowhere left to go, either the medications can't be increased any further, or my body stops responding. It doesn't feel like a sustainable long-term solution."* There is a need for treatments which will reduce the over-reliance on steroids in the management of LN. Standard care makes significant use of steroids as induction treatment and is typically part of maintenance treatment for at least 3-5 years after remission. LN most commonly occurs as an early-onset symptom of SLE and is much more prevalent in juvenile-onset lupus. This means that the lifetime burden of steroids and risk of adverse events and steroid-associated comorbidities is significant. Most recently updated clinical guidelines on the management of LN (e.g. EULAR, 2023) advocate more strongly for early combination therapy and more restricted use of steroids. Monitoring is crucial to detect, diagnose, and treat LN early, before damage accumulates. Our wider survey in 2025 highlighted that many people are not being appropriately monitored, with some reporting never having had a urine test, or only being tested and diagnosed after their LN had progressed. Alongside an unmet need in treatment itself, responses to our surveys also indicate an unmet need in treatment access and provision, such as establishing more MDT and joint clinics between rheumatology and nephrology, better rapid access at times of flare, and a need for specialist psychological support. This is also reflected in published reports such as that by RAIRDA [5].

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We were unable to survey anyone who has previously been treated with obinutuzumab. However, based on a description of the treatment administration method, some people are optimistic about the convenience of this treatment and reduced interference with daily life. The infusion represents an advantage for those who struggle with treatment compliance due to complex tablet regimens and brain fog, for example, and for some receiving treatment in a hospital setting felt safer. *"Not being able to forget to take it could also be a potential benefit."* "*The hospital setting offers reassurance. Receiving the infusion under medical supervision provides a sense of safety, knowing that trained staff are monitoring me throughout the process and can address any immediate reactions or concerns."* Patients are hopeful about the treatment's effectiveness in controlling their lupus nephritis (LN). For many who would be eligible for obinutuzumab, standard therapy has not provided adequate disease control. For those where it has, people worry that their current treatment may stop working (as many have experienced this with previous treatment), with serious long-term consequences. Therefore, obinutuzumab provides a needed alternative with the potential of an improved quality of life. With their LN better controlled, it could reduce the number of hospital visits and admissions they may otherwise have needed, which would be a positive change for them and their family/carers. It could potentially mean they are able to continue in employment and experience further benefits to their social and psychological wellbeing. *"If obinutuzumab proves more effective in controlling lupus nephritis, especially in reducing flare-ups or lowering my reliance on steroids, that would represent a significant improvement over my current treatment regimen."* *"Overall, I'm open to this treatment option and see clear advantages in terms of convenience, peace of mind, and the potential for better disease management."*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Lupus presents differently in each patient and response to treatment can vary similarly. A treatment that works well for one patient will not necessarily work for another. Adverse reactions to medications are seen in many people with SLE, resulting in a need to switch to another treatment option. It is therefore likely that some patients will not be able to tolerate obinutuzumab or will not respond as hoped. As previously stated, we were unable to survey anyone who has previously been treated with obinutuzumab. Based on a description of the treatment administration method, some people had concerns about access, particularly for people who live alone, live far from a

	specialist hospital, or who would have to take time off work or childcare for infusions. *"Getting to the location, cost and support especially if you are on your own."* *"Unless you can work it's going to be hard to have a whole day out - plus would the strain on hospitals be ok?"* *"Carers may be affected depending on time I would need to be at hospital."* If approved, consideration should be given so there is equity of access for those in rural areas, those far from specialist centres, or those who struggle to attend hospital appointments due to work or family commitments. As infection risk is a concern for some, and some have struggled to access booster vaccinations against covid-19, any infection risk from obinutuzumab needs to be considered and it should be ensured that people have access to appropriate vaccination and post-viral treatments.

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.	**People who are refractory for current treatments:** For these individuals, standard therapy, even those that have proven to be effective for others, are not a viable option. Given the heterogeneity of lupus and the variability in treatment response, there is no single 'best' treatment and additional options such as obinutuzumab can help address this significant unmet need. **People with juvenile-onset systemic lupus erythematosus (JSLE):** LN is more likely in JSLE, occurring in 50–82% of cases (versus 20–40% of adults), with only 40–60% of patients achieving complete remission [13]. Around 15% of children with LN go on to develop chronic kidney disease 5, and the presence of LN is consistently associated with higher mortality in people with SLE. As lupus has no cure, children with JSLE will become adults with a longer duration of LN that is likely to be more severe, along with greater cumulative treatment exposure and increased risk of associated side effects. Having another treatment option that is steroid-sparing such as obinutuzumab may be very beneficial for this group of people. **People of ethnic minorities:** LN disproportionately affects people from ethnic minority backgrounds, particularly those of African, Caribbean, South Asian, and Chinese heritage, with higher prevalence, greater severity, and poorer treatment response (in both outcomes and risk of adverse effects) compared to White populations [14] [15] [16]. Whilst there is mixed evidence whether this is driven by genetic or social determinants (such as health inequalities), the impact remains clear. The disproportionate burden of lupus nephritis among ethnic minority populations is a key equalities concern. Obinutuzumab may offer a potential new option for those most affected, more

	likely to be severely affected, and historically underrepresented in clinical trials. In the Phase 2 & 3 NOBILITY trials, a high proportion of participants were from ethnic minority groups, strengthening the relevance and generalisability of the findings for these populations. In addition, ethnic minorities face higher risks of comorbidities like diabetes and hypertension, which can worsen the impact of lupus nephritis and its treatment [17].These disparities highlight the need to consider whether steroid-sparing treatments like obinutuzumab could reduce treatment-related side effects and comorbidity risks, especially given the heavy reliance on corticosteroids in current care. **People who struggle with treatment adherence/compliance:** Managing tablet regimens can be difficult, especially when complex, experiencing fatigue and/or brain fog, and coping with the demands of daily life. As obinutuzumab is received as an infusion in a hospital setting, it can offer a meaningful advantage for those that struggle with treatment compliance and prefer the structure, safety and supervision of this method of administration. Groups of people with LN who would benefit less from this treatment than others include **people who struggle to attend clinic/hospital, if access pathways are not considered:** Many have full time responsibilities alongside managing the day-to-day impact of living with lupus. The obligation of hospital visits can lead to pressure to take unpaid leave, pay childcare costs, find and pay for appropriate travel (which can involve long commutes), and rely on friends and family (if present) for physical and emotional support. Therefore, if obinutuzumab treatment is not easily accessible locally, a hospital setting for treatment administration can be less favourable.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Health inequalities:** There are significant health inequalities across the UK in the diagnosis, treatment, and outcomes of lupus and lupus nephritis. Many people remain undiagnosed or unaware they are in the early stages of disease, and the heterogeneity of lupus nephritis highlights the need for a range of effective treatment options. Access to care varies widely, with notable inequities affecting women, people from Black, Asian and other minority ethnic backgrounds, and those living in the most deprived areas [18]. These groups are less likely to receive timely testing and treatment and face higher risks of progression to kidney failure. A recent UK-based study also identified geographical variation in treatment protocols and access to specialist management, meaning some patients may not have access to current comparator treatments [8]. This creates a deeper need for an approved and accessible option such as obinutuzumab. **People of ethnic minorities:** There is increased disease incidence, prevalence, progression and severity and comorbidity risk among those with Black or Asian ethnic ancestry [14] [15] [16]. There is mixed evidence whether this is due to genetic/biologic differences or health inequalities and socioeconomic factors [16] [19] [20] [21] [22]. Regardless of the cause of these findings, the fact it tends to be more severe in these groups is an important equalities issue for consideration, both in terms of a need for more treatment options for this population and a greater need for treatments which may be steroid-sparing and could reduce the risk of co-morbidities and side

	effects. **Socioeconomic status:** People from lower socioeconomic backgrounds may face greater barriers to accessing current LN treatments, particularly those that require specialist input or shared care arrangements. These challenges may include geographical distance from specialist centres, travel costs, or time away from work or caregiving responsibilities. This is especially important given that lower socioeconomic status was reported to be strongly associated with reduced survival amongst patients with LN-induced end-stage renal disease, further compounding health inequalities [14]. **Sex:** SLE is more prevalent in women than men (at a ratio of approximately 9:1). However, the prevalence of lupus nephritis specifically has been found to be around 5:1. This means that, although there is higher prevalence among women, men with SLE may be at higher risk of developing lupus nephritis [23]. **Age:** As discussed in question 11, people diagnosed with LN during childhood (juvenile-onset systemic lupus erythematosus [JSLE]), often experience a longer disease course, more severe disease and greater treatment exposure as lupus has no cure. This can result in a higher treatment burden from a younger age and long-term complications. Age is therefore an important equality consideration, particularly given the limited number of approved treatments for JSLE and childhood-onset LN. Access to new treatments like obinutuzumab may help reduce this disparity and improve outcomes for an underserved group. **Pregnancy:** Uncertainty around fertility and pregnancy can have a significant impact on the quality of life of people with lupus nephritis, many of whom are of childbearing age. Active disease is linked to poorer maternal and foetal outcomes, making pregnancy a major concern for those affected [24]. Cyclophosphamide is still used to treat lupus nephritis despite presenting a risk of infertility. The role of obinutuzumab as an additional treatment option for those wishing to conceive should be carefully considered.

Other issues

13. Are there any other issues that you would like the committee to consider?	If there is insufficient evidence to approve obinutuzumab for use during this appraisal, it should be considered for managed access schemes: 1. If obinutuzumab was found to be effective, but not more cost effective than comparators, it should still be made available on the NHS, at the very least, for those patients who are refractory to current treatments with no feasible treatment options. 2. It could also be considered for managed access for children and/or adolescents, if more evidence is required for this age group, as they are more likely to develop lupus nephritis. If not included in the cost-effectiveness analysis, the committee should consider:

	- Morbidity secondary to LN - The value of prevention of progression of a chronic, incurable disease, which may reduce the need for future treatments (e.g. the need for dialysis or transplant), and the financial and quality of life (QoL) implications of this. - That many standard QoL measures often fail to adequately capture important symptoms such as fatigue, and that qualitative research and patient-reported priorities should inform QoL assessments. Forthcoming British Society for Rheumatology (BSR) guidelines (expected late 2025) are likely to align with recent EULAR updates (2023), which support earlier combination therapy, reduced steroid use, and earlier biologic consideration. These future standards should be taken into account if current BSR guidelines are used to contextualize treatment pathways.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Lupus nephritis has a significant impact on people living with the disease and their close family, including impacts on mortality, morbidity, quality of life, mental health, and ability to engage in work and social life. • As a heterogenous disease, there is no "best" treatment, and some people are refractory to all current treatments • There is an unmet need for more treatment options to better control flares, and prevent the accumulation of damage and disease progression. • There is a particular need for treatments which can reduce the reliance on steroids, due to short- and long-term negative impact. • There are particular groups who may particualrly benefit from more treatment options, particularly those from Black and Asian ancestries, and those adults who developed SLE in childhood, as there is a higher risk of severe disease and of progression to end-stage-renal-disease.

Thank you for your time.

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APPENDIX:

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Single Technology Appraisal

Obinutuzumab with immunosuppressive therapies for treating lupus nephritis [ID6420]

Professional 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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	British Society for Rheumatology
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** or No A specialist in the treatment of people with this condition? Yes or **No** A specialist in the clinical evidence base for this condition or technology? Yes or **No** Other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Society for Rheumatology (BSR) is a professional body for rheumatology professionals – this submission has been completed by BSR's Special Interest Group for SLE.
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.**	BSR has not received any funding from Roche in the last 12 months.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

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.)	To induce and maintain remission in patients with active lupus nephritis. Thereby to preserve renal function and overall health lifelong.
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.)	Overall response needs to be assessed by rheumatologist and/or nephrologist treating the patient as there are many factors that differ between patients. EULAR set guidelines for treatment response as follows: • 3 months: protein-creatinine ratio reduced by 25% • 6 months: protein-creatining ratio reduced by 50% • 12 months: <70 mg/mmol • In each case, with stable or improving kidney function • With prednisolone dose 7.5mg or less by 12 months In the case of patients with class V lupus nephritis, a slower improvement is acceptable. The 12 month target was validated against long-term outcomes in multiple clinical studies (Dall'Era M *et al. Arthritis Rheumatol.* 2015;67:1305–13). If a patient had previous nephritis, failed multiple therapies, other comorbidities etc. then these targets would be adapted or interpreted differently.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes- Lupus nephritis (LN) is a major cause of increased morbidity and mortality in SLE. The most common standard therapy used in the UK is mycophenolate mofetil. We can estimate achievement of the above treatment targets from the placebo arms of clinical trials in which mycophenolate mofetil was used as standard of case. In such trials rate of achievement of these targets was low (e.g. 27% in AURORA 1. Tamirou F *et al*. *Lupus Sci Med.* 2015;2**:**e000123; in the range of 20%–30% in phase 3 trials of belimumab and voclosporin; 2. Fanouriakis A *et al. Ann Rheum Dis.* 2024;83:15–29; 3. Anders HJ *et al.* Abstract 0357 ACR Convergence 2022). Older long

	term clinical studies show that failure to achieve a full response is associated with markedly worse long term renal outcome (i.e. relapses, renal failure or premature death), although these latter consequences may take years or even decades to be fully manifest. Overall, Up to 44% of patients with class III or IV LN progress to end-stage renal disease (ESRD) within 15 years, ultimately requiring renal replacement therapy such as dialysis or kidney transplantation. (PMID: 31733714, PMID: 26815601). Such outcomes have severely negative impacts on morbidity and mortality and have very high healthcare costs and are associated with very poor quality of life and inability to work.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Historically, treatment recommendations stated that to induce renal response, immunosuppressive treatment includes steroids with mycophenolate mofetil (MMF) or IV low-dose cyclophosphamide (Eurolupus regime) or rituximab in refractory cases (if patient fulfils the "Clinical Commissioning Policy Rituximab for refractory Systemic Lupus Erythematosus-SLE in adults and post-pubescent children [200402P]" criteria). This is likely still the most common treatment approach in the UK and is associated with a need for higher dose corticosteroids than is now recommended. However, with the publication of new evidence, guidelines are being updated. We know the poor long-term outcomes of these single-immunosupressant options as described above. We now have evidence for the superior responses of combination therapies (MMF combined with voclosporin, belimumab or Obinutuzumab). In light of this, in the past 12 months British, European and American guidelines have all been re-written to recommend combination therapy first line for class III, IV and V lupus nephritis. There is already a NICE TA for the combination of MMF and Voclosporin first line in lupus nephritis, and for belimumab for certain subsets of SLE patient who may or may not have nephritis. (MMF and voclosporin- TA882 or MMF and belimumab if TA752 criteria for active SLE criteria are fulfilled). However Voclosporin is not suitable for all patients. For example, it cannot be used in patients with significantly impaired renal function (due to risk of severe adverse events). It is not thought to be effective for extra-renal manifestations of lupus that may be present, in contrast to the other immunosuppressive medications mentioned. And there is a significant pill burden and potential adherence issues that are known to strongly impact

	outcomes in this disease. IN addition is should be noted that not all patients given any of the current therapies respond hence the need for alternative options for induction and treatment of relapses. Other important aspects of care, emphasised in the new 2025 BSR Guidelines, include care of patients in combined rheumatology-renal clinicals, or via MDTs, use of lower gluocorticoid doses, and use of combination therapies in the maintenance phase, as well as higher dose cyclophosphamide or rituximab in special situations. These new guidelines are not yet fully published but were presented at BSR conference in April 2025 and we would be happy to share a copy of the manuscript on request from NICE. Despite the older and newer guidelines, it must be emphasised that a recent survey revealed marked variation in care across UK rheumatologists and nephrologists, often differing from existing guidelines (PMID: 38469156). This variation is likely to affect long-term outcomes, so a NICE recommendation for Obinutuzumab with much better outcomes could be highly impactful.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	British Society for Rheumatology guidelines – Gordon C et al. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults, *Rheumatology*, Volume 57, Issue 1, January 2018, Pages e1–e45, https://academic.oup.com/rheumatology/article/57/1/e1/4318863. This version of the guidelines did not give specific recommendations for lupus nephritis, instead referring to EULAR / ERA guidelines from 2012 which are now considerably outdated. Updated BSR 2025 guidelines would be in place by the time that Obinutuzumab was available in UK. Some key points regarding selection of therapies now being recommended: • First line for induction: methylprednisolone and reduced dose oral prednisolone • First line for induction: one of Obinutuzumab +MMF, or Belimumab + MMF, or Voclosporin + MMF, or Tacrolimus + MMF • Other options for induction if first line therapies are unsuitable: Belimumab + Eurolupus protocol cyclophosphamide, Rituximab + MMF, MMF alone, Eurolupus or NIH dose cyclophosphamide alone • First line for maintenance: continue the same first-line combination therapies for 3 years or longer • No glucocorticoid use in maintenance There are many other recommendations about the delivery of care, use of specialist centres and combined clinics, use of biopsies, and adjunctive non-immunosuppressive therapies.

	Although there is phase 3 RCT evidence to support the use of belimumab in LN, this is not explicitly recommended by NICE. The NICE review of this therapy for this indication was not completed. However, the NICE approval for belimumab in non-renal SLE does not exclude its use for patients with nephritis (e.g alongside other features). We emphasised that the BSR guidelines are based on the best evidence but treatment choices must consider NICE and NHS funding criteria as well, anticipated to evolve over the lifespan of the guideline.
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.)	The new BSR guidelines mentioned above provide a well-defined pathway of treatment. There is scope to modify treatment choices based on specific patient factors within the above options, to be guided by specialist centres of MDTs. In cases with partial or non-response, the pathway is less well defined but expert advice is advised and likely to still choose from the above options. In actual real world practice, we again reference the survey of UK clinicians (77 respondents - 62.3% rheumatologists and 37.7% were nephrologists) which showed that first-choice treatment of class IV LN in pre-menopausal patients varies among clinicians (MMF [(53.2%], followed by CYC [19.6%], rituximab [12.5%] or a combination of immunosuppressive medications [11.7%]) with differences between nephrologists' and rheumatologists' choices. Only 27% rheumatologists reported having a formal departmental protocol for treating patients with LN (PMID: 38469156). The greater specificity in the new BSR guidelines about treatment options may increase conformity, and there will be considerable work on disseminating and implementing these.
9c. What impact would the technology have on the current pathway of care?	Up to 44% of patients with class III or IV LN progress to end-stage renal disease (ESRD) within 15 years, ultimately requiring renal replacement therapy such as dialysis or kidney transplantation. Complete response is required to ensure good long-term outcome and rates of complete response with current standard therapy are low (listed above). Some other therapies have significant toxicity, in particular, cyclophosphamide is teratogenic and associated with reduced fertility posing significant concerns given that the majority of lupus patients are women of childbearing age. Voclosporin can lead to an additional decline in renal function which makes it unsuitable for many patients. Glucocorticoids lead to numerous long term toxicities. Notably in the field of lupus nephritis, an RCT compared higher and lower dose glucocorticoid regimens and found 19% vs. 10% serious infections and 17% vs.

	0% zoster infections for the higher and lower dose regimens respectively (Zeher et al. Lupus, 2011-12, Vol.20 (14), p.1484-1493). . Key impacts expected from Obinutuzumab based on published trials and this context are: - Higher rates of renal remission, which should lead to less renal failure long-term - Lower rates of renal relapse (outcomes of relapses are far worse than initial episodes of nephritis) - Higher adherence due to IV route of administration (a key predictor of outcome in lupus nephritis – voclosporin combined with MMF has a high pill burden and potential toxicity) - Expected higher efficacy for extra-renal manifestations due to the B cell target and demonstrated reduction in anti-dsDNA antibodies and improvement in complement levels (associated with higher disease activity both renal and non-renal) - Lower long-term glucocorticoid use - More treatment options when voclosporin, belimumab, tacrolimus, cyclophosphamide and mycophenolate are unsuitable
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology will allow and additional first-line treatment option alongside other first-line choices within the treatment pathway for patients with active lupus nephritis class III, IV or V.
10a. How does healthcare resource use differ between the technology and current care?	Day case until visits are required for administration of Obinutuzumab (weeks 0 and 2, then repeated every six months or at physician discretion). Each visit is a full day. Belimumab also requires day case unit visits for infusions, but these are shorter, albeit every month long term. Voclosporin and mycophenolate are oral but have more prescription and blood monitoring work for primary and secondary care. Intravenous therapies may improve adherence, which is a key determinant of long-term renal outcome in lupus nephritis.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Recognised centres commissioned to provide specialised rheumatology services or renal services that have expertise in the assessment and management of SLE. Combined rheum-renal clinics and/or MDT approval is advised for advanced therapies or SLE. Obinutuzumab could be given at nonspecialised centres if the appropriate use of obinutuzumab has been ratified at/by a specialised centre.
10c. What investment is needed to introduce the	No extra investment envisaged. Rituximab, which is another biological medicine that selectively targets B cells, and is administered in a similar way, is already used for SLE and other rheumatological conditions, so most

technology? (For example, for facilities, equipment, or training.)	centres will already have adequate training, specialist nurse support and experience with B-cell depleting therapies. Many centres also have experience in delivering Obinutuzumab, in cases of patients with anti-drug antibodies to rituximab (PMID: 35266512).
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes-as above, obinutuzumab is an evidence-based treatment that not only improves renal outcomes and reduces glucocorticoid burden. And improves serological abnormalities (anti-dsDNA and low complement) often associated with non-renal lupus manifestations.
11a. Do you expect the technology to increase length of life more than current care?	Yes – ESRD and chronic kidney disease are associated with significant morbidity and mortality. Prompt Renal responses with this drug are associated with reduced rates of chronic renal failure and end-stage renal disease that are associated with premature death. Additionally, the steroid sparing effect associated with obinutuzumab treatment would result in less glucocorticoid toxicity, which itself can be life limiting e.g. by causing serious infection, cardiovascular disease, stroke, diabetes, osteoporosis etc.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes – both in terms of clinical remission from lupus nephritis itself, preservation of renal function long-term, and associated steroid sparing benefits including prevention of complications such as cardiovascular disease, infection and osteoporosis. Current UK standard of care is not sufficient and is associated with poor HR-QOL.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes- Patients of Afro-Caribbean and Asian ancestry (16.2% of England and Wales population- **GOV UK: Population of England and Wales**) have a higher incidence of SLE and lupus nephritis and in addition, experience more severe disease compared to those of European ancestry and so may benefit more from the availability of Obinutuzumab as another therapeutic option. The trials did include people with diverse racial and ethnic backgrounds and there is no known group for whom it would be less effective, but it would not be recommended in patients with hypogammaglobulinemia due to risk of infection.

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 there any practical	Administration of obinutuzumab is not expected to be more difficult to use than current care. Rituximab, which is another biological medicine that selectively targets B cells, is already used for SLE and other rheumatological conditions, so most centres will already have adequate training, specialist nurse support and experience with B-cell depleting therapies. Some centres also have experience in delivering obinutuzumab, in cases of active severe lupus with anti-drug antibodies to rituximab that have failed other therapies. Beyond an additional appointment for education on Obinutuzumab, if patients can be brought into remission and reduce their steroid exposure, overall

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.)	healthcare resource use should be reduced e.g. fewer clinic appointments, less investigations for renal relapse and reduced consequences of cumulative steroid use, and importantly a significantly reduced number of patients progressing to require renal replacement therapy and/or kidney transplant.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Decisions on initial induction therapy for lupus nephritis is advised to be made in specialist centres, combined clinics or via MDTs, particularly when biologic or other high cost therapies are being used. Care should be administered by combination of rheumatology and renal services thereafter. Patient should have objective evidence of disease using a renal biopsy (in some cases this is not possible, and expert opinion by specialists in the treatment of lupus nephritis should be sought with other forms of evidence for nephritis such as blood and urine tests). All patients treated with Obinutuzumab for lupus nephritis should be registered with the BILAG Biologics Register (BILAG-BR) with their consent. Data from the BILAG-BR has previously demonstrated that real-world populations of biologic treated SLE patients are not representative of clinical trial recruitment (PMID 38796923), therefore recruitment into the BILAG-BR will allow to assess the long-term safety and effectiveness of the drug in the UK population.
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?	Yes – The full long-term consequences of inadequate treatment of lupus nephritis may not be fully manifest for years or decades. In all humans, renal function gradually declines with age, although does not usually reach clinically impactful levels until later elderly years. In a single episode of lupus nephritis, even with good treatment, a certain degree of renal injury occurs. This will lead to a new trajectory of decline that brings forward the age at which renal dysfunction begins to impact on health. Further, outcomes of repeat episodes of nephritis are significantly worse than the first, with lower rates of complete response to therapy and higher rates of renal dysfunction. For this reason, patients who have inadequate treatment of an initial episode of nephritis and/or multiple relapses may experience renal dysfunction that impacts on morbidity and shortens life many decades earlier. Such outcomes will not be captured within studies of only a few years length, but would be predicted by the observed renal response rates in these studies. Glucocorticoids in SLE are associated with damage accrual (PMID: 24834926). The reduction of glucocorticoid use will improve Health-related quality of life (HRQoL), but that will be difficult to quantify. Extra-renal disease activity can cause rashes, arthritis, lung, heart or brain inflammation and blood problems. These can be life- or

	organ-threatening, or influence quality of life. These other types of lupus respond well to B cell targeted therapies, but were not part of the primary endpoint of the trial.
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?	Yes- the mode of action is different from the drugs we currently have available and the mode of delivery and efficacy in extra-renal disease activity also differ from the existing treatments. It is important to note that Obinutuzumab is a humanized type II anti-CD20 monoclonal antibody distinct from rituximab which was a chimeric monoclonal antibody that caused antibody formation in some patients limiting its efficacy.The availability of a choice of therapies is especially important in a complex multi-system heterogeneous autoimmune disease, where therapies are not always be tolerated or effective, and in the lifetime of a patient switches in therapy may be needed for recurrent episodes of acute lupus nephritis, although relapse rates with Obinutuzumab should be lower than with other drugs.
16a. Is the technology a 'step-change' in the management of the condition?	Yes
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes- as above, 44% of patients with class III or IV LN progress to end-stage renal disease (ESRD) within 15 years, ultimately requiring renal replacement therapy such as dialysis or kidney transplantation. Obinutuzumab improves renal outcomes and reduces glucocorticoid burden with limited safety impact that is comparable to existing therapy. In addition, the availability of new therapies with different mechanisms of action is particularly valuable for patients who have had toxicity, inefficacy or relapse after other therapies, in whom the outcomes of untreated disease would be worse and given the significantly lower complete response rates reported with current therapy than with obinutuzumab.
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?	No unexpected safety signals were identified in the phase III study of Obinutuzumab. The percentage of patients with adverse events was similar in the obinutuzumab group and the placebo/standard of care group. There was a small increase in serious adverse events related to covid-19 in the obinutuzumab group compared to placebo, although that reflects the conduct of the trial during a severe phase of the pandemic and importantly before vaccination was available – this is unlikely to be replicated in normal practice going forward. Indeed, in the earlier phase 2 trial in a similar patient population, serious

	infections were numerically less frequent with obinutuzumab compared to placebo. Over long-term exposure (e.g. many years which may not be required), repeated cycles of obintuzumab might lead to hypogammaglobulinaemia, which has a more definite effect on infection risk. This is well understood by rheumatologists from the use of rituximab over the past 20 years. We monitor immunoglobulin levels over each cycle of therapy and consider longer retreatment intervals or switching to a different therapy if immunoglobulin levels are falling excessively. In the worst cases where immunoglobulin levels fall excessively and cause increased frequency of infection, immunoglobulin replacement can be needed. This is effective but expensive, limited supply and inconvenient. However, this outcome is rare in our experience using rituximab for SLE (somewhat more common in ANCA vasculitis).

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	Not applicable
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes, renal response rates, glucocorticoid dose, and infections are reported in the trial. Efficacy on extra-renal disease activity was not part of the primary endpoint but secondary outcomes included reduction of anti-dsDNA antibodies and improvement in complement levels which are relevant to non-renal lupus disease as well as renal lupus.Longer term outcomes are known to be predictable from these early outcomes. We would expect the therapy to maintain efficacy over time and prevent relapses. The published phase 3 data go out to 18 months but combination therapies for lupus nephritis are usually continued for at least 3 years (based on experience with voclosporin, belimumab, rituximab and tacrolimus combined with mycophenolate or cyclophosphamide). This longer-term follow up is being collected for obinutuzumab in a long-term extension. Longer term data on prevention of relapses would be helpful to

	support the use of obinutuzumab in maintenance therapy. However, from previous experience with the similar therapy, rituximab we would expect efficacy to be maintained over years with retreatment as necessary. We have strong long term evidence that, unless anti-drug antibodies occur, repeat cycles of rituximab reproduce the efficacy of previous cycles. And safety remains good unless hypogammaglobulinaemia occurs which, as described above, is uncommon and can be monitored and avoided.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	As explained above, in addition to renal response, Obinutuzumab was proven to be an effective glucocorticoid sparing agent (secondary outcome measure - prednisone dose of 7.5 mg per day or lower between weeks 64 and 76 was observed in more patients in the obinutuzumab than in the placebo group- 42.7% vs. 30.9%; 95% CI, 0.6 to 23.2). If the steroid sparing effect is achieved, we may see less steroid toxicity and damage accrual e.g., cardiovascular disease, diabetes, osteoporosis etc. suggestive of better long-term clinical outcomes as these are strongly associated with duration and dose of steroid exposure.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No. The treatment is approved and has been widely used for the treatment of chronic lymphocytic leukaemia and follicular lymphoma for around 7 years. The potential increased risk for severe covid has been noted for B cell depleting therapies such as rituximab and obinutuzmab during the pandemic. However, a large real world study of rituximab-treated patients in the UK showed that rates of severe covid reduced significantly in later less virulent pandemic waves and with the impact of vaccination. Other types of infection have not been increased by therapy, and in other randomised trials in SLE or lupus nephritis, serious infections have been numerically substantially lower with rituximab or obintuzumab compared to placebo (probably enhanced by successful steroid reduction).
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	No

NICE technology appraisal guidance TA882?	
21. How do data on real-world experience compare with the trial data?	Limited real-world evidence from the UK suggests that Obinutuzumab is effective in lupus nephritis with no significant safety signals (PMID: 35266512 and PMID: 40186329). These patients had refractory disease, with worse pre-treatment prognosis than those in the REGENCY and NOBILITY trials.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Yes - as above, patients of Afro-Caribbean and Asian ancestry (16.2% of England and Wales population- **GOV UK: Population of England and Wales**) experience more severe lupus nephritis compared to white population, are at increased risk of poor response and have higher rates of renal failure, so these patients in particular need more efficacious therapies than are currently available and are expected to benefit more from Obinutuzumab as diverse populations were studied in the trials of this therapy.
22b. Consider whether these issues are different from issues with current care and why.	It is difficult to determine whether the poorer renal outcomes observed in patients of Afro-Caribbean and Asian ancestry are primarily driven by genetic factors, well-documented racial and ethnic disparities in healthcare access and quality, late presentation and/or poor adherencebut administration of an efficaceous drug like this in hospital which only needs 6 monthly adminstration should improve long term outcomes as well as short term outcomes in these vulnerable patients and should help them to remain in work.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• With the current standard of care therapy, complete response rates are poor and up to 44% of patients with class III or IV LN will progress to end-stage renal disease (ESRD) within 15 years, ultimately requiring renal replacement therapy such as dialysis or kidney transplantation. • Certain subgroups of patients, such as African or Asian ancestries or younger age of onset are more likely to develop lupus nephritis, experience more severe disease, and more relapses. • Obinutuzumab has demonstrated superiority over standard of care treatment in a large randomised controlled clinical trial, with evidence for significantly improving renal outcomes as well as a steroid sparing effect with no unexpected safety signals. • The mode of delivery is convenient (infusions every six months). This is less frequent than comparators like cyclophosphamide and belimumab. It also carries an adherence advantage, which is a crucial determinant of outcome in lupus nephritis. • Overall healthcare resource use will be reduced through fewer clinic appointments, tests and investigations for renal relapse, reduced requirement of renal replacement therapy or kidney transplant and reduced comorbidity resulting from excessive glucocorticosteroid use.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Obinutuzumab with immunosuppressive therapies for treating lupus nephritis [ID6420]

Professional 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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- Your response should not be longer than 13 pages.

NICE National Institute for Health and Care Excellence

1. Your name	[redacted]
2. Name of organisation	The Renal Pharmacy Group (part of UKKA)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? No – specialist renal pharmacist. A specialist in the clinical evidence base for this condition or technology? No – experience with using this drug in 27 patients at the time of this submission. Other (please specify):
5a. Brief description of the organisation (including who funds it).	The RPG is part of the UKKA. The UKKA was created through merger of the Renal Association, British Renal Society and its affiliates, to support the multi-professional team with delivery of kidney care, education and research – enabling people to live well with kidney disease. UKKA is funded by its members, grants, events, project work and capitation.
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.**	Chiesi £960 RPG Otsuka £3,600 RPG
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.)	• To induce remission in active disease and stop progressive, permanent loss of renal function. Slow progression to end stage renal failure and dialysis. • Maintain patients in remission thorough keeping b-cells deplete. • Restore, maintain quality of life and to be able to remain in employment.
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.)	Complete renal response (CRR) would be defined as (Regency Phase III trial has been used as a marker, in addition to local practice) : • Reduction of urine protein-to-creatinine ratio (UPCR) < 0.5 g/g or then UPCR < 0.8 g/g without intercurrent events was also used as a secondary endpoint. (Note: local albumin-to creatinine ratio is used). • Improvement of estimated glomerular filtration rate (eGFR) ≥ 85% of baseline following acute event deterioration. Or the • Prednisone tapering: Achieving CRR while reducing prednisone to ≤7.5 mg/day was considered a meaningful glucocorticoid-sparing effect. • Reduction in LN flares and stabilisation of eGFR over a prolonged period of time (months to years) with minimal redosing with obinutuzumab. • Nil, to minimal intercurrent event such as: Need for rescue therapy, treatment failure. • Time taken to B-cell deplete and maintaining depletion. Conversely, time taken to b-cell repletion.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. There are a few key areas, where there appears to be an unmet need: 1. Patient with clear hypersensitivity to rituximab. Currently there are few alternatives and as a cohort are likely to have greater exposure to steroid based therapies. 2. Patients demonstrating a refractory response to rituximab, or highlighted as having ant-drug antibodies to rituximab. 3. Lupus nephritis often affecting younger cohorts, therefore want to limit steroid exposure and minimal visits to hospital for infusions and monitoring. 4. Severe disease – particularly class IV with high protein-to-creatinine ratio.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	A combination of high dose steroids, , A combination of therapies depending on patient case includes reducing dose steroids, mycophenolate mofetil (class V) or azathioprine (maintenance), hydroxychloroquine, cyclophosphamide and calcineurin inhibitors. Biologics: Belimumab (locally obinutuzumab has been used in NHS where trusts have agreed to fund. This is on the back of international experience recommended within **Kidney Disease: Improving Global Outcomes (KDIGO)** KDIGO 2024 guidelines and **European Alliance of Associations for Rheumatology (EULAR)** EULAR 2025 update. Previously ofatumumab IV was available on a patient access scheme – this has now ceased and withdrawn from the market.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	The TWO most comprehensive and current guidance are: 1. The **Kidney Disease: Improving Global Outcomes (KDIGO)** guidelines are among the most comprehensive and globally recognized for LN management 2. The European Alliance of Associations for Rheumatology (EULAR) updated its LN recommendations in 2025 3. In addition, NICE has issued or is developing guidance on several key therapies for **lupus nephritis (LN)**, including **calcineurin inhibitors (CNIs)**, **biologics like belimumab**, **mycophenolate mofetil (MMF)**, and **hydroxychloroquine (HCQ)**.
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 variation of practice nationally between different centres where patients fall out of standard pathways. LN is a condition that is likely to be managed differently at specialist centres in comparison to a local district general hospital. With regards to obinutuzumab for this – there seems to be consensus that the addition of this as a treatment is a welcome addition and would be of benefit. The dosing structure of administration is being challenged as original dosing structures are taken from cancer treatments where the burden of b-cells driven disease is likely to be greater. ICHT experience is that we have dosed 1g of obinutuzumab only and then monitored and redosed based on symptoms and rate of b-cell depletion and repletion.

9c. What impact would the technology have on the current pathway of care?	If **obinutuzumab** receives **NICE approval** for **lupus nephritis (LN)**, it would have a **significant impact** on current care pathways in the UK: 1**. Expanded Treatment Options for Refractory Disease** Obinutuzumab would offer a new line of therapy for patients who are unresponsive to rituximab, MMF, or cyclophosphamide. It could be particularly beneficial for those with secondary non-response or anti-drug antibodies to rituximab. 2. **Integration into Standard Care Pathways** NICE approval would likely lead to inclusion in national treatment algorithms, alongside MMF, CNIs, and belimumab. Potentially positioned as a second-line or adjunct therapy for Class III/IV LN, especially in patients with high-risk features or persistent proteinuria. **3. Improved Outcomes and Reduced Flare Rates** Clinical trials show obinutuzumab significantly improves complete renal response, reduces LN flares, and preserves eGFR. This could translate into fewer hospital admissions, lower steroid burden, and delayed progression to ESRD. **4. Impact on Commissioning and Prescribing** Prescribers would require training and guidance on dosing, monitoring, and infusion protocols. 5**. Equity and Access** NICE's appraisal process emphasises reducing inequalities in access to advanced therapies. Approval would ensure standardised availability across NHS trusts, avoiding postcode prescribing disparities, which currently exist as it is dependent on if the local trust chooses to fund. **6. Research and Real-World Data Collection** Approval would likely stimulate real-world evidence generation, registries, and post-marketing surveillance for this indication. This could help refine patient selection and long-term safety monitoring.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes – similar.
10a. How does healthcare resource use differ between the technology and current care?	Fundamentally this is about reducing inequity. NICE's appraisal process emphasises reducing inequalities in access to advanced therapies. Approval would ensure standardised availability across NHS trusts, avoiding postcode prescribing disparities, which currently exist as it is dependent on if the local trust chooses to fund.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This should be aimed at secondary care/ tertiary care.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Funding to use the drug is the primary one. The drug is not too different from rituximab prescribing and administration pathway.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes see answers to section 9c.
11a. Do you expect the technology to increase length of life more than current care?	Yes. Obinutuzumab would offer a new line of therapy for patients who are unresponsive to rituximab, MMF, or cyclophosphamide. It could be particularly beneficial for those with secondary non-response or anti-drug antibodies to rituximab. Hence, slow down rate of progression to ESRF and dialysis.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As mentioned above in section 8 and 9c. As this is an infusion based therapy – patients will need to be able to travel to an approved treatment centre for therapy. Those living far from such places may struggle or those with limited access to transport.

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 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 – unlikely to this will increase difficulties for patients or HCPs over current care. Currently after trialling a biologic like rituximab and there is not an appropriate response then there is limited scope and option for further treatment. This would be an appropriate alternative – so continued treatment and monitoring is likely to occur associated with biologics treatments. **Operational and Logistical Barriers** **Infusion capacity:** Obinutuzumab is administered intravenously, typically in multiple doses. This may require additional infusion slots, nursing staff, and pharmacy support. **Training needs:** Clinicians, nurses and pharmacists will need education on dosing, safety, and patient selection, especially in centres unfamiliar with oncology-style biologics
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	**Safety and Monitoring Requirements for Standard biologics** **Infection risk**: Obinutuzumab causes profound B-cell depletion, increasing susceptibility to infections. Ensuring vaccination status and infection prophylaxis will be critical. **Infusion-related reactions**: Though generally well tolerated, infusion protocols require premedication and monitoring, which may strain outpatient infusion services
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?	Already mentioned above.
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?	Similar to other new drug therapies in any treatment area that expands advance disease treatment options.
16a. Is the technology a 'step-change' in the management of the condition?	Yes. Obinutuzumab has the potential to transform LN care, especially for refractory cases.

16b. Does the use of the technology address any particular unmet need of the patient population?	Yes as above.
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?	This would be similar to any biologics introduction and we don't forsee anything additional side-effects to any other b-cells depleting agent. Obinutuzumab is a potent b-cells depleter and therefore deplete therefore. A brief summary: **1. <u>Common and Serious Adverse Effects</u>** **Infusion Reactions**: Generally mild or absent in LN patients, especially with premedication (e.g., methylprednisolone, antihistamines). Unlike rituximab, obinutuzumab is less immunogenic, reducing the risk of anti-drug antibodies and severe reactions 1. **Infections:** B-cell depletion increases susceptibility to infections. In one UK case series, 1 out of 9 patients died from severe COVID-19, highlighting the importance of vaccination and infection monitoring. No serious infections were reported in vasculitis patients treated with obinutuzumab. **Other Events:** One patient experienced SLE enteritis, a flare-related complication**.** No significant increase in adverse kidney outcomes was observed in the REGENCY trial. **<u>2. Impact on Disease Management</u>** **Monitoring Requirements:** Patients require regular monitoring of B-cell counts, **renal** function (eGFR, proteinuria)**,** infection markers**,** and vaccination status should be reviewed before initiating therapy. **Steroid-Sparing Potential:** Obinutuzumab enables reduction in glucocorticoid use, improving long-term safety and quality of life. In trials, more patients achieved prednisone ≤7.5 mg/day, reducing steroid-related complications like weight gain, osteoporosis, and mood changes. **Treatment Failure and Retreatment:** In refractory SLE, treatment failure occurred in 1 of 9 patients. Retreatment intervals are not yet standardised but may be longer than rituximab due to prolonged B-cell depletion.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The clinical trials investigating obinutuzumab for lupus nephritis (LN) do reflect many aspects of current UK clinical practice, but there are also some notable differences and limitations. **<u>Areas of Alignment with UK Practice</u>** **1. Standard Background Therapy** Trials like REGENCY and ALLEGORY used mycophenolate mofetil (MMF) and oral corticosteroids as background therapy, which aligns with UK first-line treatment for Class III/IV LN. **2. Steroid-Sparing Goals** Obinutuzumab trials aimed to taper prednisone to ≤7.5 mg/day, consistent with UK and international efforts to reduce long-term steroid exposure. **3. Patient Selection** Participants had autoantibody-positive active LN, similar to the population treated in UK renal and rheumatology clinics. UK commissioning policy also targets patients with secondary non-response to rituximab, a group included in UK case series and supported by trial data. **<u>Areas of Divergence or Limitation</u>** **1. Licensing and Commissioning Status:** Obinutuzumab is not yet licensed for LN in the UK, and current NHS England policy does not recommend routine commissioning, except in specific refractory cases. **2. Exclusion of Severe Renal Disease:** Some trials excluded patients with significant renal impairment, which may limit applicability to those with advanced LN or chronic kidney disease.

	3. Trial Setting vs. Real-World Practice: Trials were conducted in controlled environments with strict monitoring and infusion protocols, which may differ from resource-constrained NHS settings.UK infusion services may face capacity challenges if obinutuzumab is widely adopted. **4. Lack of Head-to-Head Comparisons:** Trials did not compare obinutuzumab directly with belimumab, voclosporin, or rituximab, making it harder to position within UK treatment algorithms.
18a. If not, how could the results be extrapolated to the UK setting?	Encourage publication of local practice where the areas of divergence is being addressed. Through networks such UK kidney association (UKKA).
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	• Reduction of urine protein-to-creatinine ratio (UPCR) < 0.5 g/g or then UPCR < 0.8 g/g without intercurrent events was also used as a secondary endpoint. (Note: local albumin-to creatinine ratio is used). • Improvement of estimated glomerular filtration rate (eGFR) ≥ 85% of baseline following acute event deterioration. Or the • Prednisone tapering: Achieving CRR while reducing prednisone to ≤7.5 mg/day was considered a meaningful glucocorticoid-sparing effect. • Reduction in LN flares and stabilisation of eGFR over a prolonged period of time (months to years) with minimal redosing with obinutuzumab. • Nil, to minimal intercurrent event such as: Need for rescue therapy, treatment failure. • Time taken to B-cell deplete and maintaining depletion. Conversely, time taken to b-cell repletion. Most were included in trials.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but	Nil of note

have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Local practice experience only in centres – get to be published.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA882?	No.
21. How do data on real-world experience compare with the trial data?	Similar – main difference is dosing structures chosen vary between centres most not choosing the REGENCY trial structure but adhoc ONE or TWO 1g doses then review as per standard monitoring.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Approval would ensure standardised availability across NHS trusts, avoiding postcode prescribing disparities, which currently exist as it is dependent on if the local trust chooses to fund.
22b. Consider whether these issues are different from issues with current care and why.	Same.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	Obinutuzumab has the potential to **transform LN care**, especially for **refractory cases** and where steroid burden must be minimised. Implementation will require: • Clear **clinical guidance and place in therapy.** Clinicians may struggle to position obinutuzumab relative to existing biologics like belimumab and voclosporin, as head-to-head trials are lacking. **Specialty preferences** may take over e.g. rheumatologists may be more familiar with rituximab and belimumab, while nephrologists may prefer voclosporin, leading to variability in uptake • Robust **commissioning frameworks.** Needs to be NHSE (or equivalent). Define optimal sequencing: There's no consensus yet on whether obinutuzumab should be used as first-line biologic, in combination, or reserved for refractory cases. **Currently would suggest it to be positioned as an alternative to rituximab, where there is a clear allergy or infusion related reaction, potential refractory case or where clear rituximab anti-bodies present.** • Investment in **infusion infrastructure.** There may be variability in access to infusion infrastructure across parts of the NHS. Consideration to this needs to be given to deliver therapy. • Ongoing **data collection and evaluation.** Though there is significant data in the public domain in relation to other indications. There are limitations to what has been published for SLE and LN. Encourage collaborative work through UKKA to publish.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Obinutuzumab with immunosuppressive therapies for treating lupus nephritis [ID6420]

Professional 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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- 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
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	The UK Kidney Association
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The UKKA was created through merger of the Renal Association, British Renal Society and its affiliates, to support the multi-professional team with delivery of kidney care, education and research – enabling people to live well with kidney disease. UKKA is funded by its members, grants, events, project work and capitation.
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.**	Funder / Amount / Purpose Baxter/Vantive — £32,700 — EVENT SPONSORSHIP Chiesi — £960 — RPG Chiesi — £3,300 — EVENT SPONSORSHIP Novartis — £318,000 — RADAR Otsuka — £3,600 — RPG Otsuka — £7,000 — MEMBERSHIP Otsuka — £39,700 — EVENT SPONSORSHIP
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.)	Lupus nephritis is one of the most serious, life threatening manifestations of SLE. The risk of chronic kidney disease and end-stage renal failure (ESRF) is significant with 10% of patients reaching ESRF at 5 years and 20% at 15 years. Current treatment options not only have a significant number of adverse effects (for example corticosteroid use), but do not result in a sustained remission in a significant proportion of patients. The aim of treatment in lupus nephritis is to achieve a sustained remission. This can be defined as normal kidney function with a reduction in proteinuria (<0.5-0.7g/day) by 12 months, which is only achieved in around 20-30% of patients after 6-12 months of treatment. Treatment can be divided into induction phase of treatment to induce a disease remission followed by maintenance treatment to prevent flares and further risk of chronic kidney damage. Treatment with immunosuppression has a duration of several years due to the chronic, relapsing nature
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.)	A significant response can be divided into a partial remission or a complete remission, with no renal flares while not exposing the patient to serious adverse complications of therapy. A complete response is defined as normalisation of serum creatinine with urine protein <0.5g.day. A partial response is generally defined as a creatinine clearance no more than 10% below baseline, or normal, with a 50% reduction in urine protein (or a decrease from nephrotic range proteinuria to non-nephrotic). Renal survival (remaining free of dialysis), chronic kidney disease and mortality are also significant factors with respect to long term follow-up and the success of treatment, as well as avoiding significant treatment related complications
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a significant unmet need for further therapies in this condition. Only a minority of patients achieve a complete remission. Not achieving a remission puts the patient at risk of further renal damage and the associated morbidity and mortality associated with CKD and ESRF. Additionally, the current treatments have significant treatment associated complications and adverse effects. Corticosteroids are associated with many adverse effects, and non-adherence is a significant factor with respect to poor treatment outcomes. Immunosuppressive agents such as cyclophosphamide have an important role in the treatment of his disease but are associated with decreased fertility which is a factor in a disease with predominantly affects women of child-bearing age. Steroids, cyclophosphamide and also mycophenolate mofetil are all associated with infectious complications. Rituximab also has a very important role despite its disappointing Phase 3 evidence, a meta-analysis has demonstrated its use and clinically it is very frequently used and has a very helpful role. However, there is a significant risk of infusion reactions/allergies meaning it can no longer be given to patients therefore ending up with very few treatment options. There is therefore an unmet need for further therapies in patients with difficult to treat- resistant disease who have run out of treatment options and need kidney saving therapies.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	1st line immunosuppression treatment for patients with Class III and IV lupus nephritis - Prednisolone with mycophenolate mofetil - Depending on disease activity/disease severity and renal function (and patient choice taking into account fertility): prednisolone and low dose intravenous cyclophosphamide (500mg every 2 weeks for a total of 6 doses then switch to mycophenolate mofetil) - In those patients with a previous high burden of immunosuppression with cyclophosphamide, additionally in those patients of Asian, Hispanic or African ancestry, MMF may be a preferred option. - addition of a calcineurin inhibitor (such as voclosporin or tacrolimus- depending on local availability) is reserved in those patients who may not tolerate high doses of MMF, or in which cyclophosphamide is not desirable. - MMF is used for maintenance therapy. 2nd line - Use of azathioprine if MMF, CNI, cyclophosphamide not tolerated - If pregnancy planned in a patient in remission Biological therapy- Rituximab Despite disappointing trial evidence (LUNAR), Rituximab is an incredibly useful agent in the treatment of lupus nephritis Rituximab will be added to treatment (prednisolone and MMF) in those patients with active disease who:- (i) Poor response to steroids and MMF (ii) Adverse effects of high dose steroids as a steroid sparing/minimising agent (iii) Unable to tolerate higher doses of MMF and needing an escalation in immunosuppression (iv) high risk disease and reluctance for a cyclophosphamide based regime, can be added to prednisolone and MMF. Biological therapy- Obinutuzumab

	- Given individual named patient basis and great difficulties due to lack of funding in NHS. Fully humanised anti-CD20 used in select patients when rituximab contraindicated. Biological therapy belimumab - BLISS-LN trial added belimumab to standard treatment and increased the response rate at 2 years compared to standard treatment - currently not 1st line treatment for lupus nephritis. Can consider especially in those patients unable to tolerate rituximab and intravenous therapy preferred rather than oral. Immunosuppression in patients with Class V lupus nephritis - Similar to Class III/Class IV treatment - Higher use of CNI, and addition to prednisolone and mycophenolate in membranous (class V) LN. **UPDATED GUIDANCE IN 2025** <u>BSR (British Society of Rheumatology) updated lupus nephritis guidelines in draft 2025</u> <u>CLASS III or IV</u> Induction therapy: IV methylprednisolone 250-500mg for 3 days followed by oral corticosteroids Followed by: TRIPLE THERAPY **(i) MMF and Obinutuzumab: this is the treatment of choice as decided by UK specialists.** (ii) MMF and voclosporin (or tacrolimus) (iii) MMF and belimumab <u>CLASS V</u> Combination regimen consisting of oral corticosteroids, MMF and Calcineurin inhibitor

	If not appropriate or tolerated, consider: • corticosteroids + MMF+ anti-CD20 therapies • corticosteroids + MPAA + belimumab • corticosteroids + EuroLupus dose cyclophosphamide + belimumab
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Current guidance: • British society of Rheumatology (I am on the committee for updating the guidelines in 2025) • Joint European League against Rheumatism (EULAR) • KDIGO (Kidney disease improving global outcomes)
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.)	Many patients are treated within renal units or specialist lupus clinics attended by nephrologists and rheumatologists working together. There maybe some regional variation in treatment depending on access to infusion wards for intravenous treatment and drug availability (for example rituximab, voclosporin) but within specialist lupus nephritis clinics there should not be variation. Due to well defined treatment protocols, the pathway of care is well defined.
9c. What impact would the technology have on the current pathway of care?	Obinutuzumab would be an incredibly useful addition to patients current treatment. Due to the efficacy in this treatment, especially in the context of allergic reactions to rituximab, Obinutuzumab is so very useful that often lupus centres will use local departmental funding to access this drug. Unfortunately, this method has resulted in only the extreme of cases having access when significant numbers of patients are highly likely to benefit. This individual unit approach will also lead to treatment inequality in which significant numbers of patients across the UK who are not being seen in large centres will not be able to benefit from this treatment when Trusts do not have the resources to fund this locally.

	In order to ensure that patients across the UK have equal access and therefore optimal treatment (irrespective of the treating centre) this needs to be commissioned to give renal response the best possible opportunity in all parts of the UK.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It is already used in many lupus centres. It will be used in infusions wards which are already set up and established. it is similar to rituximab with treatment protocols already in place and expertise present.
10a. How does healthcare resource use differ between the technology and current care?	When patients have had a reaction to rituximab, our treatment options are limited. Plus the recent Phase 3 data in which Obinutuzumab was added to standard of care (prednisolone and MMF) resulted in a better response compared to standard of care. This was a positive Phase 3 study and having access to this medication will improve our patient outcomes resulting in less end-stage kidney failure in the long term if we achieve higher proportion of patients in a remission.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Obinutuzumab will be used within the setting of specialist lupus nephritis clinics
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment would be required.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	<u>Phase 3 study: Efficacy and Safety of Obinutuzumab in active lupus nephritis</u> RA Furie et al. New England Journal of medicine Feb 7th 2025 This trial demonstrated in adult patients with active lupus nephritis, Obinutuzumab plus standard therapy was more efficacious than standard therapy alone in providing a complete renal response. The overall renal response using standard therapy is low. Therefore the addition of Obinutuzumab and this trial result is highly significant in improving renal outcomes for our patients.

11a. Do you expect the technology to increase length of life more than current care?	The single biggest determinant of morbidity and mortality in SLE is the presence of renal involvement. By improving the renal response, we are therefore reducing the risk of ESRF (end-stage renal failure) and this will significantly impact the life expectance of our patients. Additionally, by reducing the rates in ESRF in the UK, this is highly significant due to the crisis we have with dialysis capacity as well as kidney transplant availability. Therapies to reduce using these limited and expensive resources will be highly beneficial to the patient and society as a whole.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. - By improving disease response, we are hopefully limiting the amount of use of corticosteroids. the use of steroids is well recognised to impact a patients quality of life. High doses of steroids have a severe impact on the wellbeing of patients especially with respect to mental health and also adverse effects including weight gain, skin changes, bone density, mood changes including the risk of psychosis with high dose - By improving the current response rate, this will result in a lower use of more potent therapies such as cyclophosphamide in some patients. Cyclophosphamide is associated with decreased fertility, infections as well as frequent visits to the hospital infusion ward for treatment. -Non-responders (or partial response) risks kidney failure and the decreased quality of life associated with renal replacement therapy for which there is a higher risk of poor kidney outcomes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	SLE disproportionably affects women (9 times more than men) Patients of African ethnicity are recognised to have more severe disease, and to respond better to a MMF based regime (in which Obinutuzumab is given) rather than cyclophosphamide based treatment.

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 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.)	Obinutuzumab will likely be easy to use than the current care. This is because the use of rituximab which is widely used does result in allergic infusion reactions in a significant proportion of patients. Obinutuzumab does not cause these reactions and is therefore a safer drug to use. Patients who would benefit have active kidney disease so will be frequently monitored. There will be no additional 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?	All tests are part of routine clinical care.
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?	Patients of ethnic minorities, as well as patients living in more deprived areas, are disproportionally affected by lupus nephritis as well as having poor renal outcomes and at higher risk of kidney failure. Intravenous treatment is highly beneficial in patients who for multiple social reasons may find treatment (tablet) adherence as well as clinical adherence challenging. An intravenous treatment alongside medications is highly desirable.
16. Do you consider the technology to be	There is currently a large unmet need in the treatment of lupus nephritis due to the low proportion of patients achieving either (i) a complete remission, or (ii) a sustained, relapse-free remission.

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?	For a Phase 3 trial to have a positive result is critical and demonstrates just how useful this medication will be and I would expect it to have a significant benefit. This has been demonstrated in the trial as well as personal experience using this medication and the excellent clinical response.
16a. Is the technology a 'step-change' in the management of the condition?	This is a rare disease with limited treatment options. This drug is a very useful addition to current treatment options. In view of the significant issues we have with rituximab and allergic reactions this is an incredibly useful treatment in patients who have remained resistant to current treatment and in whom have either been treated with cyclophosphamide or it is desirable to avoid due to fertility concerns.. Additionally, Obinutuzumab works significantly better than rituximab and is better than our current standard of care and represents a real improvement in how we treat kidney disease.
16b. Does the use of the technology address any particular unmet need of the patient population?	There is a low proportion of patients who have a complete response to treatment in lupus nephritis. The addition of other therapies maybe limited. For example, in patients with a previous high burden of cyclophosphamide, or in patients who wish to preserve fertility, cyclophosphamide will need to be avoided. Additionally, a significant proportion of patients cannot be given rituximab due to severe reactions. In these scenarios, treatment options are very limited and hence there is a great unmet need in the treatment of lupus nephritis.
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?	Obinutuzumab is a very well tolerated medication. There was no difference in adverse events between drug and placebo in the trial. The most commonly reported adverse events were infections. However the alternative is higher doses of steroids plus medications such as IV cyclophosphamide which not only works less well with lower remission rates but also exposes the patient to low white cell counts, infections and also affects fertility. I would not expect a significant adverse impact on a patient's quality of life due to the treatment. I would expect an improvement due to better disease control.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. The Phase 2 and 3 trials compared Obinutuzumab plus standard of care versus standard of care which is widely used in the UK as 1st time treatment

18a. If not, how could the results be extrapolated to the UK setting?	NA
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The important outcome is the risk of CKD, ESRF and mortality. The trial data has limited very long term follow-up so these questions remain unanswered. However, the renal response with respect to renal function and proteinuria at 76 months have been answered by this trial. We know that being in a complete renal remission is critical for long term renal function and this trial demonstrates Obinutuzumab was a more efficacious therapy resulting in a higher response rate. This higher response rate is very important in decreasing the risk of renal scarring and future CKD and ultimately progression to ESRF. Additionally, treatment with Obinutuzumab resulted in a lower use of prednisolone which is a key outcome for patients as steroid use results in a significant impact on quality of life for patients and a treatment regime which allows us to minimise steroid use is highly desirable and a key outcome.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The outcome in the trial was renal response at 76 weeks which was a composite of urine protein creatinine ratio and stable renal function with no rescue medication and a protocolised use of steroids. With respect to the renal outcomes. Proteinuria at 12 months is one of the best predictors of long term outcome and is a well recognised and acceptable endpoint in patients with glomerular disease. Additionally renal function after 12 months and the presence of abnormal renal function is a good indicator of the risk of CKD and therefore long term renal survival. The use of rescue therapies would be a worrying indicator of more resistant disease therefore putting the patient at risk of a long term poor clinical outcome.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of. This drug has been used in haematology as well as many renal/lupus units using this medication. We have significant experience of B-cell depletion with rituximab
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 TA882?	Re. voclosporin: useful treatment is a subset of patients with lupus nephritis. No more recent comparator treatments
21. How do data on real-world experience compare with the trial data?	Similar data. UCLH experience of Obinutuzumab and lupus (UCLH experience) presented as a poster British Society of Rheumatology 2025. All had a clinical benefit (9 patients). More than 9 have now been treated. Obinutuzumab is an incredibly useful treatment in patients with lupus nephritis.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	As previous written, patients from ethnic backgrounds are at higher risk of poor long term renal outcomes. There is also some evidence that patients of African ethnicity may respond better to a MMF based regime rather than cyclophosphamide. Obinutuzumab is used in combination with prednisolone and MMF and although the trial data not powered to detect differences in response according to ethnicity, this treatment protocol may potentially be more beneficial in patients of African ethnicity who are at higher risk of resistant disease as well as progression to end stage kidney failure and respond less well to alternative therapy such as cyclophosphamide.
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.	• Obinutuzumab resulted in a significantly better renal response • A better renal response/less proteinuria decreases the risk of chronic renal damage • We are limited with rituximab due to infusion reactions, plus it is an inferior treatment • The combination of prednisolone, MMF and Obinutuzumab is the best data we have for a renal response • This is a safe combination to use

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Obinutuzumab with immunosuppressive therapies for treating lupus nephritis [ID6420]

NHS organisation submission (ICBs and NHS England)

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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- 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
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[redacted]
2. Name of organisation	NHS England
3. Job title or position	[redacted]

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? Yes Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? Yes Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? No An expert in treating the condition for which NICE is considering this technology? No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	A number of guidelines for systemic lupus erythematosus (SLE) including lupus nephritis (LN) are available, from EULAR, KDIGO and ACR. BSR guidelines for SLE have been updated in 2025, presented at the BSR conference 2025. The BSR guidelines recommend that obinutuzumab be considered as a first line therapy for induction and maintenance of remission in LN as per trial data, recognising that this would need to be within the scope of any NHS England or NICE guidance.
7. 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.)	The guidelines do offer a well-defined pathway for patients with LN, both for settings of care (e.g. there is a clearly set up network of Specialised Rheumatology centres as well as renal units) and for selection of therapies. In clinical practice, there is often variation which is partly driven through patient factors e.g. severity of disease and response/lack of response and toxicity with previous agents. The presence of a NICE TA for obinutuzumab in LN would help to provide further guidance for clinicians to reinforce and develop existing pathways.
8. What impact would the technology have on the current pathway of care?	The current pathway unfortunately includes provision of resources or interventions such as renal dialysis or transplantation for end stage renal failure (ESRF) which occurs in 44% of LN patients. Current agents also can produce significant toxicity, such as cyclophosphamide (infection, malignancy) voclosporin (further renal impairment) and significant multisystem toxicities with glucocorticoids. The use of obinutuzumab would be expected to lead to higher rates of LN remission and therefore a reduction in the occurrence of ESRF and these toxicities. It also adds a further treatment option for patients who have difficult to treat disease, either through inefficacy of or toxicity with currently available agents.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	Obinutuzumab is currently used in a very limited way in some centres as a treatment for SLE patients who are no longer responding to rituximab, having had specific antibody mediated side effects. NHS England does not currently fund its use Clinical Commissioning Policy Obinutuzumab for systemic lupus erythematosus with secondary non-response to rituximab (adults and post-pubescent children).

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Obinutuzumab will be additional to – or could replace – aspects of current care i.e. it will provide a further treatment option for patients with LN. This can be in place of a current first line treatment option or an alternative or extra option for patients who are no longer suitable for currently available therapies.
10a. How does healthcare resource use differ between the technology and current care?	No extra resource should be required. Patients would still be in the same clinical systems as currently. The drug is given as 2 infusions every 6 months, but this is already the case for use of rituximab, which is an agent that is not licensed for use in LN and has not been in successful clinical trials for LN i.e. the resource need for infusion units etc would not be increased practically. It may lead to a reduction in infusion unit use, given one other option is belimumab which requires monthly infusions. There is less requirement for blood and clinical monitoring than with belimumab or voclosporin.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Approval for use of Obinutuzumab would be given by a Specialist Rheumatology or appropriate Renal MDT, with the drug being given in either a specialist centre or a local hospital (the latter as part of a network) if necessary. Patients should be followed up in a specialist Rheumatology/Renal combined clinic or similar subspecialty renal clinic (i.e. with skilled experience in the management of LN).
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No new facilities are required, and infusion units are familiar with the use of rituximab (an agent with a similar mechanism of action but with limitations in LN use as described above in Q10a response).
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	No additional testing is needed -the diagnostic investigations would be the same and monitoring of disease outcome would also be the same as is currently standard in clinical practice.
11. What is the outcome of any evaluations or audits of the use of the technology?	Obinutuzumab has shown positive results for significantly improving the rate of complete renal response in LN over standard therapy in a Phase III trial (NEJM 2025; 392: 1471-1483)

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	LN disproportionately affects patients of Afro-Caribbean and Asian ancestry both with regards to disease incidence and severity. These groups would therefore particularly benefit from further treatment options with better outcomes, e.g. with obinutuzumab, than are currently available. The use of obinutuzimab would not have any negative impact on any patient group in terms of equality issues.
12b. Consider whether these issues are different from issues with current care and why.	The issue that LN disproportionately affects patients in the above ethnic groups with worse health outcomes in these groups is already recognised currently as an unmet need in LN care.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Obinutuzumab with immunosuppressive therapies for treating lupus nephritis [ID6420]

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.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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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 **<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.

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.

NICE National Institute for Health and Care Excellence

Part 1: Treating lupus nephritis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Tabitha Turner-Stokes
2. Name of organisation	Imperial College Healthcare NHS Trust (Hammersmith Hospital)
3. Job title or position	Clinician Scientist in Nephrology (Wellcome Early Career Award Fellow) and Honorary Consultant Nephrologist at the Hammersmith Hospital
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 lupus or lupus nephritis? ☒ A specialist in the clinical evidence base for lupus, lupus nephritis 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.	NA
8. What is the main aim of treatment for lupus nephritis?	Early and effective treatment of inflammation to minimise kidney scarring and, crucially, to prevent future flares of kidney disease. Each flare of lupus nephritis

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	risks further scarring and loss of eGFR which can lead to progressive CKD and ultimately end stage kidney disease(ESKD)/kidney failure. As patients typically present with lupus at a young age, their prospects of reaching ESKD (requiring lifelong dialysis or a kidney transplant) within their lifetime is high and this is deeply impactful upon their work and family prospects, and particularly notably fertility in this predominately young female patient population. CKD and ESKD are associated with vastly increased morbidity and mortality, particularly from cardiovascular disease. It is critical to initiate early and effective treatment and reduce disease flares to avoid these devastating outcomes.
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)	Widely used definitions for disease remission in lupus nephritis (used in clinical trials) are: Complete remission: Reduction in proteinuria to <500-700mg per day (uPCR <50-70mg/mmol), no greater than 15% loss in eGFR Achieving complete remission (as opposed to partial remission – usually defined as a 50% reduction in proteinuria to <3g per day and no greater than 15% loss in eGFR) is essential to preserve eGFR in the long-term and protect patients from progressive CKD. In particular, reducing proteinuria to <700mg per day by 1 year following induction immunosuppression for active lupus nephritis, is a widely accepted clinical target that is associated with better prognostic outcomes in the longer term i.e. stabilisation of kidney function.
10. In your view, is there an unmet need for patients and healthcare professionals in lupus nephritis?	There is a clear unmet need for better treatments for lupus nephritis. Sustained rates of complete remission are generally no better than 40%, which carries an unacceptable risk of progressive CKD and future end stage kidney disease in this young patient population. Current treatments, in particular steroids and cyclophosphamide carry significant toxicity profiles and there is now a unified

	call from specialists internationally to deliver “triple therapy” with MMF + steroids + another agent (Obinutuzumab, belimumab or voclosporin) from the outset. This is because we know that scarring accrues early and leads to irreversible loss in eGFR. We therefore need to get kidney inflammation under control as effectively and as quickly as possible – and, importantly, reduce the risk of further flares of lupus nephritis.
11. How is lupus nephritis 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?	Lupus nephritis is widely treated in the NHS with MMF (or less commonly cyclophosphamide) and steroids. Until recently, this has been internationally regarded as standard of care (SoC). But recently updated international guidelines from both the American Society of Rheumatology (ACR) and British Society of Rheumatology (BSR) call for “triple therapy” upfront, recommending the addition of either belimumab or voclosporin to standard of care. The BSR guidelines (awaiting official publication) will be the first to recommend obinutuzumab in addition to MMF and steroids as an option for triple therapy (following publication of the positive Regency trial earlier this year). These updated recommendations reflect the increasing recognition that lupus nephritis results in accrual of kidney scarring early, which results in permanent loss of eGFR that leads to future CKD. Thus, early intensive therapy to achieve rapid and effective control of active lupus nephritis is essential to reduce the future risk of progressive CKD and end stage kidney disease in these young patients (who have a lifetime of disease that follows a relapsing remitting course ahead of them). The use of triple therapy upfront has also been shown in recent clinical trials (BLISS-LN and REGENCY) to reduce the rate of disease flares, which is also essential to protect kidney function as each flare of lupus nephritis leads to substantial further irreversible loss of eGFR (Anders, HJ., Saxena, R., Zhao, Mh. *et al.* Lupus nephritis. *Nat Rev Dis Primers* **6**, 7 (2020). https://doi.org/10.1038/s41572-019-0141-9) Within the NHS belimumab can be added to SoC in specialist centres but is not accessible by all. Only patients with serologically active lupus (low complement

	or raised dsDNA antibody titre) and a SELENA SLEDAI score >10 are eligible for treatment on the NHS. Unfortunately, this is not the case for all patients with active lupus nephritis (who are not uncommonly serologically negative despite having ongoing histopathological evidence of kidney inflammation on biopsy), precluding this treatment in this important patient group who are at risk of their kidney disease being undertreated. Within the NHS, voclosporin can be added to SoC and is more widely accessible outside of specialist centres, but can't be safety used in patients with significant scarring on biopsy/preexisting CKD due to the risk of nephrotoxicity and precipitating further progression in CKD. B cell depletion is widely accepted by lupus specialists to be effective in treating SLE/lupus nephritis. Clinical trials of the first generation anti-CD20 monoclonal antibody rituximab (EXPLORER, LUNAR) failed in part due to study design (high background treatment, particularly with steroids) and in part due to the limited B cell depletion achieved (limited duration of peripheral depletion with repopulation in most patients within 3-6 months of treatment). However, subgroup analysis from the LUNAR trial showed that patients who achieved complete peripheral B cell depletion had higher rates of renal remission, and there are multiple published cohort studies reporting treatment efficacy. More recently, published data on the use of CD19 CarT cell therapy have shown that deep and sustained B cell depletion can achieve an "immunological reset" within the B cell compartment that can result in prolonged drug-free clinical remission. And now the Regency trial shows that full and sustained B cell depletion with the 3rd generation anti-CD20 mAb obinutuzumab increases disease remission and reduces disease flares when added to SoC. Moreover, B cell depletion for the treatment of SLE/lupus nephritis has clear biological rationale given the well-established roles of B cell dysregulation and autoantibody production in drive disease pathogenesis. Thus, B cell depletion is an effective treatment for lupus nephritis and we have a critical unmet clinical need to be able to provide this

	therapy for treatment of patients within this NHS. This would have notable impact on the care of patients with lupus nephritis and ensure that all patients with lupus nephritis can access "triple therapy", as recommended by updated international guidelines. Not all patients can currently access triple therapy as belimumab and voclosporin treatment are not possible for certain patient groups (as detailed above).
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)	Obinutuzumab is administered intravenously. In the Regency trial the dosing regimen used was 1g on day 1, week 2, week 24, week 26 and week 52. Administration within the NHS would require a short admission to a day unit. Intravenous treatments require administration in a secondary care setting, often in specialist units to ensure patients have access to the appropriate monitoring. Many patients with SLE are already managed in specialist centres due to the requirement of regular monitoring when receiving treatment with immunosuppressive medications. Some existing treatments for lupus nephritis administered within the NHS require IV administration. This is typically delivered in a day unit setting e.g cyclophosphamide (typically given as 6x 500mg IV doses over 3 months), and belimumab (given as 3x 2 weekly IV doses initially and then monthly IV doses ongoing). Rituximab is administered within the NHS in some specialist units for patients with SLE (through NHS specialist commissioning policy) and is generally administered as 2x 1g doses 2 weeks apart. Thus, facilities are already in place in many specialist centres that manage patients with SLE to deliver intravenous treatments, with the necessary equipment and appropriately trained staff. I would not expect administration of obinutuzumab to require any additional facilities, equipment, or staff training.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The results of the recently published Regency trial provide randomised controlled trial evidence that Obinutuzumab provides clinically meaningful benefits to patients with lupus nephritis, when added to current SoC. It

• 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?	significantly increases renal remission, reduces serological SLE activity (suggesting control of the underlying autoimmunity driving disease), and reduces the risk of disease flares. These positive clinical outcomes were reported at 76 weeks. As highlighted above, effective, early control of kidney inflammation/active lupus nephritis and reduction of disease flares is critical to protect these patients from irreversible loss of kidney function that leads to progressive CKD and a very real risk of developing ESKD within their lifetime. Thus, obinutuzumab provides a critical opportunity for patients with lupus nephritis to receive a treatment that will protect them from these devastating outcomes. CKD and ESKD are associated with substantially increased morbidity and mortality. Dialysis has a well-established, highly negative impact on quality of life. Population based studies estimate that 10-30% of patients with lupus nephritis will develop ESKD over 15 years. Therefore, by reducing the risk of CKD and ESKD in patients with lupus nephritis, obinutuzumab would be expected to have a substantial impact on both length and quality of life, compared to standard of care.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with pure Class V lupus nephritis were not included in the Regency trial so the efficacy in this patient group is not known. I am not aware of any groups of patients with Class III or IV lupus nephritis for whom treatment with obinutuzumab would be less effective. The Regency trial was a global, international study that included an ethnically diverse population. Less than 50% of the patients enrolled were Causasian. Black or African American, Asian, and Hispanic or Latino ethnic groups were represented in 14.8%, 5.9% and 57.6% of the study population respectively. These ethnic groups have a high prevalence of lupus nephritis with a high risk of

	complications and death and are therefore a key group of patients for which better treatments are needed. A subgroup analysis of complete renal response in black vs. other ethnic groups in this trial showed that obinutuzumab was as effective in both groups. Although a more detailed subgroup analysis including other ethnic groups has not yet been published, I would not expect (based on the currently available data) obinutuzumab to be less effective in these at risk ethnic groups for whom additional treatment options as urgently needed. Additionally, complete renal response at 76 weeks was consistent across other patient subgroups in the Regency trial, including patients with class IV LN, those with concomitant class V, those with a greater degree of proteinuria at the start of treatment (uPCR >3mg/mg ~ 3g/day) and those with a greater degrees of serological activity. The fact that obinutuzumab was equally effective in patients with and without serological disease activity as important as existing NICE approval for belimumab (another option for triple therapy) is currently restricted to patients with serologically active SLE, regardless of whether they have active lupus nephritis or not. Patients with active lupus nephritis often do not have evidence or serological SLE activity and it is critical that these patients are able to access triple therapy to achieve complete renal remission and improve their long-term renal outcomes.
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)	This technology should be accessible to all specialist centres currently treating patients with lupus nephritis. There should not be any practical limitations precluding its use in these centres because, as highlighted above, there are systems and staff training currently in place to administer other intravenous treatments to patients with lupus nephritis. I would not expect obinutuzumab to be any more or less difficult to use (by patients or health professionals) than other intravenous medications currently used for treating lupus nephritis, including cyclophosphamide and belimumab. Additionally, it does not require any monitoring requirements beyond those currently in place. Treatment

	monitoring would require measurement of lymphocyte subsets (already in place in specialist centres as many use rituximab through national specialist commissioning) and other routine blood tests commonly used for monitoring patients on immunosuppression. In my specialist centre, we have local funding arrangements/approvals in place to administer obinutuzumab to patients with SLE who are allergic to rituximab and this has not required any additional facilities or had any practical implications beyond those required for the administration of other intravenous treatments for SLE (cyclophosphamide, belimumab, rituximab).
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients should have routine screening (as used prior to starting other immunosuppression) prior to using obinutuzumab, including FBC, immunoglobulins (IgG, IgA, IgM), lymphocyte subsets, virology (HBcAb, HBsAb, HBsAg, HCV, HIV) and pregnancy testing. I would not expect any additional testing specific to obinutuzumab to be required. Patients with evidence of previous HBV infection (those positive for HBcAb) should receive HBV prophylaxis with input from hepatology, as is the case when using other immunosuppressive agents to avoid HBV reactivation. It should be used with caution in patients with hypogammaglobulinaemia and may require input from immunology/immunodeficiency specialists in this setting.
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	I do not have particular expertise in this area but would expect that the positive impact that obinutuzumab would be expected to have on reducing flares in patients with lupus nephritis may not be accounted for in the QALY calculation. Flares of lupus nephritis have high cost implications for the NHS as they often involve hospital admissions (for management of severe nephrotic syndrome or renal replacement therapy support) and weekly specialist outpatient clinic attendance (for intensive immunosuppressive treatment and monitoring). They

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	are also deeply impactful on work in these young patients, often resulting in substantial time off for sickness and a new requirement for benefits etc. It is also important to recognise that, as with most clinical trials, the outcomes reported in the Regency trial are relatively short-term i.e. 76 weeks. There are no published data yet on longer term renal outcomes (eGFR decline, commencement of renal replacement therapy) as its takes years to see the effect of treatment on these important outcomes. However, it is clear from multiple trials in multiple different kidney diseases, that early reduction in proteinuria (within 12-18 months of treatment) is strongly predictive of better long-term renal outcomes i.e. preservation of eGFR and reduced risk of ESKD. In the Regency trial, patients treated with obinutuzumab in addition to SoC had greater reductions in proteinuria and showed an increase in eGFR from baseline at 76 months (vs. the placebo group, who lost eGFR). These are clear indications that patients treated with obinutuzumab are likely to have improved long-term renal outcomes, particularly as obinutuzumab achieves sustained B cell depletion and thus continues to have a mechanism of action well beyond the initial treatment period (95.1% of patients remained B cell deplete at 76 months).
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?	As highlighted above, specialists treating patients with lupus nephritis have known for a long time that B cell depletion works, despite the fact that the original RCTs of rituximab were negative (limitations of these trials already highlighted above). Obinutuzumab itself as a drug represents an incremental change in technology as it has a very similar mechanism of action to the 1st generation anti-CD20mAb rituximab. However, the relatively small modifications that have led to the developed of this 3rd generation anti-CD20 mAb have resulted in a step-change in treatment efficacy that could have a substantial impact on patients with lupus nephritis. This is because obinutuzumab achieves reliable, deep and sustained B cell depletion (much more reliably than that achieved with rituximab) and this has clear benefits with respect to treatment response. The Regency trial provides the first randomised control trial evidence that B cell depletion works in SLE and this is a game changer. We now finally

	have the evidence base needed to justify the use of B cell depletion as first line, in addition to Soc with MMF and steroids, to optimise treatment of lupus nephritis and ensure that all patients can be treated in line with updated international guidance (NB not all patients are eligible/suitable for triple therapy with belimumab or voclosporin added to SoC – this has already been highlighted above).
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 most common side effects reported in the Regency trial were COVID-19 infections and these occurred early during the COVID-19 pandemic. This is less relevant to the current UK population as most people have now either had natural COVID-19 infection, or been vaccinated. Increased risk of infections is a recognised side effect of B-cell depleting therapy, as it is for treatment with other immunosuppressive drugs. This risk can be mitigated by advising patients to adhere to national recommendations on vaccinations for immunosuppressed patients which include annual flu/covid boosters, 5 yearly pneumococcus vaccination, shingles vaccination using the non-live Shingrix vaccine and HPV vaccination according to age eligibility.
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?	Yes, the SoC treatment used in the Regency trial, to which obinutuzumab was added, reflects that used in current UK practice.

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 [TA882]?	No
23. How do data on real-world experience compare with the trial data?	As already highlighted above, real world data from multiple, large, well-characterised, retrospective cohort studies on the efficacy of rituximab in lupus nephritis suggest that this is an effective and important treatment option for patients. This is in contrast with the RCTs on the efficacy of rituximab in SLE/lupus nephritis which were negative, in large part due to study design and the variable B cell depletion achieved with rituximab. There is very limited real world data published on the use of obinutuzumab in lupus nephritis, and mainly in the refractory disease setting, rather than first line in addition to SoC as "triple therapy". However, the ethnic diversity of patients included in the Regency trial, the SoC used and the degree of proteinuria are reflective of real world practice.
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	As already highlighted, patients from Black/African ancestry, Asian and Hispanic ethnic groups are at increased risk of more severe SLE and of developing lupus nephritis compared to Caucasian patients. These groups have been under-represented in historic lupus nephritis trials and Black patients respond less well to some of our existing treatments (i.e. cyclophosphamide as illustrated by the ALMS trial). There is therefore a critical unmet need to develop better treatments for lupus for these high-risk patient groups. These ethnic groups were well represented in the Regency trial of obinutuzumab and treatment efficacy was similar in Black vs other ethnic groups in the reported

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.	subgroup analysis of the trial (although more granular post-hoc subgroup analyses have not yet been reported). Obinutuzumab therefore represents an important and effective treatment option for patients from these ethnic minority groups who are highly vulnerable to more severe disease for which current treatments are often not effective.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Early, intensive treatment of lupus nephritis with medications targeting multiple pathways is critical to minimise kidney scarring, prevent flares and preserve kidney function, reducing the risk of chronic kidney disease (CKD) and end-stage kidney disease (ESKD), which carry high morbidity and mortality.

Achieving complete renal remission (defined typically as reduction in proteinuria to <500-700mg/day and <15% loss of eGFR) is essential for long-term kidney protection - but current standard therapies achieve sustained complete remission in less than 50% of patients, highlighting an unmet need.

Updated international guidelines (ACR 2024, BSR, expected 2025) now recommend triple therapy with MMF or cyclophosphamide + steroids + an additional therapy such as belimumab, voclosporin or obinutuzumab (BSR) as initial treatment for lupus nephritis to improve remission and reduce flares, particularly given the early accrual of irreversible kidney scarring observed on serial kidney biopsies.

Data from the Regency trial show that obinutuzumab is effective across diverse ethnic groups including Black, Asian and Hispanic patients who are at higher risk of severe SLE and lupus nephritis, providing improved renal remission and reduced disease flares when added to standard of care.

Intravenous administration of obinutuzumab is feasible in existing NHS specialist centres, requiring no additional facilities or training beyond what is already used for treatments like cyclophosphamide, belimumab or rituximab, with routine immunosuppression monitoring and infection risk mitigation.

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Single Technology Appraisal

Obinutuzumab with immunosuppressive therapies for treating lupus nephritis [ID6420]

Clinical expert statement

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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 **<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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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.

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Part 1: Treating lupus nephritis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Alan Salama
2. Name of organisation	Lupus UK
3. Job title or position	Member of grants committee for lupus UK
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 lupus or lupus nephritis? ☒ A specialist in the clinical evidence base for lupus, lupus nephritis 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)	☐
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	I have recently received honoraria from Vifor, Sarepta. I have historically received honoraria for speaking from other companies including Roche but this is over 5 years ago.
8. What is the main aim of treatment for lupus nephritis?	Lupus is a multi-system relapsing-remitting disease and to date no means of achieving long term cure for the majority of patients has been found. Rather, the aim of treatment is to supress disease activity, which causes various symptoms

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	in diverse organ systems and reduce the risk of long term and permanent organ damage. As lupus frequently affects the kidneys (lupus nephritis) the aim of therapy in lupus nephritis is to specifically preserve kidney function, by reducing kidney inflammation and doing this sufficiently quickly to prevent the inflammation in the kidney turning to scarring which leads to irreversible chronic kidney disease and ultimately end stage kidney failure, necessitating dialysis or a transplant. Despite modern treatment protocols this remains a persistent problem, emphasising the need for more effective therapy. As lupus is an autoimmune disease the treatments are aimed at suppressing the overactive immune system- while minimising the flipside of such treatments which would be infectious, metabolic, cardiovascular and malignant complications. Since disease relapses are common, treatments with immunosuppressive medications are often prolonged (or maybe lifelong) increasing the risk of non-compliance especially in younger patients.
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 reduction (to < 50 mg/mmol) or disappearance of proteinuria, a normalisation of kidney function assessed by measures of serum creatinine and where possible a confirmation that there remains no disease activity on kidney biopsy. KDIGO considers complete remission to be a UPCR of <50 mg/mmol, stabilisation or improvement of kidney function (between 10-15% of baseline). Partial remission allows for more proteinuria (reduction by 50% or more and less than 300 mg/mmol) and eGFR within 15% of baseline.
10. In your view, is there an unmet need for patients and healthcare professionals in lupus nephritis?	Undoubtedly yes. Current first line treatments fail to induce remission in the majority of patients necessitating the use of additional therapies or repeated rounds of treatments. In addition, there has been a reliance for too long on high dose corticosteroid medications which we believe themselves contribute to increased cardiovascular and infectious morbidity and mortality.
11. How is lupus nephritis 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	First line of treatment for the majority would be a combination of mycophenolate mofetil in combination with high dose prednisolone. This not infrequently is not sufficient to induce remission and so a switch to cyclophosphamide may be considered or more often before this step, adjuctive therapy with a B cell depleting agent- which to date has been rituximab. However, rituximab works less effectively in lupus nephritis – as it does not induce a long term B cell

across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	depletion (thus requiring repeated dosing) while in a number of patients it induces an allergic reaction preventing further re-dosing and removing an essential adjunctive therapy. In certain patients who are heavily proteinuric or nephrotic adjunctive calcineurin inhibitors are often used, if kidney function is not severely impaired, as they are not only immunosuppressive but also very effectively anti -proteinuric. In addition to drug therapy, general lifestyle management is instituted- reducing risks of cardiovascular complications, stopping smoking, weight loss, salt intake etc. Careful attention is paid to blood pressure control. In those with a degree of chronic kidney damage – generic CKD management is included which may require RAAS blockers, or SGLT2 inhibition. Current guidelines are being revised – eg British society of rheumatology to highlight more aggressive early treatment with multiple therapies- to allow steroid minimisation and to prevent establishment of CKD. Current guidelines include KDIGO(2024) EULAR(2024), and BSR(2025) which emphasise use of combination therapies (rather than sequential therapy) to induce a more rapid remission.
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)	It will be used in secondary care and under the supervision of specialised services, with physicians experienced in the care of lupus nephritis patients. It will be used in a number of ways- 1. In patients unable to use rituximab or non responsive to rituximab 2. In patients in whom treatment with cyclophosphamide is undesirable 3. In combination with other immunosuppressive medication – such as mycophenolate and with corticosteroids. No additional investment is needed to use this technology as rituximab is already being used – and this will be used in the same manner.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Unlike rituximab there is robust randomised clinical trial data showing efficacy. In addition, real world experience highlights the benefit in terms of

• 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?	strength and duration of response. Since this drug produces a more profound and longer lasting B cell depletion – it will enable tapering of steroids more rapidly(as was shown in the clinical trials) and therefore improve patients' quality and potentially length of life, as there are data implicating steroids in driving the accelerated cardiovascular morbidity.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
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)	Neither, as already stated this drug is delivered in exactly the same way as rituximab which is widely used in the management of lupus nephritis. In fact, it will have the advantage of potentially not needing as many day case visits to deliver repeated frequent rituximab dosing due to its greater efficacy.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing will be required – there may even be less testing required as B cell depletion will be more consistent and more effective, meaning that testing for B cell numbers may not be required as often.
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	It is likely to improve quality of life as it will allow for more rapid steroid dose reduction and this is one of the main issues patients highlight as problems in the treatment regimens. Glucocorticoid toxicity index which measures the side effects related to steroid use may not be routinely used in a Quality of life calculation and this is an important outcome measure.

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 it is a superior version of rituximab which is frequently used in the management of patients and now has good trial evidence that given upfront induces remission more frequently than placebo.
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?	It is an effective immunosuppressive – so clearly has a risk of infectious complications. However, I am not aware that it is associated with greater infection risk compared to other immunosuppressives.
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?	They do, in that rituximab is often added to mycophenlate mofetil and steroids and this is likely how it will be used. It could replace rituximab and provide a more effective means of B cell depletion. The most important outcomes are resolution or reduction of proteinuria and stabilisation or improvement in renal function and these were primary outcome measures in the clinical trials. No significant adverse event signal was recorded in the trial, with the caveat that while COVID was prevalent there were increased risks of COVID infection in the treated patients - which I would expect in any patients treated with combined or augmented immunosuppression.
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 [TA882]?	No
23. How do data on real-world experience compare with the trial data?	We have been impressed by the response in patients treated with Obinutuzumab.

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.	SLE and lupus nephritis frequently affects patients from black and ethnic minority groups and mostly affects women – often of child bearing age. There are undoubtedly disparities in who is currently having access to the medication depending on geography and the units in which they are cared for. To make treatment more equitable NICE approval would allow access across the country as currently individual units may chose to use this and cover the costs, which is not the case everywhere.

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

This technology is a clinically proven superior treatment to currently used rituximab and will result in better patient outcomes

This can readily substitute for rituximab as it is delivered in exactly the same way meaning no additional resources needed

This technology has the potential to reduce the burden of chronic kidney disease

This technology has the potential to treat patients with lower doses of corticosteroids

This technology appears to be better tolerated than rituximab

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Single Technology Appraisal

Obinutuzumab with immunosuppressive therapies for treating lupus nephritis [ID6420]

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 lupus nephritis or caring for a patient with lupus nephritis. 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).

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.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **17th November 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.

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Patient expert statement

Part 1: Living with this condition or caring for a patient with lupus nephritis

Table 1 About you, lupus nephritis, current treatments and equality

1. Your name	Dalila Tremarias
2. Are you (please tick all that apply)	☒ A patient with lupus nephritis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with lupus nephritis? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	LUPUS 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 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 lupus nephritis? **If you are a carer (for someone with lupus nephritis) please share your experience of caring for them**	I was first diagnosed with SLE as a teenager in 2002. In my late twenties, a kidney biopsy confirmed lupus nephritis (LN). After several years in remission, I have recently been diagnosed again with active lupus nephritis. My initial LN diagnosis came as a shock, as I didn't recognise the symptoms. Since then, the condition has affected my working hours, quality of sleep, and brought the fear of disease progression, as well as the sadness of seeing treatments stop being effective. Experiencing the cycle again—undergoing a kidney re-biopsy, starting a new therapy, managing its side effects and complications, coping with active disease, the stress of maintaining good treatment adherence, waiting anxiously for urinary markers to respond, and dealing with recurrent hospital care and monitoring—has been extremely challenging.
7a. What do you think of the current treatments and care available for lupus nephritis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	I lived with SLE without lupus nephritis for at least a decade, and I can say that LN is very difficult both to live with and to manage. Access to a range of treatments is absolutely essential, as many of us are diagnosed young, not everyone will tolerate or respond to the same therapy, and the disease can recur. While we currently have some diversity in treatment options, I believe we should also prioritise diagnosing LN much earlier and developing tailored strategies with existing therapies to help patients achieve remission and make better use of the treatments already available.
8. If there are disadvantages for patients of current NHS treatments for lupus nephritis (for example, how	

they are given or taken, side effects of treatment, and any others) please describe these	One of the most difficult decisions we face as lupus nephritis patients is choosing, through shared decision-making, our next therapy once our current treatment has stopped working or when several previous treatments have failed. This naturally heightens our fear, anxiety, and stress. A major disadvantage we face is the uncertainty of selecting the most appropriate therapy for our specific lupus nephritis activity at that time. Access to a range of treatments, along with greater precision in selecting the most appropriate therapy, is needed.
9a. If there are advantages of obinutuzumab 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 obinutuzumab 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**	I don't have first-hand experience with this treatment, as it has not been available to me as part of my care. However, simply knowing that a new treatment with a different mechanism of action exists offers some relief, especially after trying others that have not been effective. It is also important to consider how treatment is delivered, as this can significantly reduce the treatment burden we experience.
10. If there are disadvantages of obinutuzumab over current treatments on the NHS please describe these. For example, are there any risks with obinutuzumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	It will be important to consider when this new treatment will become available (after what other therapies), which groups of people with lupus nephritis it will be suitable for, and what monitoring will be required.
11. Are there any groups of patients who might benefit more from obinutuzumab 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,	Having access to a new treatment would be highly valuable, as for many of us our lupus nephritis continues to flare, and we are seeking to achieve remission and prevent end-stage renal disease.

dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering lupus nephritis and obinutuzumab? Please explain if you think any groups of people with this condition are particularly disadvantage 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.	Lupus nephritis is a challenging condition that requires access to a range of treatments, as well as specialist care capable of providing a kidney biopsy, close monitoring and managing complications from active disease and treatment side effects, including recurrent infections. It is important to ensure that people with lupus nephritis can access new therapies, as well as the high-quality care that the condition requires.
13. Are there any other issues that you would like the committee to consider?	N/A

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Living with LN has been very challenging, affecting my daily live, and creating both emotional and physical burdens.
- LN is difficult to manage, treatment responses vary, and early diagnosis, along with selecting the right treatment, is important for achieving remission and preventing damage.
- As an LN patient, choosing the next treatment is one of the hardest aspects, increasing fear and uncertainty, while holding on to the hope that it will finally achieve the much-desired remission.
- Access to new treatments with different mechanisms of action is important, especially for those whose LN continues to flare.

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External Assessment Group (EAG) Report

Obinutuzumab with immunosuppressive therapies for treating lupus nephritis [ID6420]

Produced by	Newcastle University
Authors	Nicole O'Connor*, Research Assistant Giovany Orozco Leal*, Research Associate Lakshmi Jayachandran, Research Associate Kate Lanyi, Research Associate Eugenie Evelynne Johnson, Research Assistant Sheila A Wallace, Research Fellow Julia Whitehall, Research Associate Ryan PW Kenny, Research Associate Oleta Williams, Research Assistant Louise Tanner, Research Associate Stephen Rice, Senior Lecturer Gurdeep S Sagoo, Senior Lecturer Gill Norman, Principal Research Associate *Nicole O'Connor and Giovany Orozco Leal are joint first authors
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Date completed	Date completed (03/10/2025)

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Declared competing interests of the authors

None.

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Lucy Carter, Consultant Rheumatologist, Newcastle upon Tyne NHS Foundation Trust

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Nicole O'Connor was the clinical effectiveness lead, wrote sections of the clinical effectiveness assessment and edited the report.

Giovany Orozco Leal was the economics lead, wrote sections of the economics assessment, undertook economic modelling and edited the report.

Lakshmi Jayachandran wrote sections of the health economics assessment and undertook economic modelling.

Kate Lanyi wrote sections of the clinical effectiveness assessment.

Eugenie Evelynne Johnson provided analysis of submissions from patient and professional organisations, supported analysis of the decision problem and edited the report.

Sheila A Wallace wrote sections of the clinical effectiveness sections and supported the information specialist critique and the project leads.

Julia Whitehall wrote sections of the health economics assessment and supported the statistical critique of the indirect treatment comparisons.

Ryan PW Kenny provided statistical support for the critique of the indirect comparisons.

Oleta Williams was the information specialist and wrote the critiques of the search processes for clinical effectiveness and economics reviews.

Louise Tanner supported the critique of the clinical trials and edited and commented on the report.

Stephen Rice provided advice on the economic model and commented on the report.

Gurdeep S Sagoo provided health economics support, edited the report and acted as project co-lead.

Gill Norman provided clinical effectiveness support, edited the report and acted as project co-lead.

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Report key:

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Abbreviations

AD Active disease

AE Adverse events

AIC Akaike's Information Criterion

AZA Azathioprine

BEL Belimumab

BI Budget impact

BIC Bayesian information criterion

BSA Body surface area

BSR British Society for Rheumatology

CADTH Canadian Agency for Drugs and Technologies in Health

CEA Cost-effectiveness analysis

CEAC Cost-effectiveness acceptability curve

CEM Cost-effectiveness model

CHMP Committee for Medicinal Products for Human Use

CI Confidence interval

CKD Chronic kidney disease

COI Cost of illness

CPRD Clinical Practice Research Datalink

CRD Centre for Reviews and Dissemination

CrI Credible interval

CRR Complete renal response

CS Company's submission

CSR Clinical study report

CUA Cost-utility analysis

CYC Cyclophosphamide

DSU Decision Support Unit

EAG External Assessment Group

eGFR Estimated glomerular filtration rate

ESRD End stage renal disease

EULAR European Alliance of Associations for Rheumatology

FAD Final appraisal document

FDA Food and Drug Administration

HCRU Healthcare resource use

HR Hazard ratio

HRQoL Health-related quality of life

HSUV Health state utility value

HST Highly Specialised Technology

HTA Health technology assessment

IC Indirect comparison

ICER Incremental cost-effectiveness ratio

ISN/RPS International Society of Nephrology/Renal Pathology Society

ITC Indirect treatment comparison

ITT Intention-to-treat

IV Intravenous

IVC Intravenous cyclophosphamide

KDIGO Kidney Disease Improving Global Outcomes

LN Lupus nephritis

LY Life year

MeSH Medical subject headings

MMF Mycophenolate mofetil

MPAA Mycophenolic acid analogue

NA Not applicable

NHS National Health Service

NICE National Institute for Health and Care Excellence

NIHR National Institute for Health Research

NMA Network meta-analysis

NR Not reported

OBI Obinutuzumab

ORR Overall renal response

OS Overall survival

PAS Patient access scheme

PFS Progression-free survival

PRESS Peer Review of Electronic Search Strategies

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PROPSERO Prospective Register of Systematic Reviews

PRR Partial renal response

PSA Probabilistic sensitivity analysis

PSS Personal Social Services

PSSRU Personal Social Services Research Unit

QALY Quality-adjusted life year

QoL Quality of life

RCT Randomised controlled trial

RTX Rituximab

SAE Serious adverse events

SD Standard deviation

SE Standard error

SLE Systemic lupus erythematosus

SLR Systematic literature review

SMC Scottish Medicines Consortium

STA Single Technology Appraisal

TA Technology Assessment

TAC Tacrolimus

TEAE Treatment emergent adverse events

TTO Time trade-off

TTOT Time-to-off treatment

UK United Kingdom

ULN Upper limit of normal

USA United States of America

VOC Voclosporin

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 potentially 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. Section 1.3 explains the key issues in more detail. Secondary issues and modelling errors identified by the EAG are explored in Sections 1.4 and 1.5. Background information on the condition, technology and evidence, and non-key issues are presented in later sections of the EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of EAG's key issues

Table 1.1 provides a brief overview of the EAG's key issues.

Table 1.1: Summary of key issues

ID 6420	Summary of issue	Impact on results	Report sections
1	**Use of time to renal flare as a surrogate to predict the probabilities of transition to CKD stage 4**: There is not an established direct association between renal flare and transition to CKD stage 4. Furthermore, the way in which time to renal flare is measured in the key trials does not account for prior renal flares or the number of renal flares after the first, meaning that the true risk of transition to CKD stage 4 may be underestimated.	Large	2.3.2, 4.2.5
2	**Handling of treatment waning within the company's economic model:** Differences in treatment duration after stopping treatment at 3 years have a decisive impact on cost-effectiveness, yet most clinical trials have a follow-up under 2 years.	Large	4.2.5
3	**Assumption that the follow-up time-points from the network meta-analysis can be extrapolated to three years within the economic model:** The company's decision model assumes that outcomes from the network meta-analysis correspond to a follow-up timepoint of 3 years. The EAG considers that outcomes from the meta-analysis should correspond to the follow-up time of the studies used.	Large	4.2.5
4	**Transparency in modelling of concomitant treatments, particularly glucocorticoids**	Small	4.2.7

ID 6420	Summary of issue	Impact on results	Report sections
	and administration cost: The EAG noticed differences in the assumed administration costs of concomitant therapies across the MMF combination therapies presented. The EAG is concerned that administration cost assumptions can have a noticeable impact and need to be reported clearly.		
Abbreviations: CKD = chronic kidney disease; EAG = Evidence Assessment Group; MMF = mycophenolate mofetil			

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

1. Removing the hazard ratio (HR) of time to renal flare and assumed differences in the risk of progression from AD to CKD stage 4 for obinutuzumab + mycophenolate mofetil (OBI + MMF), voclosporin + mycophenolate mofetil (VOC + MMF), rituximab + mycophenolate mofetil (RTX + MMF).
2. Assuming a follow-up time for outcomes in the decision model aligned with the follow-up of the REGENCY trial.
3. Assuming no treatment waning beyond three years.
4. Assuming no vial sharing.
5. Including the impact of treatment-related adverse events on costs and quality-adjusted life years (QALYs) for the duration of therapy.
6. Using the effectiveness estimates reported for the network meta-analysis (NMA) results in the company submission in the decision model.
7. Assuming an alternative treatment distribution for the cost of rescue therapy.

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 QALY. An incremental cost-effectiveness ratio (ICER) is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled in the company's base-case analysis to affect QALYs by:

- Reducing the probability of progressing from active disease to chronic kidney disease (CKD) stage 4 relative to other therapies.
- Improving the proportion of patients with complete renal response (CRR) or partial renal response (PRR), which reduces the proportion of patients at risk of kidney disease progression.
- Improved treatment duration beyond the 3-year stopping rule.

Overall, the technology is modelled to affect costs by:

- Reducing the probability of progressing from active disease to CKD stage 4 relative to other therapies.
- Improving the proportion of patients with CRR or PRR, which reduces the proportion of patients at risk of kidney disease progression.
- Improved treatment duration beyond the 3-year stopping rule.
- Reducing rescue therapy costs.
- Increasing healthcare costs related to treatment-related adverse events.

The modelling assumptions that have the greatest impact on the ICER are:

- Reducing the probability of progressing from active disease to CKD stage 4 relative to other therapies.
- Improving the proportion of patients with CRR or PRR which reduces the proportion of patients at risk of kidney disease progression.

1.3 EAG's key issues

The following section details the EAG's key issues surrounding the company submission.

Issue 1: Use of time to renal flare as a surrogate to predict the probabilities of transition to CKD stage 4

Report section	2.3.2, 4.2.5
Description of issue and why the EAG has identified it as important	In the CS, the company use time to renal flare from the REGENCY trial as a proxy to predict the probability of transitioning to CKD stage 4 in the economic model. The EAG have major concerns surrounding this and its impact on the economic model. First, the justification provided by the company for using time to renal flare as a proxy for the probability of disease progression is derived from clinical opinion and a single-centre retrospective cohort conducted in Mexico (Perez Arias et al. 2023).[1] This does not substantiate a direct correlation between the proxy outcome and disease progression. NICE DSU Technical Support Document 20 states evidence that surrogate outcomes predict longer-term outcomes should preferably be derived from a meta-analysis of RCTs.[2] Second, the Perez Arias et al. (2023) study cited by the company notes that it is progressive renal flares that may increase the chance of a poorer kidney prognosis.[1] However, in the REGENCY trial and in the economic model the company use a time to event outcome, time to renal flare, to predict the transition to CKD stage 4. This outcome does not account for previous renal flares a patient has had, or the amount of subsequent renal flares. Given that Perez Arias et al (2023) and clinical advice to the EAG both note that it is the progressive nature of flares that may be linked to poorer kidney prognosis, the EAG believe that time to renal flare is an inadequate proxy outcome for disease progression.[1] Finally, the EAG also have concerns surrounding the appropriateness of using a Bucher analysis to compare evidence on renal flares for obinutuzumab, voclosporin, and belimumab, as the REGENCY and AURORA-2 studies were conducted in two different populations. Moreover, these methods are presented separate from the main network meta-analysis used to compare renal response outcomes. The economic model structure already accounts for the impact of improved renal response in reducing progression to kidney disease. The proposed approach implies that risks of progression to CKD stage 4 from active disease change according to therapy and used a surrogate outcome (time to renal disease) as a measure of this change, which risks

Report section	2.3.2, 4.2.5
	double counting the effectiveness impact of obinutuzumab.
What alternative approach has the EAG suggested?	In lieu of data surrounding the cumulative incidence of renal flares from the CS, the absence of data on CKD stage 4 progression, and the uncertain relative effectiveness between obinutuzumab, voclosporin, and belimumab, the EAG have removed the assumption surrounding time to renal flare as a proxy for transition to CKD stage 4 in their base-case economic model.
What is the expected effect on the cost-effectiveness estimates?	Removing the transition probabilities to CKD stage 4 from the economic model has a substantial effect on cost and QALY estimates less favourable to obinutuzumab.
Could any additional evidence or analyses be provided to resolve this key issue?	The decision model could include the short and long-term impact of renal flares on cost-effectiveness by adding flares as a separate health-state. This would require data on the incidence of flares, their impact on kidney disease risks, and the differences in risks from treatment. Further evidence of the correlation between progressive renal flares and CKD progression, ideally using meta-analytical methods suggested by NICE DSU Technical Support Document 20, would help further substantiate the justification for using renal flares as a proxy measure.[2] Furthermore, there needs to be evidence from clinical trials or real-world evidence that measures the incidence of renal flares instead of time to renal flare. Given the short follow-up duration of the clinical trials relative to the time a significant number of patients progress to CKD stage 4, there is an important data gap in kidney disease progression outcomes for lupus nephritis patients.
Abbreviations: CKD = chronic kidney disease; CS = company submission; DSU = Decision Support Unit; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence	

Key issue 2: Handling of treatment waning within the company's economic model

Report section	4.2.5
Description of issue and why the EAG has	The EAG is of the opinion that maintenance of treatment effectiveness beyond stopping treatment is highly uncertain. The sources of evidence for

Report section	4.2.5
identified it as important	continued effect of treatment and its waning were studies with follow-up periods below the three-year stopping rule in the CS.[3] To justify the continued treatment effectiveness and its waning, the company presented evidence of association between complete B-cell depletion and CRR from Gomez Mendel et al (2018).[4] However, this was a post-hoc analysis of the LUNAR study, with a primary endpoint at 78 weeks. Much of the evidence was also based on clinical expert opinion on the mechanisms of action for each drug.
What alternative approach has the EAG suggested?	The EAG suggest adopting a conservative assumption of no treatment waning, due to the absence of stronger evidence, but maintained the assumption of a continued treatment effect of 1 year for OBI, 6 months for BEL and RTX and no effect for VOC, post the 3 years for treatment.
What is the expected effect on the cost-effectiveness estimates?	By assuming that there would be no treatment waning effect post continued treatment effectively reduced the relative treatment efficacy period after the 3 years of treatment for obinutuzumab. However, this on its own did not change the company's conclusions. Additional analyses by the EAG suggest that the length of treatment effect duration after stopping treatment is an important determinant of cost-effectiveness; this is a key concern given the weak evidence base for these assumptions.
Could any additional evidence or analyses be provided to resolve this issue?	Evidence from trials which has extended period of follow-up periods (more than 3 years) would be useful in informing whether there would be treatment waning effect after stopping the drug and the nature of the waning effect.
Abbreviations: BEL = belimumab; CRR = complete renal response; CS = company submission; EAG = External Assessment Group; RTX = rituximab; VOC = voclosporin	

Key issue 3: Assumption that the follow-up time-points from the network meta-analysis can be extrapolated to three years within the economic model

Report section	4.2.5
Description of issue and why the EAG has identified it as important	The timepoints of treatment follow-up from neither the REGENCY trial nor the NMA corresponds to three-year timepoint in the executable decision model.[5,6] In the company submission, the follow-up time points of

Report section	4.2.5
	the studies included in the NMA were not clearly reported.[3] As such, in response to B4 in the PfCs, the company reported treatment endpoints for various studies (timepoints at or below two years), none of which corresponded to the assumption that they can be used as three-year timepoints in the company decision model.[7] This would mean that the proportion of patients achieving CRR and PRR would remain constant between the timepoints – 76 weeks (~1.5 years) and week 157 (3 years) - which the EAG believes to be an inappropriate assumption.
What alternative approach has the EAG suggested?	The EAG is of the opinion that the company should consider that NMA outcomes have timepoints corresponding to study follow-up points and not treatment stopping rules. In this case, the EAG used the 76-week timepoint in REGENCY as reference to calculate time-related probabilities.
What is the expected effect on the cost-effectiveness estimates?	Assuming the wrong outcome timepoints can lead to a misrepresentation of the evidence and lead to erroneous calculations of the proportion of patients in CRR and PRR over time in the decision model. This could potentially have a significant impact on the cost-effectiveness estimates.
Could any additional evidence or analyses be provided to resolve this key issue?	The EAG has assumed a 1.5 year (76 week) timepoint for the NMA outcome in its base-case analysis to better reflect the evidence available.
Abbreviations: CRR = complete renal response; EAG = External Assessment Group; NMA = network meta-analysis; PfC = points for clarification; PRR = partial renal response	

Key issue 4: Transparency in modelling of concomitant treatments, particularly glucocorticoids and administration cost

Report section	4.2.7, 5.2.1
Description of issue and why the EAG has identified it as important	The frequencies and associated costs of concomitant drug administration applied in the company's base case varied across treatment interventions and comparators,[8] but were not transparently reported in the CS, for mycophenolate mofetil (MMF) and glucocorticoids (methylprednisolone and prednisone).[3]

Report section	4.2.7, 5.2.1
	The CS stated the dosing schedule aligned with the REGENCY trial. However, variations in MMF and glucocorticoid (commonly named as corticosteroid) treatment dosing schedules for each intervention in the CS model were not clearly reported and the sources were not clearly mentioned.[3,8]. Additionally, long-term use of corticosteroids is associated with cumulative toxicity and associated chronic adverse effects. The impact of these long-term effects was not accounted for in the CS model.[8]
What alternative approach has the EAG suggested?	The dose, frequency and associated costs for each treatment arm should clearly and transparently reported, with sources and justifications. The EAG has used the information available to replicate and validate the concomitant treatment costs used in the model. Additional adverse events related to differences in the use of corticosteroid use should also be included, where possible.
What is the expected effect on the cost-effectiveness estimates?	The difference in drug acquisition costs of MMF and glucocorticoids would not have a huge impact on ICERs on their own (since their unit prices are relatively low). however, the modes and number of administration (e.g. IV or vaccinations at the hospital, oral delivery at home) can have a significant burden on patients and the NHS.[3] This issue also pertains to transparency and consistency of model inputs and assumptions. Furthermore, corticosteroid cumulative toxicity associated adverse events and its management can have a significant role in patient quality of life, and healthcare resource use.
Could any additional evidence or analyses be provided to resolve this key issue?	Additional sources of evidence that informed the treatment using concomitant drugs could be useful to validate the model inputs of treatment costs and resource use. This should include accounting for the differences in use of concomitant drugs between the treatment arms.
Abbreviations: CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; IV = intravenous; MMF = mycophenolate mofetil; NHS = National Health Service	

1.4 Secondary issues identified by the EAG

The following section highlights secondary issues that the EAG believes to represent areas of uncertainty but have a less significant impact than the issues identified in Section 1.3.

Issue 1: Assumption that all treatment-related adverse events only affect costs and resolve in the first 6 months (1 model cycle) in the company base-case model

Report section	3.3.3, 5.2.3
Description of issue and why the EAG has identified it as important	In the company's base-case analysis, it is assumed that the impact of treatment-related adverse events (AEs) in quality of life is already accounted for in the baseline quality of life values for each patient. The EAG considers that this assumption ignores the impact of potential differences in AE incidence across treatment arms. Furthermore, the company's base-case considers the impact of differences in treatment-related AEs only in health-care resource use, where the incidences of adverse events for OBI + MMF were sourced from REGENCY trial.[3] All other treatment regimens with MMF were assumed to have the same incidence of AEs from the MMF arm of REGENCY.[7] The lifetime cost of AEs in each treatment arm was calculated as the average AE costs per patient week multiplied by the rate of events and it was applied up-front at Cycle 1.[8] It is unclear to the EAG whether most AEs resolve during the first six-month cycle, or whether some treatment-related events can recur for the duration of the treatment.
What alternative approach has the EAG suggested?	The EAG is of the opinion that the impact of AE differences should be applied to both resource use and patient quality of life. Moreover, the EAG has extended the duration of AE costs to match the duration of treatment.
What is the expected effect on the cost-effectiveness estimates?	The changes in the modelling approach of AE proposed by EAG increased the impact of adverse events on costs but had a minor impact on QALY differences.
Could any additional evidence or analyses be provided to	The approach to modelling adverse events in the model may underestimate the impact of treatment-related events due to the assumptions used surrounding event duration and impact on patient

Report section	3.3.3, 5.2.3
resolve this key issue?	utility. It was further unclear which events are more likely to recur over the treatment duration, and what the current role of COVID-19 on treatment-related events is.
Abbreviations: AE = adverse events; EAG = External Assessment Group; MMF = mycophenolate mofetil; QALY = quality-adjusted life year	

Issue 2: Rescue therapy costs within the company's economic model

Report section	4.2.7
Description of issue and why the EAG has identified it as important	The CS seemed to draw an equivalence between rescue therapy costs and subsequent treatment costs.[3] However, according to clinical advice to the EAG, rescue therapy in LN is not synonymous with subsequent treatments. This assumption was made in the absence of data on subsequent therapy, as the follow-up times in most clinical trials are below the proposed 3-year treatment stopping rule. Furthermore, there was a lack of clarity in the CS around the assumed proportion of patients who received rescue therapy in each treatment arm, and the assumed distribution of rescue therapies patients were expected to receive.[3] The EAG also noted inconsistencies with respect to the percentage of patients who received rescue therapy in different treatment arms between the CS document and the company's submitted model, as well as the inclusion of the distribution of anifrolumab and obinutuzumab, which are currently not reimbursed in the English NHS.[3,8]
What alternative approach has the EAG suggested?	The EAG suggest that, for the purpose of maintaining consistency, the proportion of patients who received rescue therapy in the VOC, BEL and RTX arms be assumed to be equivalent to that of the OBI treatment group, and that the treatment distribution in the VOC, BEL and RTX arms followed the distribution of MMF alone based on expert opinion. The patients who received anifrolumab, BEL and OBI were redistributed to cyclophosphamide and cyclosporin.
What is the expected effect on the cost-effectiveness estimates?	The decision model only accounted for the impact of rescue therapy on costs and not on patient QALYs. Making more consistent assumptions led to reductions in the cost differences where OBI was the main comparator.

Report section	4.2.7
Could any additional evidence or analyses be provided to resolve this issue?	Additional data after the proposed 3 years of stopping treatment are necessary to inform any assumptions of subsequent treatment rates, therapies used, and the impact of subsequent therapies on effectiveness. The decision model only accounted for the healthcare costs of rescue therapy. Therefore, it was unclear what is the relation between treatment efficacy and rescue therapy risk and vice-versa, to fully account for the cost-effectiveness impact of rescue therapy assumptions.
Abbreviations: BEL = belimumab; CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; LN = lupus nephritis; MMF = mycophenolate mofetil; NHS = National Health Service; OBI = obinutuzumab; QALY = quality-adjusted life year; RTX = rituximab; VOC = voclosporin	

1.5 Company's modelling errors identified by the EAG

Modelling errors were identified and corrected by the EAG using the company's decision model submitted after the points for clarification (PfCs); see Section 5.2.1 for further details. The results of the initial decision model submitted before the clarifications and the analysis undertaken by EAG to replicate these results are given in Appendix 7.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 1.2 provides a summary of all the exploratory changes that the EAG has undertaken in the updated company base-case. The cost-effectiveness results of these exploratory changes are given in Table 1.3, Table 1.4, Table 1.5 and Table 1.6.

Deterministic results showed that OBI + MMF compared to MMF alone was more costly and more effective, increasing costs by [redacted] and QALYs by [redacted] for a total ICER of [redacted]/QALY, above NICE's cost-effectiveness threshold of £20,000/QALY. Deterministic results showed that OBI compared to VOC was less costly and less effective, reducing costs by [redacted] and reducing QALYs by -[redacted], resulting in an ICER of £705,549/QALY. OBI + MMF was less costly and more effective when compared to BEL + MMF and RTX + MMF.

Table 1.2: List of EAG exploratory analyses on company base-case.

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
0	Company decision model submitted with the points for clarifications response.	Company decision model with corrections to errors found by the EAG.	Several minor errors were spotted in the company's executable model file.	Section 5.2.1
1	Hazard ratio of time to renal flare applied to the probability of progressing from active	Removing the hazard ratios of time to renal flare from the probability of progressing	The EAG considers the model structure accounts for improvements	Section 4.2.5

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
	disease to CKD stage 4. Data from REGENCY applied to obinutuzumab, ITC results from AURORA-2 and BLISS-LN applied to voclosporin and belimumab.	from active disease to CKD stage 4. Instead assume that improvements in response lead to a reduction of patients at risk of CKD stage 4.	in renal response leading to lower kidney disease progression. The approach of estimating differences in kidney disease progression based on the hazard ratio of time-to-renal flare was considered too strong an assumption given the evidence base supporting it.	
2	CRR and PRR timepoints from the NMA assumed to correspond to 3 years of treatment. Weibull function used to transform probabilities to 6-month cycles.	CRR and PRR timepoints from the NMA assumed to correspond to 1.5 years of treatment. Exponential function used to transform probabilities to 6-month cycles.	Better alignment with the follow-up of the key clinical studies used in the NMA.	Section 4.2.5
3	Treatment effect duration, and waning after 3 years: OBI: 1 year, 1 year VOC: 0, 6 months BEL: 6 months, 6 months	No treatment waning, treatment effect duration after 3 years: OBI: 1 year VOC: 0 BEL: 6 months RTX: 6 months.	Assumptions of treatment effect duration and waning after 3 years were considered highly speculative given the absence of trial data beyond 2	Section 4.2.5

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
	RTX: 6 months, 6 months.		years of treatment.	
4	Assumption of vial sharing for IV delivery.	No vial sharing assumed for IV delivery.	Better alignment with NICE methods guidance.	Section 4.2.7
5	Baseline patient HRQoL estimates include the impact of adverse events. Cumulative impact of adverse events on costs applied in the first 6-month cycle.	Cumulative impacts of treatment-related adverse events applied to patient HRQoL and costs. Impact of adverse events applied for the 3-year duration of treatment.	Differences in treatment-related adverse events were highlighted as one of the primary concerns to patients.	Section 4.2.8
6	CRR and PRR timepoints from the NMA assumed to correspond to 3 years. Weibull function used to transform probabilities. Estimates from company calculations.	CRR and PRR timepoints from the NMA assumed to correspond to 1.5 years. Exponential function used to transform probabilities. Estimates from EAG's own calculations.	CRR and PRR estimates in the economic model showed small differences to the values reported from the NMA results in the submission documents. The EAG presented our own estimations of treatment effect based on values from the submission.	Section 5.2.1
7	Treatment distribution for rescue therapy in the company base-case	Alternative treatment distribution for rescue therapy based on the	The alternative proposed approach to the rescue therapy costs	Section 4.2.7

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
	included treatment not reimbursed in the NHS.	MMF arm of REGENCY and therapies reimbursed in the NHS.	has a better alignment with the care delivered for LN in the English NHS.	
8	Treatment drug and delivery costs for interventions and concomitant therapies based on the executable model submitted by the company.	Treatment drug and delivery costs for interventions and concomitant therapies based on EAG assumptions informed by REGENCY, TA882, and BLISS-LN.	Assumptions around doses, deliveries, and concomitant treatment costs were not clearly laid out in the company submission. The EAG has attempted to replicate these costs based on the available literature.	Section 4.2.7

Abbreviations: BEL = belimumab; CKD = chronic kidney disease; CRR = complete renal response; EAG = External Assessment Group; HRQoL = health-related quality of life; ITC = indirect treatment comparison; IV = intravenous; LN = lupus nephritis; MMF = mycophenelate mofetil; NHS = National Health Service; NMA = network meta-analysis; OBI = obinutuzumab; PRR = partial renal response; RTX = rituximab; TA = technology appraisal; VOC = voclosporin

Table 1.3: Deterministic results of EAG's exploratory analyses using company's base case – versus MMF alone

Exploratory analysis number	MMF alone		
	Incremental costs (£)	Incremental QALYs	ICER £/QALY
-	[redacted]	[redacted]	£1,454
0	[redacted]	[redacted]	£5,096
1	[redacted]	[redacted]	£19,669
2	[redacted]	[redacted]	£2,434
3	[redacted]	[redacted]	£6,353
4	[redacted]	[redacted]	£5,084
5	[redacted]	[redacted]	£5,703
6	[redacted]	[redacted]	£4,006
7	[redacted]	[redacted]	£1,884
8	[redacted]	[redacted]	£7,582
EAG's base-case	[redacted]	[redacted]	£23,943

Exploratory analysis number	MMF alone		
	Incremental costs (£)	Incremental QALYs	ICER £/QALY
Abbreviations: EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; QALY = quality-adjusted life year			

Table 1.4: Deterministic results of EAG's exploratory analyses using company's base case – versus VOC + MMF

Exploratory analysis number	Voclosporin + MMF		
	Incremental costs (£)	Incremental QALYs	ICER £/QALY
-	[redacted]	[redacted]	*Dominant
0	[redacted]	[redacted]	*Dominant
1	[redacted]	[redacted]	**£1,819,600
2	[redacted]	[redacted]	*Dominant
3	[redacted]	[redacted]	*Dominant
4	[redacted]	[redacted]	*Dominant
5	[redacted]	[redacted]	*Dominant
6	[redacted]	[redacted]	*Dominant
7	[redacted]	[redacted]	*Dominant
8	[redacted]	[redacted]	*Dominant
EAG's base-case	[redacted]	[redacted]	**£705,549
*Obinutuzumab dominant (more effective and less costly) **ICER for voclosporin vs obinutuzumab is above the £20,000/QALY threshold Abbreviations: EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; QALY = quality-adjusted life year; VOC = voclosporin			

Table 1.5: Deterministic results of EAG's exploratory analyses using company's base case – versus BEL + MMF

Exploratory analysis number	Belimumab + MMF		
	Incremental costs (£)	Incremental QALYs	ICER £/QALY
-	[redacted]	[redacted]	*Dominant
0	[redacted]	[redacted]	*Dominant
1	[redacted]	[redacted]	*Dominant
2	[redacted]	[redacted]	*Dominant
3	[redacted]	[redacted]	*Dominant
4	[redacted]	[redacted]	*Dominant
5	[redacted]	[redacted]	*Dominant
6	[redacted]	[redacted]	*Dominant
7	[redacted]	[redacted]	*Dominant

Exploratory analysis number	Belimumab + MMF		
	Incremental costs (£)	Incremental QALYs	ICER £/QALY
8	[redacted]	[redacted]	*Dominant
EAG's base-case	[redacted]	[redacted]	*Dominant

*Obinutuzumab dominant (more effective and less costly)
Abbreviations: BEL = belimumab; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; QALY = quality-adjusted life year

Table 1.6: Deterministic results of EAG's exploratory analyses using company's base case – versus RTX + MMF

Exploratory analysis number	Rituximab + MMF		
	Incremental costs (£)	Incremental QALYs	ICER £/QALY
-	[redacted]	[redacted]	*Dominant
0	[redacted]	[redacted]	*Dominant
1	[redacted]	[redacted]	*Dominant
2	[redacted]	[redacted]	*Dominant
3	[redacted]	[redacted]	*Dominant
4	[redacted]	[redacted]	*Dominant
5	[redacted]	[redacted]	*Dominant
6	[redacted]	[redacted]	*Dominant
7	[redacted]	[redacted]	*Dominant
8	[redacted]	[redacted]	*Dominant
EAG's base-case	[redacted]	[redacted]	*Dominant

*Obinutuzumab dominant (more effective and less costly)
Abbreviations: EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; QALY = quality-adjusted life year; RTX = rituximab

1.7 Outline of confidential comparator or subsequent treatment prices

A confidential appendix was included as part of the EAG report using confidential prices; see Section 5.4 for more details.

2 Background

This report critiques the company submission (CS) for obinutuzumab (OBI) with immunosuppressive therapies for treating lupus nephritis (LN) [ID6420].[3]

Sections 2.1 and 2.2 include information and perspectives gathered from submissions by patient and professional organisations submitted to NICE: Lupus UK, the British Society for Rheumatology (BSR), and the UK Kidney Association.[9-11] In addition, the EAG also engaged with clinical specialists in the topic area to inform the critique of these sections.

2.1 Critique of the company's description of underlying health problem

This section provides a critique of the company's description of Systemic Lupus Erythematosus (SLE) and LN including the pathophysiology, epidemiology, natural history, diagnosis and classification, clinical presentation, and the burden of disease (covering health-related quality of life (HRQoL), caregiver burden and treatment-related burden; CS Section 1.3.1).[3]

Table 2.1: Summary of the EAG critique of the company's description of the condition

Area of health condition addressed	Section in the CS where reported	EAG comment
Pathophysiology	CS, Section 1.3.1.2	**Appropriate** Aligns with published literature.
Epidemiology	CS, Section 1.3.1.3	**Some concerns** The EAG believes there are newer figures available regarding the epidemiology of SLE. See section 2.1.1 below.
Natural history	CS, Section 1.3.1.4	**Appropriate** Aligns with published literature.
Diagnosis and classification	CS, Section 3.1.5	**Appropriate** Aligns with published literature.
Clinical presentation	CS, Section 1.3.1.6	**Appropriate** Aligns with published literature.

Area of health condition addressed	Section in the CS where reported	EAG comment
Burden of disease (covering health-related quality of life, caregiver burden and treatment-related burden)	CS Section 1.3.1.7	**Some concerns** HRQoL: The company highlight the impact of fatigue, which ties in with one patient report in the Lupus UK submission to NICE. However, pure class V LN is not mentioned in relation to HRQoL or fatigue. Treatment-related burden: There are issues surrounding the pill burden associated with treatments for LN that also require balancing with the need for patients to spend a whole day on a hospital ward for IV treatment. The EAG notes that treatments should be tailored to individual patient choice, wherever possible. See section 2.1.2 for further details.
Abbreviations: CS = company submission; EAG = External Assessment Group; HRQoL = health-related quality of life; IV = intravenous; LN = lupus nephritis; SLE = Systemic Lupus Erythematosus		

2.1.1 Epidemiology

The epidemiology of SLE and LN is covered in CS Section 1.3.1.3.[3] The company cite Rees et al (2016), which used the Clinical Practice Research Datalink (CPRD) data for UK primary care 1999-2012,[12] for incidence and prevalence of SLE in the UK. However, Ellis et al (2024) provide more current data, covering 1990 to 2020, and also use CPRD data.[13] Overall, in the Ellis et al (2024) paper, the incidence rate of SLE in the UK was 5.47 cases per 100,000 person-years (95% CI 5.33 to 5.62), with a point prevalence of 107.14 per 100,000 in 2020 (95% CI 103.26 to 111.12).[13] Furthermore, both studies found that, in the UK overall, SLE was six times more common in females than males.[12,13] The company's figures for LN in the UK from the study by Patel et al (2006) still appear to be the most up to date, even though, as the company mention, they date from 2001 and only cover the north west of England.[14]

As the company state, many of the patients are female and of working and reproductive age at first diagnosis of LN.[3]

2.1.2 Burden of disease

Health-related quality of life (HRQoL)

In CS Section 1.3.1.7.1, the company compare HRQoL of patients with class I/II LN with those with class III/IV LN but do not cover pure class V disease.[3] A study of 499 patients in several centres in Italy conducted between January 1970 and December 2016 found that approximately 15% to 20% of LN patients had pure class V disease.[15] The HRQoL and fatigue also appear to be worse in LN class V patients.[16] This is covered in greater detail in Section 3.2.1.

Treatment burden

Treatment burden is presented in CS Section 1.3.1.7.3[3] Clinical advice to the EAG noted that there can be a considerable pill burden with LN treatment, as also stated within the CS. The CS mentions that VOC and 'pill-based MMF' can add to the bill burden, especially if the LN patients are on other oral tablets such as corticosteroids and hydroxychloroquine.[3] Pill burden and other treatment burden is also covered in CS Section 1.3.4.[3]

Clinical advice to the EAG noted that, despite problems with adherence to pill-based treatment for many LN patients, some patients can cope with the large number of pills and some people with LN do not want to spend a day on a hospital ward to receive IV treatment or do not live near enough to a treatment centre for this to be a preferred option. There may also be potential equality issues surrounding geographical location and being able to access OBI treatment. Although none of the people that participated in a survey run by Lupus UK had received OBI, people expressed potential concerns about access to the treatment due to the need to visit a hospital for IV infusion.[9]

"Getting to the location, cost and support especially if you are on your own." - person responding to survey from Lupus UK submission.[9]

"Unless you can work it's going to be hard to have a whole day out - plus would the strain on hospitals be ok?" - person responding to survey from Lupus UK submission.[9]

By contrast, also in the Lupus UK submission, one patient found it reassuring to be on a ward for the IV treatment with healthcare professionals nearby.[9] As such, treatment can be tailored to the patient's needs and preferences, according to clinical advice to the EAG. The fact that many LN patients are female and of working and reproductive age could also add to the burden of treatment such as needing to take a day off work or arrange childcare.

2.2 Critique of the company's overview of current service provision

This section provides a critique of the company's description of current service provision in the UK (CS Section 1.3.2), treatment guidelines (CS Section 1.3.3), unmet need (CS Section 1.3.4), and proposed position of OBI in the treatment pathway (CS Section 1.3.5).[3] Equality considerations are covered in CS Section 1.4 and will also be considered in this section.[3]

Table 2.2: Summary of the EAG critique of the company's overview of current service provision

Area of current service provision addressed	Section of the CS where reported	EAG comment
Targeted therapies	CS, Section 1.3.2.1	**Some concerns** The company cover a limited number of targeted therapies whereas the NICE decision problem and forthcoming BSR guidelines update cover a wider range of possible therapies. See section 2.2.1.
Treatment guidelines	CS, Section 1.3.3	**Some concerns** The main guidelines currently available are covered by the CS in this section but there are wide variations in treatment of LN according to a recent survey

Area of current service provision addressed	Section of the CS where reported	EAG comment
		and patient and professional organisations' submissions to NICE. See Section 2.2.2.
Unmet need	CS, Section 1.3.4	**Appropriate** Aligns with the published literature. Covers treatment burden more fully than was covered in CS Section 1.3.1.7.
Company's proposed position of the intervention in the treatment pathway	CS, Section 1.3.5	**Some concerns** Clinical advice to the EAG agrees with the company's proposed positioning of the intervention although, optimally, it would be added to GCs, MPA and hydroxychloroquine. See Section 2.2.3.
Equality considerations	CS, Section 1.4	**Some concerns** Only potential equality considerations relating to ethnicity are presented by the company within the CS. Gender, age, pure class V LN, geography and reproductive issues are not covered. See Section 2.2.4 for more information.
Abbreviations: CS = company submission; EAG = External Assessment Group; GC = glucocorticoid; MPA = mycophenolate analogue		

2.2.1 Targeted therapies

Targeted treatments for LN are covered in Section 1.3.2.1 of the CS.[3] This section of the CS covers the targeted treatments VOC, belimumab (BEL) and RTX.

In the CS (Section 1.3.2.1.1), the company state that the uptake of BEL for LN in England is low due to the complexity of local guidelines governing its use and lack of national reimbursement.[3] Cyclophosamide and tacrolimus, both included within the NICE decision problem, are only mentioned briefly in CS Section 1.3.2.1.2.[3]

However, referencing their upcoming clinical guidelines for managing LN, the British Society for Rheumatology (BSR) noted in their submission to NICE that first line therapy for induction may include: methylprednisolone and reduced-dose oral prednisolone; and one of OBI + MMF, or BEL + MMF, or VOC + MMF, or tacrolimus + MMF. If first-line therapies were unsuitable, other options for induction include: BEL + Eurolupus protocol cyclophosphamide; RTX + MMF; MMF alone; or Eurolupus or NIH dose cyclophosphamide alone.[10] Of note, the BSR also stated that, while the NICE review of BEL was not completed, the NICE approval for BEL in non-renal SLE did not exclude its use for patients with LN.[10] This aligns with clinical advice received by the EAG.

Clinical advice to the EAG also stated that there is no single first choice treatment for LN. It further advised that choice of treatment may depend on an individual's comorbidities, as LN may be accompanied by other SLE-related symptoms, as well as patient preference. Treatment can and will be changed if there is not a complete response to the current treatment or if a relapse occurs. Additionally, although the dose of concomitant corticosteroids may start high to achieve a complete response, the dose would be tapered to achieve minimisation where effective control permits to reduce steroid burden.

2.2.2 Treatment guidelines

Treatment guidelines from the European Alliance of Associations for Rheumatology (EULAR), Kidney Disease – Improving Global Outcomes (KDIGO) and the currently-unpublished BSR 2025 updated guidelines are compared by the company in the CS (Section 1.3.3).[3] Clinical advice to the EAG noted that these international guidelines are taken into consideration by healthcare providers in England, along with those from the American College of Rheumatology.[17] Despite these guidelines, clinical advice to the EAG noted the treatment landscape for LN has been constantly evolving as, until recently, there were no approved drugs for treating the condition. Furthermore, a recent survey found a wide variation in treatment available across the UK, as well as variations in the use of guidelines and protocols and specialist clinical provision.[18]

Additionally, submissions from patient and professional organisations to NICE stated that there are inequalities in the way in which care for LN is provided across the country. Lupus UK noted that the provision of care for people with lupus is inconsistent across England and Wales,[9] while the BSR noted that a recently-published survey highlighted how there was differentiation in care across the UK, which often differed from existing guidelines.[10,18] One of the EAG's clinical advisors also noted that there can be delays in adopting the most up-to-date clinical guidance for LN. The UK Kidney Association stated that treatment could depend on access to infusion wards for IV treatment and drug availability, though suggested that there should not be variation within specialist LN centres.[11]

The updated EULAR guidelines for SLE with kidney involvement, which were mentioned as "in press" in the CS (Section 1.3.3), are not yet published, although the SLR that provided contributing evidence is available.[19] Therefore, the EAG cannot comment on the effect this updated guidance may have on clinical practice.

2.2.3 Positioning of obinutuzumab in the care pathway

The company's proposed position of OBI in the treatment pathway is as a first line therapy: "OBI is expected be used as an option within a first-line triple immunosuppressive regimen for patients with LN" (CS Section 1.3.5).[3] The company suggest that OBI can be used for both induction and maintenance therapy alongside glucocorticoids and MPAA. This aligns with the BSR submission to NICE for this appraisal.[10] Clinical advice to the EAG agrees with this positioning, however optimally it would be added to glucocorticoids, mycophenolate analogue and hydroxychloroquine.

2.2.4 Equality considerations

Equality considerations are covered in CS Section 1.4.[3] Only potential equality considerations relating to ethnicity are mentioned in the CS.

However, there are several other potential equality considerations surrounding treatment for LN. In terms of age, clinical advice to the EAG noted that LN in children is rare and so often diagnosis, advice and treatment are given through very few specialist centres, which may be difficult for children and their parents/carers to access. Clinical advice to the EAG also noted that, after the age of 12 years, clinical

presentation is the same as in adult disease and so there is the question of whether there should be the same access to treatments for LN for this age group as for adults. Furthermore, Lupus UK highlighted that those diagnosed in childhood (juvenile-onset SLE) often experience longer disease course and greater severity of disease, as well as longer treatment exposure.[9]

According to clinical advice to the EAG, approximately 15% of LN patients have pure class V lupus nephritis only but are also rarely included in trials. Further discussion surrounding pure class V LN is presented in Section 2.3.1.

As mentioned in Section 2.1.1, women of childbearing age are more commonly affected by SLE (and LN). The average age of diagnosis coincides with reproductive age for women and so the lack of suitable treatments that can be used leading up to conception and during pregnancy is problematic. Given that LN predominantly affects women, submissions to NICE and clinical advisors to the EAG highlighted the impact of LN treatments on fertility and their incompatibility with pregnancy. Clinical advice to the EAG was that none of the drugs listed within the CS and no current first-line treatments could be used during pregnancy, while MMF cannot be used during the conception period. This means there is an issue surrounding the lack of treatment options available during pre-conception periods and in pregnancy.

Finally, as noted in Section 2.1.2, there may also be potential equality issues surrounding geographical location and access to treatment.

2.3 Critique of the company's definition of decision problem

This section provides a critique of the company's interpretation of the decision problem (CS Section 1.1).[3]

Table 2.3: Summary of the decision problem

-	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with lupus nephritis.	People with lupus nephritis.		**Some concerns** The EAG is satisfied that the population of the decision problem is in line with the NICE scope. The only concern to note is that the NICE scope is broad, including all patients with LN. However, in the REGENCY and NOBILITY trials the population is adults with class III or IV with or without class V. This excludes patients with class V alone which may reflect a narrower population than the NICE scope. Further, the NICE scope did not limit the population to adults only; the company did not include paediatric patients in the REGENCY and NOBILITY trials.

-	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				See Section 2.3.1 for further details.
Intervention	Obinutuzumab with immunosuppressive therapies	Obinutuzumab with immunosuppressive therapies		**Appropriate** The intervention in the NICE scope matches that in the company decision problem.
Comparator(s)	Established clinical management without OBI including: • induction alongside hydroxychloroquine and corticosteroids including: • cyclosporin with or without mycophenolate • cyclophosphamide • mycophenolate • rituximab with mycophenolate • tacrolimus with or without mycophenolate • voclosporin with mycophenolate mofetil • belimumab with mycophenolate • maintenance treatment with mycophenolate,	Established clinical management without OBI including: • mycophenolate • rituximab with mycophenolate • voclosporin with mycophenolate mofetil alongside corticosteroids • belimumab with mycophenolate	In section 3.2.3 the company provides the rationale that following consultation with medical experts they do not believe that the excluded comparators are widely used in UK clinical practice.	**Some concerns** The company uses a narrower set of comparators compared to the NICE scope. Of particular note, the company excluded tacrolimus, cyclophosphamide and BEL from their economic analysis in the original CS. The EAG was advised by a clinical expert that these treatments are used in UK clinical practice and they are included in current treatment guidelines, such as the updated 2025 BSR guidelines.[10] Therefore, the EAG has concerns that the exclusion of these comparators has not been adequately justified by the

-	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	azathioprine or a calcineurin inhibitor (such as tacrolimus).			company. To note, the company added BEL to the economic model following request from the EAG during the PfCs.[7] See Section 2.3.2 for further details.
Outcomes	The outcome measures to be considered include: • renal response rate and severity of renal-related events (e.g., flares) • rate and duration of remission • incidence of end-stage renal disease • corticosteroid use • mortality • adverse effects of treatment • health-related quality of life.	The outcome measures to be considered include: • renal response rate and severity of renal-related events (e.g., flares) • rate and duration of remission • incidence of end-stage renal disease • corticosteroid use • mortality • adverse effects of treatment • health-related quality of life.		**Key issue** The EAG acknowledge that the company include all the outcome measures within the NICE decision problem within the CS. However, the EAG have concerns about how transitions to CKD stage 4 in the economic model has been informed by a surrogate outcome in the CS (time to renal flare). See Section 2.3.3 for further information.
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.	Incremental cost per quality-adjusted life year. Lifetime time horizon. Costs considered from an NHS and Personal Social Services perspective.		**Appropriate** The EAG are satisfied that the company's base-case analysis does not violate the reference set out by NICE in the decision problem.

-	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	Patient access scheme for obinutuzumab considered.		However, there are issues surrounding the population, comparators and outcome measurements that impact on the overall economic assessment.
Subgroups	No subgroups	N/A	N/A	N/A
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	The company discuss equity considerations in CS, section 1.4.	N/A	**Some concerns** The EAG is satisfied that the company have considered potential equality issues surrounding the greater prevalence of LN in ethnic minority populations in the UK. However, the EAG are concerned that the company

-	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	authorisation granted by the regulator.			have not discussed other equity-related issues, such as treatments for the paediatric population and women of childbearing age. See Section 2.3.4 for further information.
Source: CS, Section 1.1, Table 1[3] Abbreviations: BEL = belimumab; EAG = External Assessment Group; HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; OBI = obinutuzumab; UK = United Kingdom				

2.3.1 Population

The company defines the population of interest in the CS as LN, which is consistent with the wording of the NICE scope. However, in both the REGNENCY and NOBILITY trials, the eligible population only included adults with class III or IV LN, with or without concurrent class V, and excluded patients with pure class V disease. Clinical advice to the EAG suggested that 15% of people with LN in the UK have pure class V disease. In their response to the PfCs, the company noted that the rationale for excluding pure class V LN from REGENCY and NOBILITY was based on the clinical distinctions of different classes of LN, which are also represented in treatment guidelines from the BSR and KDIGO.[7] The EAG accept that the KDIGO 2024 guidelines separate treatment options for class III and IV LN from pure class V.[20] However, clinical advice to the EAG noted that the presentation and treatment of pure class V is different to class III/IV; this is also reflected in the latest KDIGO 2024 guidelines, which separates recommended treatment and the treatment pathway for each.[20] As such, the EAG has concerns surrounding the clinical comparability of trials that include pure class V disease in their population with REGENCY and NOBILITY, which only include participants with class III/IV LN. See Section 3.4.3 for further details.

Furthermore, the company also excluded the paediatric population from the REGENCY and NOBILITY trials, as the youngest participant in each trial was 18 years old (CS Section 2.3.3.1, Table 7 and Appendix K, Section 12.2, Table 57).[3,21] The NICE scope does not define the population as being focused on the adult population alone. As described in Section 2.2.4, excluding the paediatric population has potential equality issues. The EAG asked the company to comment on the exclusion of the paediatric population within the PfCs. The company noted in their response that “it would be inappropriate for the Company to make a submission including that patient population without supporting data, irrespective of the final NICE scope.” They also noted the ongoing phase 2 POSTERITY trial, which is not part of the submission to NICE but does include the paediatric population.[7]

For these reasons, the EAG believes that the company’s definition of the population is narrower than that of the decision problem. For these reasons, the EAG believes

that the company's definition of the population is narrower than that of the decision problem while accepting that it aligns with the UK marketing authorisation.

2.3.2 Comparators

The NICE scope listed a broad range of comparators for LN. However, the company limited the number of comparators in the economic model to MMF, VOC + MMF and RTX + MMF, all in combination with corticosteroids. In their response to the PfCs, the company described the rationale behind this decision as being based on three key reasons: limited clinical use; limited publicly available data from the UK; and a lack of sufficient comparative data or a connected network for cost-effectiveness analysis against some comparators.[7]

The EAG does not agree with the company that cyclophosphamide and tacrolimus are less relevant to UK clinical practice. In their submission to NICE, the BSR state that, in their updated 2025 guidelines, tacrolimus + MMF is a first line therapy for induction, while Eurolupus or NIH dose cyclophosphamide alone can be considered for first-line induction if other therapies are considered unsuitable.[10] Furthermore, cyclophosphamide was used as the first choice of treatment in class IV LN by 19.6% of 77 respondents in a recent survey of UK practice.[18] However, the EAG accepts the company's argument that they were unable to produce connected networks including tacrolimus and cyclophosphamide in their network meta-analysis (NMA); Figure 9 within the CS demonstrates that it was not possible to create a network that either directly or indirectly connected these treatments with OBI + MMF and other comparators in their NMA (CS Section 2.10.3).[3]

However, BEL + MMF was included in the company's connected NMA network (CS Section 2.10.3, Figure 9).[3] The company suggested in their response to points for clarification that they did not include BEL as a comparator due to its limited use in the UK for treating LN, the lack of a NICE recommendation for its use in LN and the absence of BEL from the decision problem of other relevant appraisals (including TA882).[7,22] While the EAG acknowledges that BEL does not currently have a NICE recommendation specifically for LN, in their submission to NICE the BSR listed BEL + MMF as a first-line treatment option for induction in their updated 2025 guidelines, which can then be continued as a first-line maintenance therapy for three years or

longer.[10] Furthermore, clinical advice to the EAG highlighted that BEL is a relevant comparator in the current clinical context. These factors highlight the relevance of BEL + MMF to current clinical practice. Despite this, the EAG acknowledge that the company provided an updated cost-effectiveness analysis comparing OBI + MMF with BEL + MMF as part of their responses to the PfCs.[7] See Section 4.2.4 for further details and critique on the inclusion of BEL + MMF in the economic model.

2.3.3 Outcomes

In general, the outcomes the company used within the REGENCY trial are aligned with the NICE decision problem. Although the company used a composite surrogate outcome to measure CRR in REGENCY and NOBILITY, as the criteria used to define CRR were stricter than in other studies, the EAG believe this definition may provide a more conservative estimate of effects. This view was supported by clinical advice to the EAG.

However, the EAG believe the inclusion of renal flares as an outcome to predict the risk of progression from CKD stages 1 to 3 to CKD stage 4 within the economic model is a key issue. Firstly, the company noted that their clinical advisors had highlighted a study by Perez-Arias et al (2023) to establish the correlation between renal flares and CKD progression within the PfCs.[1,7] NICE's manual for health technology evaluations (PMG36, Section 4.6.6) states that surrogate outcomes need to be predictive of the final outcome and evidence for this should preferably be derived from a meta-analysis of RCTs using methods outlined in Technical Support Document 20.[2,23] The EAG note that the study by Perez-Arias et al (2023) was a retrospective cohort of LN patients from a single institution in Mexico City.[1] As such, the study by Perez-Arias et al (2023) is not in itself enough evidence to confirm a strong correlation between renal flares and CKD progression, as per NICE's definition.[23]

Further to this, the EAG note that the REGENCY study does not report on number or frequency of renal flares but time to renal flare from week 24 to week 76 (CS Section 2.6.1.3.12).[3] This time to event outcome in REGENCY does not account for how many renal flares participants had prior to week 24 of the trial, nor how many renal flares participants had after the first instance, both of which would impact on a

participant's likelihood to progress to CKD stage 4. Indeed, the study by Perez-Arias et al (2023) highlighted by the company suggests that it is a progressive number of flares and not the time to renal flare that may be associated with poorer kidney prognosis.[1] Clinical advice to the EAG also noted that the relationship between renal flares and CKD is not straightforward, as time spent in renal flare may potentially be as important as the incidence of renal flare. Furthermore, in both REGENCY and NOBILITY, outcomes relating to renal flares are described as "exploratory" only (CS Sections 2.6.1.3.12 and 2.6.2.3).[3,22] These issues mean the measurement of renal flares in both REGENCY and NOBILITY likely does not fully capture the potential true risk of participants progressing to CKD stage 4.

Finally, time to renal flare or frequency of instances of renal flares were not formally considered within the company's NMA (CS Section 2.10). Instead, an ad hoc Bucher analysis was conducted to estimate treatment effects for this outcome (CS Section 3.3.2.3).[3] There are few details reported on how the Bucher analysis was undertaken in CS Section 3.3.2.3 and the EAG have concerns that the Bucher analysis comparing OBI + MMF with VOC + MMF may have been inappropriate due to heterogeneity in the patient population (see Section 4.2.5).[3]

For these reasons, the EAG believes that strength of the predictive nature of renal flares on progression to CKD stage 4 and the methods used to inform this transition have not been fully established by the company. See Section 4.2.5 for further details.

2.3.4 Special considerations including issues related to equity or equality

As mentioned in Section 2.2.4, only potential equality issues relating to ethnicity are discussed within the CS (Section 1.4).[3] The company do not discuss other issues that may potentially impact on health inequalities, such as the exclusion of the paediatric population and those with pure class V LN from the key trials, as well as the lack of treatment options available to pregnant women and women seeking to conceive. See Section 2.2.4 for further critique on these issues.

3 Clinical effectiveness

This section presents a summary and critique of the clinical-effectiveness evidence included in the company's submission.[3] Section 3.1 provides a critique of the company's systematic review of clinical and safety evidence. Sections 3.2 and 3.3 provide a critique of the included studies and clinical-effectiveness analyses. Section 3.4 provides a critique of the indirect treatment comparison and Section 3.6 provides the conclusions of the clinical effectiveness section.

3.1 Critique of the methods of review

The company undertook a systematic literature review (SLR) in May 2024 with an update in February 2025, to identify clinical evidence on the efficacy, safety, HRQoL and tolerability outcomes associated with OBI and comparators in adults (≥ 18 years) with chronic or active proliferative LN, ISN/RPS Class III or IV LN, with or without concurrent class V. The purpose of the SLR was to identify relevant evidence to inform a feasibility study for conduct of an NMA.

The methods for the company's SLR of clinical evidence are detailed in the CS, Appendix B and the Clinical SLR update.[3,5,21] In brief, the company reports following both Cochrane and the Centre for Reviews and Dissemination (CRD) guidance for the planning and conduct of the SLR, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) plus relevant extensions for reporting of the SLR search strategies and associated protocols.[24-28]

The EAG has highlighted several possible reporting issues related to data extraction and quality appraisal. However, after reviewing the clinical data extraction form, the EAG is satisfied that the methods used to conduct the SLR for clinical effectiveness are appropriate. A summary of the EAG's critique is presented in Table 3.1 below.

Table 3.1: Summary of the EAG'S critique of the methods implemented by the company to conduct the systematic literature review

Systematic review stage	Section in the CS where methods are reported	EAG's assessment of the robustness of the methods
Data sources	Appendix B, p.9-13	**Appropriate** An appropriate range of bibliographic databases were used. Additionally, grey literature was searched together with a wide range of conference proceedings and clinical trials registries.
Search strategies	Regency Clinical SLR Update[5] Appendix 2, p.238-249	**Appropriate** Given the very broad nature of the search, the EAG concludes that subject headings and keywords were appropriate and capture all relevant conditions. There are a few inconsistencies with truncation across textwords. The company did not fully report the details of their hand search for conference proceedings. See Section 3.1.1.1 for the full critique.
Search filters	Regency Clinical SLR Update[5] Appendix 2, p.238-249	**Appropriate** There are inconsistencies with the reporting of filters in the clinical and economic SLR, although the company provided information on the origin of the economic filters used in the company response to PfC.[7]
Inclusion criteria	Appendix B, p.6-8	**Appropriate** While the population for the eligibility criteria in the SLR is narrower than the population specified in the NICE decision problem (CS Appendix B, Table 1), the EAG is satisfied the EAG is satisfied that it is in line with the UK marketing authorisation (CS Table 2). Additionally, the SLR eligibility aimed for increased sensitivity by including evidence from adult patients with all types

Systematic review stage	Section in the CS where methods are reported	EAG's assessment of the robustness of the methods
		of active LN with the intention of focusing on evidence from patients with ISN/RPS class III or IV LN. The EAG is satisfied that this and other elements of the eligibility criteria appear reasonable and align with the UK marketing authorisation. Possible equality issues related to the narrow population criteria are discussed in Section 2.3.1
Study selection	Appendix B, p.19-20. p. 24- 28.	**Appropriate** The company carried out a multi-stage study selection process. Following the initial selection, the company conducted a mapping and prioritisation exercise on the included studies specifically for inclusion in the NMA feasibility analysis. The aim was to identify evidence most relevant to the population in the REGENCY study and to the anticipated marketing indication, implementing criteria based on population age, disease classification and treatments (Appendix B).[21] After reviewing the reported methods and PRISMA flow diagram, the EAG is satisfied that the methods used to conduct the initial study selection are appropriate. The methods used to conduct the mapping and record prioritisation stage also appear appropriate.
Data extraction	Appendix B, p. 24.	**Appropriate** The methods used for data extraction are not fully reported in the CS. However, a list of data categories and the corresponding data extraction file was provided.[29] It is recommended that data extraction be performed independently by a minimum of

Systematic review stage	Section in the CS where methods are reported	EAG's assessment of the robustness of the methods
		two reviewers in a piloted standardised extraction template to minimise bias and ensure high levels of accuracy and it is not clear within the CS if this was implemented. Additionally, it is unclear whether the reviewers contacted the study authors to obtain any missing information. That said, after reviewing the comprehensive extraction sheet provided by the company the EAG considers this to be a reporting issue and has no significant concerns.
Quality appraisal	Appendix B, p. 25	**Appropriate** The company carried out a risk of bias and generalisability assessment at the study level for each included RCT using the minimum criteria for parallel-arm RCTs specified in the NICE Process and Methods Guide 24.[30] In general, the EAG considers the tool used to conduct quality assessment reasonable and in line with NICE recommendations. The methods used to conduct the quality assessments are not clearly reported. Assessments undertaken by two reviewers independently are considered the most reliable method to avoid mistakes and the introduction of the reviewers' own biases. However, after reviewing the critical appraisal document provided by the company, the EAG considers this a reporting issue and has no significant concerns with the company's judgments and supporting rationale.[29]
Abbreviations: CS = company submission; EAG = External Assessment Group; ISN/RPS = International Society of Nephrology/ Renal Pathology Society; LN = lupus nephritis; NMA =		

Systematic review stage	Section in the CS where methods are reported	EAG's assessment of the robustness of the methods
network meta-analysis; PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCT = randomised controlled trial; SLR = systematic literature review		

3.1.1 Search methods

Searches were conducted separately for clinical effectiveness, and for economics. An appropriate range of electronic databases were searched, and the company report the use of pre-tested study design filters.[7] Searches were appraised by the EAG using the Peer Review of Electronic Search Strategies (PRESS) checklist.[31] No restrictions were placed on geography, publication date or language, but conference abstracts were limited to the last 3 years (2021-present) to prioritise the most current.[7] A critique of the search strategies for cost effectiveness can be found in Section 4.1.1. Searches were originally conducted in May 2024, and updated in February 2025, so they can be considered up to date.

The company's search strategy was broadly designed to capture randomised controlled trials but notably did not include a separate search for adverse effects, which is recommended in the latest NICE guidance (PMG36).[23] This raises the question of whether additional searching and reporting for safety outcomes should have been undertaken. The EAG thinks the company is justified in their approach and that a broad RCT filter would capture relevant studies regardless of intervention. However, this increases reliance on the condition terms being comprehensive and accurate. Coverage of transplant related terms was inconsistent, with kidney transplant included but not dialysis, and additional transplant synonyms were absent. Inconsistencies were also observed in the use of truncation (e.g. "nephropath$ versus "nephropathy" and "glomerulonephr$" versus "glomerulonephritis").

The use of the DC (date created) and DT (create date) field in the updated Embase and Medline searches, created some minor concerns. It is important to assess whether this field is the most appropriate choice compared to alternatives (e.g., year of publication), as the behaviour of DC or DT is

dependent on current indexing practices. If applied inappropriately, this could lead to either increased noise or the exclusion of relevant records.

Overall, the EAG is satisfied with the quality of the search strategies. Without comprehensive testing, it is difficult to quantify the effects of the issues mentioned on the search results, although the EAG thinks these may be minor.

3.2 Critique of the methods of the trials of the technology of interest

The source of evidence in the CS for the assessment of clinical effectiveness of OBI comes from two multi-centre, randomised, double-blind, placebo-controlled trials: REGENCY and NOBILITY. An overview of the EAG's critique of both trials is presented in Table 3.2.

Table 3.2: Summary of EAG's critique of the REGENCY and NOBILITY trial methods

Trial design or conduct concept	REGENCY		NOBILITY	
	Section in the CS where methods are reported	**EAG's assessment**	**Section in the CS where methods are reported**	**EAG's assessment**
Eligibility criteria	CS Section 2.2, Table 6	**Some concerns** The inclusion criteria for REGENCY were: adults aged 18 to 75 years with active LN class III or IV, with or without concurrent class V disease. The EAG has some concerns that the eligible population of the trial is narrower than the population in the NICE scope. See Section 3.2.1 for further comment.	Appendix K, Section 12.1, Table 56	**Some concerns** The inclusion criteria for NOBILITY were: adults aged 18 to 75 years with active LN class III or IV, with or without concurrent class V disease. The EAG has some concerns that the eligible population of the trial is narrower than the population in the NICE scope. See Section 3.2.1 for further comment.
Subgroups	Appendix J. Section 11.2, Table 55	**Appropriate** The EAG considers that subgroup categories chosen by the company are clinically appropriate, reflecting prognostic factors recognised in LN and support exploration of consistency of treatment effect across relevant groups. Subgroup analyses were also pre-specified in the statistical analysis plan, which	N/A	No subgroups were planned or analysed in the NOBILITY trial.

Trial design or conduct concept	REGENCY		NOBILITY	
	Section in the CS where methods are reported	**EAG's assessment**	**Section in the CS where methods are reported**	**EAG's assessment**
		strengthens their methodological validity.		
Baseline characteristics	CS, Section 2.3.3, Table 7	**Some concerns** The EAG notes that the patient demographics and baseline characteristics of the REGENCY trial population are likely to vary significantly to the UK patient population in LN. See section 3.2.2 for further details.	Appendix K, Section 12.12, Table 57	**Some concerns** The EAG note that the patient demographics and baseline characteristics of the NOBILITY trial population are likely to vary significantly to the UK patient population in LN. See section 3.2.2 for further details.
Intervention	CS Section 2.2, Table 6	**Appropriate** The EAG are satisfied that the intervention given in the trial arms of obinutuzumab + MMF + GCs are consistent with the NICE scope and UK Marketing Authorisation, and were balanced between treatment groups.	Appendix K, Section 12.1, Table 56	**Appropriate** The EAG are satisfied that the intervention given in the trial arms of obinutuzumab + MMF + GCs are consistent with the NICE scope and UK Marketing Authorisation, and were balanced between treatment groups.
Randomisation	CS Section 2.3.1.1.1	**Appropriate** After screening, eligible patients were randomised to receive obinutuzumab or placebo in a 1:1 ratio. Randomisation was performed by stratified block design, stratified	NOBILITY CSR, Section 3.4.2[32]	**Appropriate** After screening, eligible patients were randomised to receive obinutuzumab or placebo in a 1:1 ratio. Randomisation was managed by a central interactive voice/Web

Trial design or conduct concept	REGENCY		NOBILITY	
	Section in the CS where methods are reported	**EAG's assessment**	**Section in the CS where methods are reported**	**EAG's assessment**
		by region (United States and Canada vs. Latin America and the Caribbean vs. Other), and race (Black vs. Other). The EAG are satisfied that the randomisation was performed adequately and in accordance with the study protocol.		response system vendor by use of a block design. The factors for balancing between the treatment groups were Region (Afro Caribbean/African American vs. Others) and United States vs. non-United States sites. The EAG are satisfied that this is an appropriate method of randomisation.
Comparator	CS Section 2.2, Table 6	**Appropriate** The EAG is satisfied that the MMF + GCs comparator used in the REGENCY trial was appropriate.	Appendix K, Section 12.4, Table 60	**Appropriate** The EAG is satisfied that the MMF + GCs comparator used in the NOBILITY study was appropriate.
Outcomes	CS Section 2.2, Table 6	**Some Concerns** The EAG is satisfied that the outcomes reported in the NICE scope have been reported in the REGENCY trial. The company used surrogate markers for ESRD and the EAG has some concerns that time to renal flares measurement may contribute to some uncertainty; this is discussed further in Section 3.2.3.	Appendix K, Section 12.4, Table 60	**Some Concerns** The EAG is satisfied that the outcomes reported in the NICE scope have been reported in the NOBILITY trial. The company used surrogate markers for ESRD and the EAG has some concerns that time to renal flares measurement may contribute to uncertainty; this

Trial design or conduct concept	REGENCY		NOBILITY	
	Section in the CS where methods are reported	**EAG's assessment**	**Section in the CS where methods are reported**	**EAG's assessment**
				is discussed further in Section 3.2.3.
Dropout rate	CS Section 2.6.1.1, Table 12	**Appropriate** The dropout rate amongst all randomised patients at week 76 was relatively low in both the obinutuzumab (9.6%) and placebo (11.8%) arms. The EAG is satisfied that the dropout rate was balanced between treatment arms.	Appendix K, Section 12.4, Table 60	**Some concerns** Although treatment discontinuation was low the EAG has some concerns that study discontinuation was higher in the placebo group. See Section 3.2.4 for further details.

Abbreviations: CS = company submission; EAG = External Assessment Group; ESRD = end stage renal disease; g = gram; GC = glucocorticoid; IV = intravenous; LN = lupus nephritis; mg = milligram; MMF = mycophenolate mofetil; NICE = National Institute for Health and Care Excellence

3.2.1 Eligibility criteria

The same eligibility criteria were used for both the REGENCY and NOBILITY trials. However, there were some differences between trial populations and the LN population described in the NICE scope (see Section 2.3.1 for further critique on this point). In both REGENCY and NOBILITY patients with class V LN were excluded from the trials (CS Appendix J, Section 11.2, Table 55; Appendix K, Section 12.1, Table 56). The population in the NICE scope does not exclude based on class of LN.

Furthermore, the EAG also notes that whilst the exclusion of paediatric patients from the REGENCY trial is in line with the UK Marketing Authorisation, the NICE scope included all patients with LN and did not limit to adult patients (see Section 2.3.1 for further critique on this issue).

3.2.2 Baseline characteristics

CS Table 7 (Section 2.3.3.1) presents patient demographic and baseline characteristics for REGENCY.[3] The EAG agrees with the company's assessment that baseline characteristics including age, sex, ethnicity, race, region, eGFR, serum creatinine, UPCR, C3 complement, duration of LN, baseline LN class, and concomitant class V LN were well balanced between the intervention group and the placebo group. Most participants were female (84.4% in OBI vs 84.6% in placebo), which is comparable to sex demographics within the UK LN patient population.[14]

However, the EAG is concerned that characteristics relating to ethnicity in the REGENCY and NOBILITY trials may not be comparable to the LN patient population within the UK.[14] In REGENCY representation of Asian patients was relatively low and limited data were available for this group. Only 16 (5.9%) participants were Asian, whereas in the UK LN patient population, 9.2% of patients are of Indo-Asian ethnicity. Patients of Black or African American ethnicity and American Indian or Alaska Native ethnicity accounted for 40 (14.8%) and 51 (18.8%) respectively of patients in the REGENCY trial. This represented a higher proportion in both groups than the UK LN patient population with 5.3% of patients of Black ethnicity and no data available for

American Indian or Alaska Native.[14] The EAG therefore considers the differences between the trial population and the UK LN population to be of concern, given that race and ethnicity may be an effect modifier in treatment response in LN. Results from several studies conducted in the US and Europe have reported that LN outcomes are worse amongst non-white populations.[33,34] In the response to PfCs, the company provided baseline characteristics and demographic data for the [redacted] UK/EU participants out of the total 271 randomised.[7] In these data, there were [redacted] patients from the EU, and ethnicity data from the EU patients was similar to that reported in UK patients. However, data was only available for [redacted] UK patients which was too low for the EAG to assess similarity to the UK LN patient population.

In NOBILITY, only 5 (4.0%) participants were Asian, whereas in the UK LN patient population, 9.2% of patients are of Indo-Asian ethnicity.[14] Further, in NOBILITY, 11 (17.5%) patients were of American Indian or Alaska Native ethnicity (Appendix K, Section 12.1, Table 56).[21] No patients with this ethnicity were included in the 2001 analysis of UK LN patients, meaning that the proportion of patients in NOBILITY of American Indian or Alaska Native ethnicity is likely to be greater than the UK LN patient population.[14] No UK or EU specific baseline characteristics were available for the NOBILITY trial.

3.2.3 Outcomes

The EAG is satisfied that all outcomes specified in the NICE scope are reported in the CS for REGENCY (Section 2.2, Table 6): CRR, CRR with steroid taper, time to death or renal related event, safety and adverse events, and HRQoL outcomes.[3] Whilst surrogate outcomes used in clinical trials may not always be predictive of long-term clinical outcomes that are preferred by NICE, clinical advice to the EAG suggests that eGFR is considered a clinically meaningful parameter in assessing the progression toward ESRD, although the EAG has not identified that it is validated as such. In addition, previous observational studies have shown a relationship between change in eGFR and risk of kidney failure and mortality. This level two observational evidence indicates a possible link between change in eGFR and CKD progression in a non-LN population. Therefore, the EAG does not consider the omission of

ESRD incidence from the outcomes assessed in REGENCY as a cause for significant concern.[35,36]

However, the EAG have concerns that the measurement of time to renal flare within both the REGENCY and NOBILITY trials contributes to uncertainty surrounding the transition to CKD stage 4 within the economic model. See Section 2.3.3 and Section 4.2.5 for further critique on this issue.

3.2.4 Dropout rate

Although treatment discontinuation in NOBILITY was overall low and balanced between OBI (7.8%) and placebo (6.5%), the overall study discontinuation was much higher in the placebo group (29.0%) versus the OBI group (14.1%). A higher dropout rate in one group compared to another can result in attrition bias and increase the risk of confounding, as the characteristics between the two groups are not as balanced as they were at randomisation.[37] Patient characteristics for the placebo and OBI group were not reported for the safety-evaluable population or the efficacy evaluable population. As such, the EAG is unable to comment on whether the differential drop-out rate between the two groups may have resulted in bias.

3.3 Critique of the results of the trials of the technology of interest

In CS Section 3.1.1, the company outlines the primary and secondary outcomes for REGENCY.[3] Efficacy endpoints for NOBILITY are reported in Appendix K, Section 12.3.2 and safety reporting and analysis are reported in Appendix K, Section 12.3.3.[21] The primary efficacy endpoint for REGENCY was CRR, which was defined as a patient achieving all of the following criteria: UPCR < 0.5 g/g; eGFR ≥ 85% of baseline at week 76, as calculated using the CKD-EPI equation; serum creatinine ≤ ULN at week 76; and no occurrence of the following intercurrent events: rescue therapy, treatment failure, death, or early study withdrawal. The key secondary outcomes in REGENCY were: CRR and prednisone taper, proteinuric response, mean change in eGFR at week 76, ORR at week 50, serology (anti-dsDNA, C3, C4) and HRQoL outcomes. The company used a hierarchical approach to testing.

Table 3.3: Summary of company interpretation of trial results

Trial design or conduct concept	Section in the CS where methods are reported	EAG's assessment
Primary efficacy outcome: CRR	CS Section 2.6.1.2, Table 15 CS Section 2.6.2.1, Table 29	**Some concerns** REGENCY met its primary endpoint, achieving statistically significant difference between proportion of patients achieving CRR at Week 76 in the obinutuzumab group (46.4%) and the placebo group (33.1%). The same primary efficacy endpoint was also met in NOBILITY with a statistically significant difference reported between proportion of patients who achieved CRR at week 52 between the obinutuzumab group (34.9%) versus the placebo group (22.6%). The EAG has some concerns that the duration of the two trials – 76 and 52 weeks respectively – is not sufficient. See section 3.3.1 for further details.
Key secondary efficacy outcome: CRR with prednisone taper	CS, Section 2.6.1.3.1, Table 16	**Appropriate** The first key secondary endpoint in REGENCY, CRR with successful prednisone taper at week 76, was achieved by 42.7% of patients in the obinutuzumab arm compared with 30.9% in the placebo arm (adjusted difference 11.88%, 95% CI: 0.57 - 23.18; p=0.042). Although the confidence interval was wide, the EAG considers the analysis appropriate and is satisfied that this supports a small steroid-sparing benefit with obinutuzumab.
Key secondary efficacy outcome: Proteinuric response	CS, Section 2.6.1.3.2, Table 17	**Appropriate** At week 76, 55.5% of patients in the obinutuzumab arm and 41.9% in the placebo arm achieved a proteinuric response (adjusted difference 13.68%, 95% CI: 2.01 - 25.36; p=0.023). The EAG is satisfied that the analysis was appropriate and provides supportive evidence of positive obinutuzumab effect on reducing proteinuria. The EAG clinical expert is satisfied that proteinuria is clinically relevant. However, the EAG

Trial design or conduct concept	Section in the CS where methods are reported	EAG's assessment
		were unable to identify published evidence to determine whether it is a validated surrogate outcome measure.
Key secondary outcome: Change in eGFR	CS, Section 2.6.1.3.3, Table 18	**Appropriate** The mean change in eGFR from baseline to week 76 increased by +2.31 mL/min/1.73 m² in the obinutuzumab arm and decreased by -1.54 mL/min/1.73 m² in the placebo arm, an adjusted mean difference of +3.84 (95% CI: -1.83 to 9.51; p=0.184). The EAG considers the analysis appropriate and notes that no statistically significant effect was observed.
Key secondary outcome: Renal-related event or death	CS, Section 2.6.1.3.4, Table 19	**Appropriate** The proportion of patients experiencing a renal-related event or death by week 76 in REGENCY was 18.9% in the obinutuzumab arm and 35.6% in the placebo arm (adjusted mean difference 16.8%, 95% CI: -27.42 to -6.23; nominal p=0.0026). The EAG considers the analysis appropriate but notes that, due to failure of the preceding eGFR endpoint, this analysis is exploratory and cannot be considered confirmatory evidence of renal protection.
Key secondary outcome: ORR at week 50	CS, Section 2.6.1.3.5, Table 20	**Appropriate** The proportion of patients achieving ORR at week 50 in REGENCY was 59.1% in the obinutuzumab arm and 50.7% in the placebo arm, an adjusted mean difference of 8.36% (95% CI: - 3.41 to 20.12; nominal p=0.1670). The EAG considers the analysis appropriate.
Results – Subgroup analysis	CS, Section 2.8, Figure 7	**Some concerns** There are potential issues relating to the generalisability of subgroup results reported in REGENCY to the NHS population. No subgroup analysis was undertaken in NOBILITY. See Section 3.3.4 for further details.
HRQoL	CS, Section 2.6.1	**Appropriate** No HRQoL outcomes were assessed in NOBILITY. The company assessed

Trial design or conduct concept	Section in the CS where methods are reported	EAG's assessment
		HRQoL in REGENCY using FACIT-F, EQ-5D-5L, EQ-5D VAS, and patient global assessment at week 76. HRQoL outcomes were only exploratory due to the hierarchical testing of secondary endpoints. See Section 3.3.2 for further details.
Adverse events	CS, Section 2.11.2, Table 34	**Some concerns** In their analysis of REGENCY and NOBILITY results the company report that AEs were similar between the obinutuzumab and the placebo group. The EAG agrees that in NOBILITY AE were similar between groups but have some concerns that there may be differences between groups in REGENCY. See Section 3.3.3 for further details.
Abbreviations: AE = adverse event; CI = confidence interval; CRR = complete renal response; CS = company submission; EAG = External Assessment Group; eGFR = estimated glomerular filtration rate; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HRQoL = health-related quality of life; NHS = National Health Service; ORR = overall response rate; VAS = visual analogue scale		

3.3.1 Primary efficacy outcome

As reported in the main CS (Section 2.6.1.2), REGENCY met the primary efficacy endpoint of demonstrating a clinically meaningful and statistically significant improvement in CRR at week 76 in the OBI arm compared with the placebo arm.[3] NOBILITY also met the primary efficacy endpoint with a statistically significant difference in the proportion of patients achieving CRR at week 52 in the OBI group compared to the placebo group. However, the EAG has some concerns that the duration of the REGENCY and NOBILITY trials is not sufficient given the chronic nature of LN. The EAG clinical expert advised that some LN patients may be on treatment for more than 10 years, and as such a 12- or 18-month follow-up period may not be sufficient to estimate relapse on OBI.

Additionally, in REGENCY, the company's main analysis of the primary endpoint was based on multiple imputation. Whilst this is a recognised approach to handling missing data, it assumes that data are missing at random and does not account for the fact that bias may be introduced by missing data due to adverse events or treatment response. This introduces uncertainty around the robustness of the reported treatment differences. Although the EAG does not consider this a key issue due to the level of missing data, the resulting uncertainty is noted.

Furthermore, the criteria used for CRR in REGENCY were very stringent, requiring multiple simultaneous criteria to be met. As a result, the clinically meaningful benefit in REGENCY was uncertain.

3.3.2 HRQoL outcomes

The company assessed HRQoL in REGENCY using FACIT-F, EQ-5D-5L, EQ-5D VAS, and patient global assessment at week 76. There were no statistically significant between-group differences in FACIT-F, EQ-5D-5L, EQ-5D-5L and EQ-5D VAS outcomes. Patient global assessment decreased by -18.3 versus -13.5, but these between-group differences were not statistically tested and are of uncertain clinical relevance.

The EAG notes that, because the trial did not meet statistical significance for eGFR earlier in the pre-specified testing hierarchy, all HRQoL endpoints are exploratory only and cannot be interpreted as confirmatory evidence to support benefit of OBI for HRQoL outcomes.

3.3.3 Adverse events

The company reported that the overall adverse event (AE) incidence in REGENCY was similar between the OBI and placebo arms (92.6% vs 88.6%), with most events being mild to moderate and no withdrawals from the study due to AEs. However, the EAG notes that the incidence of serious and severe toxicity was higher with OBI, with serious adverse events (SAEs) in 32.4% of patients compared with 18.2% on placebo, and Grade 3 to 5 AEs in 32.4% versus 16.7%. Serious infections were more common with OBI (16.9% vs 7.6%), including COVID-19 pneumonia (5.1% vs 0%) and neutropenia (12.5%

vs 3.8%), which is an expected risk with B-cell depletion.[38] Infusion-related reactions were also slightly more frequent with OBI (15.4% vs 11.4%), while more than half of patients in this arm experienced an AE leading to treatment interruption or modification, mainly attributed to concomitant MMF.

The company concluded that OBI was well tolerated with a manageable safety profile and highlighted that excess SAEs were largely explained by the COVID-19 pandemic. However, the EAG notes that differences in SAEs and Grade 3 to 5 AEs remained even when COVID-19 events were excluded (27.2% vs 18.2%), suggesting a residual imbalance. Overall, the safety evidence indicates a higher toxicity burden with OBI and, while no new safety signals were identified, the EAG considers the company's interpretation to potentially understate the differences observed between treatment arms, although this is not unexpected given the placebo control.

3.3.4 Subgroups

The company reported subgroup analyses of the primary endpoint (CRR at week 76) across a range of baseline characteristics. These included demographics (sex, race, region), renal function and disease severity (baseline LN class, presence of concomitant class V disease, prior history of LN, baseline eGFR, and baseline UPCR), and serological markers (anti-dsDNA, C3 complement, and C4 complement). However, several limitations reduce the reliability of these findings. Many subgroups contained small numbers of patients, and while these (for example, males and those with low baseline eGFR) reflect the population seen in UK clinical practice, the result is wide confidence intervals and reduced statistical power. In addition, no adjustment for multiple testing was undertaken, meaning results are at risk of chance findings. The EAG therefore notes that there is considerable uncertainty in the subgroup analyses.

3.4 Critique of studies identified and included in the indirect treatment comparison or multiple treatment comparison

Due to the lack of head-to-head evidence for several commonly used comparators, the company undertook an NMA to compare the efficacy and safety of OBI + MMF against other relevant treatments for adult patients aged 18 years or over with ISN/RPS class II/IV (with or without concurrent class V) LN. The outcomes evaluated in the NMA were CRR, PRR, eGFR (mean change from baseline), ORR (either CRR or PRR) and AEs. A summary of the EAG's critique of the NMA can be found in Table 3.4.

Table 3.4: Summary of the EAG's critique of the company's NMA

Aspect of NMA design or conduct	Section in the CS where methods are reported	EAG's assessment
Statistical methods	CS, Section 2.10.1 NMA Report[6]	**Appropriate** Overall, the EAG is satisfied with the statistical approach taken within the NMA. The statistical approach is summarised in Section 31, along with some points for consideration regarding the comparators used in the NMA.
Included and excluded studies	CS, Section 2.10.2 NMA Report[6]	**Appropriate** The EAG has no concerns with the company's approach and rationale to including and excluding studies for the NMA.
Transitivity (study characteristics)	CS, Section 2.10.1 NMA Report[6]	**Some concerns** The EAG has noted some concerns about the assumption of transitivity in relation to variation in how outcome measures are defined across the studies included in the NMA, specifically in relation to the primary outcome, CRR. In addition, the EAG notes some concerns about the comparability of trials which enrol a substantial proportion

Aspect of NMA design or conduct	Section in the CS where methods are reported	EAG's assessment
		of class V LN patients, specifically in relation to voclosporin. See Section 3.4.3 for further critique.
Results	CS, Section 2.10.4 NMA Report[6]	**Some concerns** The EAG has no concerns regarding the results of the NMA, other than that most results from the base-case analysis were not statistically significant and are associated with substantial uncertainty. There appear to be discrepancies between the reporting of results within the NMA and the data used within the company's economic analyses (see Section 4.2.5).
Sensitivity analyses	CS, Section 2.10.4[6] Network meta-analysis report, Section 3.9[6]	**Appropriate** Sensitivity analyses using Bayesian fixed-effects model and random effects model with alternative priors for tau was carried out. The EAG are satisfied with the company's approach
Abbreviations: CRR = complete renal response; CS = company submission; EAG = External Assessment Group; LN = lupus nephritis; NMA = network meta-analysis		

3.4.1 Statistical analysis

The company undertook a review of possible indirect treatment comparison (ITC) methodologies, including a multi-level network meta regression (ML-NMR) to account for variability in treatment effects across the diverse studies, which may have provided more robust and accurate effect estimates. The EAG notes that the recommendation for analysis and the NICE methodological guidance is to perform a standard ML-NMR alongside NMA when individual patient data (IPD) is available to ensure consistency of findings.[5,39] Additionally, ML-NMR could have examined the impact of

variability in participant characteristics, discussed in Section 3.6.4, as effect modifiers. However, the EAG acknowledges this may be difficult due to the small number of studies. As such, the EAG agrees with the company's decision and rationale to proceed with an NMA, given the lack of RCTs comparing the effectiveness of OBI + MMF versus other relevant comparators. A summary of the methods used, with the EAG critique, is provided below.

The base-case analysis used a Bayesian NMA, two step, with a random-effects model. Inconsistency was assessed using the node splitting method, which is in line with NICE DSU TSD 4.[40] It was initially performed for the outcomes CRR and PRR independent of CRR and, because there was no evidence of inconsistency, no further assessments were performed for ORR or eGFR. The deviance information criteria (DIC) compares the relative fit of competing models with a preference for models with a lower DIC. Differences of less than 5 points were not considered meaningful, and the base-case random-effects model was preferred to incorporate between-study variability. The EAG has no concerns with the company's methodological approach.

Please note that in the NMA section of the CS and accompanying reports, voclosporin is abbreviated to VCS rather than VOC; similarly, obinutuzumab is abbreviated to OBZ rather than OBI. Throughout the remainder of the EAG report, we will use VOC and OBI for consistency. Furthermore, the company split the assessment of VOC into low-dose (VOC_LD) and high-dose (VOC_HD).

The comparators included in the NMA (MMF, BEL + MMF, RTX + MMF, VOC_LD + MMF, VOC_HD + MMF, OBI + MMF) align with the treatments and comparators listed in the NICE decision problem. However, clinical advice to the EAG suggested that VOC_HD + MMF is no longer used in UK clinical practice and may not be considered a relevant comparator. In addition, clinical experts highlighted to the EAG that while RTX is used off-label in UK clinical practice, it is not approved and failed to meet its primary endpoint in the phase III clinical trial (LUNAR).[41] Clinical advice to the EAG suggested that

the most relevant comparators captured within the NMA are MMF, low-dose VOC + MMF and BEL + MMF.

As noted previously in Section 2.3.2, clinical advice to the EAG also noted that cyclophosphamide was a relevant comparator. However, cyclophosphamide was not included in the best-case scenario NMA because it was not possible to include it in a connected network. Whilst this limits the number of relevant comparators from the NICE decision problem within the best-case NMA, the EAG agrees this was a reasonable exclusion.

The EAG acknowledge that the NMA did not exclude based on outcome and that outcomes included in the NMA were primarily determined by the eligibility criteria and time cut-off, which ensured that studies were sufficiently homogeneous to allow for comparability.

3.4.2 Included and excluded studies

One hundred and eleven records were excluded from the NMA feasibility analysis at the record prioritisation phase, based on the criteria reported below.

- Studies which reported results of adult subgroups separately, or ≥ 90% of included patients are 18+, with the study only including patients 16+ years of age.
- Studies reporting results for ISN/RPS class III/IV with or without class V separately, or if ≥ 80% of patients had ISN/RPS Class III/IV with or without Class V.
- Treatments included one of the key treatments as guided by KDIGO 2024 and EULAR 2023 recommendations.

The records and reasons for exclusions appear fully reported in Appendix 6 of the updated Clinical SLR.[5] Twenty-eight RCTs (across 91 publications) were considered for the NMA feasibility analysis and underwent data extraction. A further eight studies were reportedly excluded during exploration of the best-case network due to a lack of a clearly defined primary endpoint,

inappropriate comparator arms, and continuation designs (responder analysis).[6] The PRISMA flow diagram in Figure 3 of the Updated Clinical SLR documents nine excluded records, which includes the Aspreva Lupus Management Study (ALMS). The EAG have been able to identify reasons to exclude for AURORA-2, CALIBRATE, Contreras, Mitwali, NCT01056237, NCT04146220, MyLupus and WinLupus in Table 18 of the Clinical SLR update.[5]

The connectivity of the 20 eligible RCTs was explored at the ≤ 48 week and ≥ 48-week timepoints and a best-case scenario evidence network was determined. Inclusion of studies with a primary endpoint at ≥ 48 weeks was selected to increase comparability and to focus on longer-term outcomes. In addition, the ≥ 48-week best case scenario network was selected because it had a larger sample size and allowed comparisons with more recent treatments, specifically BEL.

The best-case scenario network is a star-shaped structure with a single closed loop, based on six RCTs with a sample size of 1608 patients, ranging from 125 to 446 for CRR.[41-46] Other outcomes evaluated in the best case network are: PRR independent of CRR; overall response rate (ORR); and SAEs. The NMA facilitated comparisons between OBI + MMF with BEL + MMF, VOC_LD + MMF, VOC_HD + MMF, and RTX + MMF, anchored by MMF.

3.4.3 Study characteristics and transitivity

The company acknowledged variation in population characteristics including age, sex and ethnicity. These appear to be unadjusted and have the potential to be effect modifiers; therefore, any results should be interpreted with caution.[5] The company also reported variation in factors related to study design, country and the number of patients recruited across the included studies.

Of concern to the EAG is the variation in how outcomes of interest were defined across the included studies, as this potentially limits their comparability, as seen in the Clinical SLR Update (Table 20).[5] For example,

the composite CRR outcome was fairly consistently defined in terms of urine protein to creatinine ratio (UPCR) (≤ 0.5 mg/mg threshold) across the six studies, but there are variations in the other elements which comprise the CRR outcome, notably in eGFR thresholds (no worsening of baseline serum creatinine by more than 10 to 20%, or eGFR change from baseline (> 60 to > 90 mL/min/1.73 m^2)). There was also variation in the measurement of serum creatine stability, exclusion of rescue therapy and steroid tapering. These differences are unadjusted for in the analyses, which could undermine the assumption of transitivity, meaning the observed effects may not be comparable. This introduces uncertainty into the strength and direction of effect for CRR. Whilst it is not possible to determine the exact impact of these differences, the EAG believes it may potentially be conservative, given the strict criteria used in REGENCY.

Furthermore, clinical advice to the EAG suggested that the use of corticosteroids within trials is a potential effect modifier. Protocol-mandated or investigator-discretion tapering regimens for corticosteroids, including IV methylprednisolone or oral prednisone, are reported in all six trials included in the NMA. However, there appeared to be variation in the exact tapering regimens and steroid usage implemented across the trials. Where possible to determine, it appeared that steroid use was balanced between treatment arms during LUNAR trial,[41] but this is currently an underexplored area within the NMA and has the potential to undermine the transitivity assumption, bringing a degree of uncertainty into the results.

As noted in Section 2.3.1, clinical advice to the EAG noted that the KDIGO clinical practice guidelines suggest that the treatment for pure class V patients differs from that of patients with class III and IV LN.[20] This is noteworthy because, of the patients enrolled in the AURA-LV study, 39 of 265 (14.7%) participants were classed as pure class V.[46] Similarly, of the patients enrolled in AURORA-1, 50 of 357 (14.0%) were also considered to be pure class V.[45] In contrast, the REGENCY and NOBILITY trials excluded patients with pure class V LN. These differences in patient composition, and specifically in the

differences in treatments received across the trials, have the potential to undermine the assumption of transitivity within the NMA.

All studies except REGENCY were assessed to be at high risk of bias and none were excluded from analyses; given the limited number of included studies, the EAG agrees with this approach. However, considering this within-study bias, when applying the Confidence in Network Meta-Analysis (CINeMA) framework the certainty in the evidence would be decreased, and this should be considered when interpreting the results.[47]

3.4.4 Results

A best-case network was constructed using six RCTs (REGENCY, NOBILITY, BLISS-LN, LUNAR, AURA-LV and AURORA-1) for CRR, PRR independent of CRR, ORR and SAEs. All used a primary efficacy analysis time point of 48 weeks or longer. A best-case network using five RCTs was reported for eGFR.

Complete renal response (CRR)

Odds ratios (ORs) for the best-case random effects model are reproduced from the CS (Section 2.10.4.1, Table 31) below for CRR alongside sensitivity analyses.[3] One sensitivity analysis used a fixed effect model and the other used a random effects model with alternative priors (see Table 3.5).

Table 3.5: OR and 95% CrI of OBI + MMF versus comparators for CRR in the best-case network, presented alongside sensitivity analysis

OBI + MMF_48w+ versus	Base case, RE model, OR (95% CrI)	Sensitivity 1, FE model, OR (95% CrI)	Sensitivity 2, RE model, alternative prior for tau, OR (95% CrI)
BEL + MMF 48w+	[redacted]	[redacted]	[redacted]
RTX + MMF 48w+	[redacted]	[redacted]	[redacted]
Low-dose VOC + MMF 48w+	[redacted]	[redacted]	[redacted]
High-dose VOC + MMF 48w+	[redacted]	[redacted]	[redacted]
MMF_48w+	[redacted]	[redacted]	[redacted]

Source: CS Table 31[3]
Abbreviations: BEL = belimumab; CrI = credible interval; CRR = complete renal response; FE= fixed-effects; HD = high dose; LD = low dose; MMF = mycophenolate mofetil; OBI =

OBI + MMF_48w+ versus	Base case, RE model, OR (95% CrI)	Sensitivity 1, FE model, OR (95% CrI)	Sensitivity 2, RE model, alternative prior for tau, OR (95% CrI)
obinutuzumab; OR = odds ratio; RE = random-effects; RTX = rituximab; VOC = voclosporin; 48w+, 48 weeks or more.			

Due to the width of the 95% credible intervals (CrIs), there was no evidence of a difference in CRR between OBI + MMF, indirectly compared with RTX + MMF and MMF, BEL + MMF, and both high-dose and low-dose VOC + MMF. The wide CrIs, as acknowledged by the company, indicate substantial uncertainty and warrant cautious interpretation of the results.

Sensitivity analyses were generally consistent with the base case analyses, except for sensitivity analysis 1, which employed a fixed effect model and reported a statistically significant improvement in achieving CRR for OBI + MMF compared to MMF alone [redacted]. It is possible that the statistically significant result in the fixed effect sensitivity analysis has been influenced by the issues around transitivity, as described in Section 3.4.3.

PRR independent of CRR

PRR results from the base-case network and sensitivity analyses for OBI + MMF compared to other treatments are presented in Table 3.6 (reproduced from CS Section 2.10.4.2, Table 32).[3] None of the treatment comparisons were statistically significant and all were subject to uncertainty due to the wide CrIs that cross the line of no effect. As such, there was no evidence of a difference between OBI + MMF compared with RTX + MMF, high-dose VOC + MMF, low-dose VOC + MMF, BEL + MMF and MMF alone in terms of PRR independent of CRR. Sensitivity analyses for OBI + MMF versus BEL + MMF were not reported in the CS, so the EAG is unable to comment further on this comparison.

Table 3.6: OR and 95% CrI of OBI + MMF versus other comparators for PRR independent of CRR in the best-case network presented alongside sensitivity analysis where available

OBI + MMF_48w+ versus	Base case, RE model, OR (95% CrI)	Sensitivity 1, FE model, OR (95% CrI)	Sensitivity 2, RE model, alternative prior for tau, OR (95% CrI)
(RTX + MMF)_48w+	[redacted]	[redacted]	[redacted]
(high-dose VOC + MMF)_48w+	[redacted]	[redacted]	[redacted]
(low-dose VOC + MMF)_48w+	[redacted]	[redacted]	[redacted]
MMF_48w+	[redacted]	[redacted]	[redacted]
BEL + MMF 48W+†	[redacted]	[redacted]	[redacted]

Source: adapted from CS Table 32, p. 66[3]
† Data for BEL+MMF at 48w+ has been copied from Figure 13, page 67 of the CS and added to this table.
Abbreviations: BEL = belimumab; CrI = credible interval; FE = fixed-effects; HD = high dose; LD = low dose; MMF= mycophenolate mofetil; NR= not reported; OBI= obinutuzumab; OR= odds ratio; PRR= partial renal response; RE= random-effects; RTX= rituximab; VOC= voclosporin; 48w+= 48 weeks or more.

Overall response rate (ORR)

ORs for the best-case random effects model and sensitivity analysis for the overall response rate are reproduced from the NMA report below (Table 3.7).[6] All comparisons in the base-case random-effects model were not statistically significant, with the exception of OBI + MMF versus MMF alone, where OBI + MMF may increase the odds of a better ORR. However, the 95% CrI is still substantially wide. These results did not change in sensitivity analysis 1 (fixed effect model), though there was no longer any evidence of a difference between OBI + MMF and MMF alone in sensitivity analysis 2, which became non-statistically significant. This suggests the result may be sensitive to choice of priors for tau. Overall, the width of the 95% CrIs mean the results should be interpreted with caution.

Table 3.7: OR and 95% CrI of OBI + MMF versus other comparators for overall response rate (ORR) in the best-case network

OBI + MMF_48w+ versus	Base case, RE model, OR (95% CrI)	Sensitivity 1, FE model, OR (95% CrI)	Sensitivity 2, RE model, alternative prior for tau, OR (95% CrI)
BEL + MMF 48w+	[redacted]	[redacted]	[redacted]
RTX + MMF 48w+	[redacted]	[redacted]	[redacted]
High-dose VOC + MMF 48w+	[redacted]	[redacted]	[redacted]
Low-dose VOC + MMF 48w+	[redacted]	[redacted]	[redacted]
MMF_48w+	[redacted]	[redacted]	[redacted]

Source: reproduced from Table 19, page 47 of the Network Meta Analysis report.[6]
Abbreviations: BEL= belimumab; CrI= credible interval; CRR= complete renal response; FE= fixed-effects; HD= high dose; LD= low dose; MMF= mycophenolate mofetil; OBI= obinutuzumab; OR= odds ratio; RE= random-effects; RTX= rituximab; VOC= voclosporin; 48w+= 48 weeks or more.

Estimated glomerular filtration rate (eGFR)

The best-case network for mean change from baseline of eGFR comprised five RCTs (1464 enrolling patients) with comparisons against BEL + MMF, VOC_LD + MMF, and VOC_HD + MMF anchored by MMF. The mean difference (MD) and 95% CrI for mean change from baseline for OBI + MMF compared to relevant comparators are presented below (see Table 3.8). Results in the base-case analysis suggested OBI + MMF may lead to high eGFR than VOC_HD + MMF and VOC_LD + MMF but the results are open to uncertainty due to substantially wide 95% CrIs. Results comparing OBI + MMF with BEL + MMF and MMF alone were not statistically significant.

Table 3.8: Mean difference and 95% CrI of OBI + MMF versus other comparators for mean CFB in eGFR in the best-case network

OBI + MMF_48w+ versus	Base case, RE model, MD (95% CrI)	Sensitivity 1, FE model, MD (95% CrI)	Sensitivity 2, RE model, alternative prior for tau, MD (95% CrI)
BEL + MMF 48w+	[redacted]	[redacted]	[redacted]
High-dose VOC + MMF 48w+	[redacted]	[redacted]	[redacted]

OBI + MMF_48w+ versus	Base case, RE model, MD (95% CrI)	Sensitivity 1, FE model, MD (95% CrI)	Sensitivity 2, RE model, alternative prior for tau, MD (95% CrI)
Low-dose VOC + MMF 48w+	[redacted]	[redacted]	[redacted]
MMF_48w+	[redacted]	[redacted]	[redacted]

Source: reproduced from Table 24, page 57 of the Network Meta Analysis report.[6]
Abbreviations: BEL= belimumab; CrI= credible interval; CRR= complete renal response; FE= fixed-effects; HD= high dose; LD= low dose; MD= mean difference; MMF= mycophenolate mofetil; OBI= obinutuzumab; RE= random-effects; VOC= voclosporin; 48w+= 48 weeks or more.

Results comparing OBI + MMF with VOC_HD + MMF and VOC_LD + MMF were robust in sensitivity analysis 1, using a fixed-effect model; OBI + MMF also potentially led to higher levels of eGFR versus MMF alone in this sensitivity analysis, although all results had wide 95% CrIs. The statistically significant result for VOC_HD + MMF was not robust within sensitivity analysis 2 using an alternative prior, indicating the result may be sensitive to prior specification, as noted by the company.

Adverse effects

Table 3.9 presents the NMA results from the base-case random-effects model for Grade 3+ AEs and SAEs. Only three RCTs (enrolling 537 patients) contributed to the Grade 3+ AE analyses comparing OBI + MMF with RTX + MMF, anchored via MMF.[41-43] The company's rationale for including only three of the six studies in the network is unclear, but there is an indication in the updated clinical SLR update that some studies did not specify the grades of AEs. The EAG can verify that adverse events in the studies reported by Furie et al (2020), Rovin et al (2021) and Rovin et al (2019) were not categorised into grades.[44,46] Six RCTs enrolling 1606 patients contributed to the best-case network for SAEs. Results of the analyses for Grade 3+ AEs and SAEs are reproduced from the company's NMA report in Table 3.9.[6]

Table 3.9: Summary of NMA results for OBI + MMF compared to other treatments from the best-case network, random-effects model

OBI + MMF_48w+ versus	Grade 3+ AE, base-case, random-effects model, OR (95% CrI)	SAEs, base-case, random-effects model, OR (95% CrI)
MMF	[redacted]	[redacted]
BEL + MMF	-	[redacted]
RTX + MMF	[redacted]	[redacted]
VOC_HD + MMF	-	[redacted]
VOC_LD + MMF	[redacted]	[redacted]

Source: reproduced and adapted from Table 28, page 65 and Table 32, page 71 of the Network Meta Analysis report.[6]
Key:
- indicates that NMA was not feasible for the comparison
Abbreviations: BEL= belimumab; Grade 3+ AEs = grade 3+ adverse events; HD= high dose; LD= low dose; MMF= mycophenolate mofetil; NMA= network meta-analysis; OBI= obinutuzumab; OR= odds ratio; RE= random-effects; RTX= rituximab; SAEs= serious adverse events; VOC= voclosporin

From the base-case random-effects model, there may be no evidence of a difference between OBI + MMF compared with MMF alone and RTX + MMF in terms of the odds of Grade 3+ AEs. In the base-case random effects model for SAEs, there were no statistically significant results, suggesting no evidence of a difference between OBI + MMF and all other comparators. The 95% CrIs are all substantially wide across results for both Grade 3+ AEs and SAEs, meaning there is uncertainty within the results.

3.5 Additional work on clinical effectiveness done by the EAG

No additional work surrounding clinical effectiveness was undertaken by the EAG.

3.6 Conclusions of the clinical-effectiveness section

3.6.1 Conclusions on the REGENCY and NOBILITY trials

Two key trials were included in the CS, REGENCY and NOBILITY; the EAG's critique of the methods and results of these are summarised in Sections 3.2 and 3.3. Both trials are international, randomised, double-blind trials, with REGENCY being the main phase III trial and the phase II NOBILITY trial

providing supportive data. The EAG is satisfied that the two trials were well designed with appropriate intervention and comparators used, as well as efficacy, safety and HRQoL outcomes assessed that aligned with the NICE scope.

The EAG has some concerns relating to the population of REGENCY and NOBILITY trials being narrower than the population defined in the NICE scope because the eligibility criteria for both trials excluded paediatric patients under 18 years and excluded patients with pure class V LN alone (see Section 2.3.1). Whilst the EAG is satisfied that the baseline characteristics were balanced between the OBI and placebo groups at baseline, there are some concerns that the baseline characteristics of participants in both the REGENCY and NOBILITY trials may not reflect the UK LN population. The EAG is concerned that the ethnicity of participants in the trial populations is likely to vary compared to the ethnicity of LN patients in the UK, as there were fewer participants of Asian ethnicity and more participants of Black African American, American Indian and Alaska Native ethnicities in the REGENCY trial compared with the UK LN population. This was similar in the NOBILITY study. The company provided baseline characteristics for the EU/UK participants in REGENCY in response to the PfCs. Although the ethnicity of this subset of participants in REGENCY was similar to the UK LN population, only a small number of trial participants were from the EU/UK. No baseline characteristics were provided for the UK/EU participants in NOBILITY, so the EAG is unable to comment further on the similarity to UK patient population.

Additionally, the EAG has some concerns that the duration of the REGENCY and NOBILITY trials are not sufficient given the chronic nature of LN. Clinical advice to the EAG suggested that some LN patients may be on treatment for more than 10 years and, as such, a 52-week or 76-week trial period may not be sufficient to estimate relapse rates on OBI.

3.6.2 Conclusions on the NMA

The EAG does not have any major concerns regarding the methodological approach taken by the company to conduct the NMA and finds many of their

decisions to be justified. However, the EAG does have some concerns surrounding the comparability of the populations of the AURORA-1 and AURA-LV trials assessing VOC + MMF to REGENCY and NOBILITY, as AURORA-1 and AURA-LV include participants with pure class V LN, whereas REGENCY and NOBILITY do not (see Section 3.4.3). The EAG believes this may potentially violate the transitivity assumption; this issue also has repercussions for the transition to CKD Stage 4 in the economic model (see Section 4.2.5).

To focus on longer-term outcomes of 48 weeks or longer, and to achieve a connected network, the company's NMA included a small number of studies (N=6). Therefore, as they could not be included in a connected network, tacrolimus and cyclophosphamide were not assessed within the NMA despite being included in the NICE decision problem.

Most indirect comparisons within the company's base-case analysis did not demonstrate statistically significant differences between OBI + MMF and any other comparators, except for an improvement in ORR when OBI + MMF was compared with MMF alone. None of the results were statistically significant for the NMAs assessing Grade 3+ AEs and SAEs. The company were only able to compare OBI + MMF with MMF alone and RTX + MMF in the Grade 3+ AE assessment. All point estimates were associated with very wide 95% CrIs; this imprecision makes it impossible to definitively determine the direction and magnitude of effect. Due to this, as well as issues relating to transitivity due to variation in outcome measurements and patient characteristics, the EAG advises cautious interpretation of the results from the NMA.

In view of the issues outlined, the EAG recommends further exploration of the data using other population-adjusted indirect comparison methodologies, such as ML-NMR using IPD and aggregate data, to account for heterogeneity across the studies in terms of treatments and patient characteristics.

4 Cost effectiveness

This section presents a summary and critique of the cost-effectiveness evidence included in the CS.[3] Section 4.1 focuses on the company's review of the cost-effectiveness evidence and Section 4.2 covers the company's economic evaluation.

4.1 Critique of the review of cost-effectiveness evidence

The company conducted a SLR to identify economic evidence relevant to adults with ISN/RPS class III/IV (with or without concurrent class V) lupus nephritis across three components: economic evaluations, cost and/or healthcare resource use (HCRU) data, and health state utility values (HSUV)/HRQoL (CS Section 3.1 and Appendix E).[3,21]

4.1.1 Search methods

The company conducted a search to identify economic studies consisting of economic evaluations, cost and/or HCRU data, and HRQoL/health state utility values (HSUVs) (Appendix 2, p.265).[48] Searches were initially conducted between 30 May 2024 and 24 June 2024, and were updated between 24 February 2025 and 3 March 2025.[21] The EAG reported critiques of the company's use of the 'dc' (date created) and 'dt' (create date) fields in the updated Embase and MEDLINE searches, and inconsistencies in the use of free text terms, which can be found in the clinical effectiveness Sections 3.1 and 3.1.1, and also applies to the economic SLR search strategies.

Similarly to the critique of the search methods for the clinical effectiveness SLR, the issues mentioned may have little effect, however the EAG cannot be certain that all relevant evidence would have been retrieved, due to the inability to conduct comprehensive testing of the strategies.

4.1.2 Evidence review

Inclusion and exclusion criteria aligned with the NICE scope without limits to the geographic location or date (excluding abstracts).[3,21,49] A total of 140 records were included for both the original and SLR update after full text screening with reasons for exclusion being provided for all records at this

stage[3,21] Data extraction from the included studies was subsequently prioritised to records reporting economic evaluations and cost and/or resource use, relevant to decision making in England.[21] Additionally, for HSUV/HRQoL components, only studies reporting utility values were prioritised for data extraction regardless of geography, owing to the paucity of studies reporting HSUVs.[21] Across included studies, 3 out of 20 studies reporting economic evaluation outcomes, and 3 out of 93 studies reporting healthcare cost and/or resource use outcomes, and 14 out of 54 studies reporting HRQoL/HSUV outcomes were prioritised for data extraction.[21] In the economic SLR report provided by the company as part of this submission, a reason was given for each record where data associated with these three economic components were not extracted (economic SLR report, Table 9).[48]

In total, 16 records were prioritised including TA882 and SMC2570 for voclosporin with MMF for treating LN,[22,50] a cost effectiveness study for MMF from the NHS perspective,[51] and a UK focused direct cost study associated with management of adult patients with SLE.[52] The remaining 12 records were all HSUV studies, reporting global utility data; only one study reported utility values collected from patients in the UK, as part of an international study.[53] Moreover, half of the included records used utility data from other publications and the reporting of LN classification was mixed, with two records focused on Class III/IV ± V or pure V (NICE and SMC),[22,50] and 1 record on class III/IV ±V.[54]. It was subsequently concluded that, while HTA documents such as those from NICE will be one of the best sources of information for informing an economic model, due to the paucity of data in patients with ISN/RPS Class III/IV ±V LN, data from broader LN populations may be required as a proxy.[3]

Lastly, the economic SLR report confirmed that methods outlined by the Cochrane Collaboration and Centre for Reviews and Dissemination (CRD) were followed, as well as the reporting recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.[24-27,48,55] The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) and data extraction forms were provided as part of the CS.[48] Moreover, the quality

of each prioritised record was appraised using reputable, peer-reviewed checklists.[56-58]

EAG comment: The EAG believes the company's approach to prioritise included records based on the country/perspective and feasibility for input into an economic model to be reasonable and acceptable, ensuring only the most relevant evidence is considered for the decision problem. However, considering the low number of prioritised records for data extraction on economic evaluation and cost and/or resource use components, other included studies that were not prioritised may have provided supportive information to inform the economic model. An overview of all 20 records reporting economic evaluation outcomes is shown in Table 4.1 (Table 10, Economic SLR report).[48]

Overall, the EAG believe the methods and approaches undertaken by the company to perform the economic SLR to be appropriate, while highlighting the lack of available economic evidence that directly aligns with the NICE decision problem.[49]

Table 4.1: Summary of the included economic evaluations (N=20)

Study ID, study design, publication type	Population	Intervention/comparator	Country perspective of analyses	Type of economic analyses	Model schematic reported
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study ID, study design, publication type	Population	Intervention/comparator	Country perspective of analyses	Type of economic analyses	Model schematic reported
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study ID, study design, publication type	Population	Intervention/comparator	Country perspective of analyses	Type of economic analyses	Model schematic reported

Study ID, study design, publication type	Population	Intervention/comparator	Country perspective of analyses	Type of economic analyses	Model schematic reported
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Economic SLR Section 4.3.2, Table 10[48]

Abbreviations: AZA = azathioprine; CADTH = Canadian Agency for Drugs and Technologies in Health; CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; COI = cost of illness; CUA = cost-utility analysis; CYC = cyclophosphamide; HTA = health technology assessment; ISN/RPS = International Society of Nephrology/Renal Pathology Society; IVC = intravenous cyclophosphamide; LN = lupus nephritis; MMF = mycophenolate mofetil; NA = not applicable; NICE = National Institute for Health and Care Excellence; SC = standard care; SLE = systemic lupus erythematosus; SMC = Scottish Medicines Consortium; TAC = tacrolimus

4.2 Critique of the submitted economic evaluation

4.2.1 NICE reference case checklist

Table 4.2: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	**Appropriate** The model's perspective focused on adult LN patients.
Perspective on costs	NHS and Personal Social Services	**Appropriate** The company submission presents patient health care resource use and costs relevant to the NHS and PSS.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	**Appropriate** The company presented a cost-utility analysis between obinutuzumab and 4 of the 7 comparator interventions included in the NICE scope. Both pairwise and incremental comparisons were included. **Secondary concerns** 4 of the 7 comparator interventions considered relevant for the submission in the NICE scope were included in the cost-effectiveness analysis. Most of these exclusions were due to the lack of comparative clinical effectiveness evidence with obinutuzumab.
Time horizon	Long enough to reflect all important differences in costs or outcomes	**Appropriate** A lifetime horizon was modelled lasting 70 years, as the mean patient

Element of health technology assessment	Reference case	EAG comment on company's submission
	between the technologies being compared	population in REGENCY was 33 years old.[3]
Synthesis of evidence on health effects	Based on systematic review	**Key issue** The EAG is concerned about the weak evidence base used to assume that impacts on renal flare prevention lead to an equivalent reduction in disease progression, and the relatively large impact this assumption has on cost-effectiveness results. **Key issue** The company submission uses relative effectiveness estimates from the network meta-analysis. The EAG found inconsistencies in the methods used to transform relative effectiveness estimates that were implemented in the decision model. **Key issue** The economic model makes assumptions around the treatment effect duration after stopping treatment and treatment waning. The EAG is concerned that due to the follow-up of the trials in the evidence base relative to the expected duration of therapy, assumptions of treatment duration and waning are highly uncertain.

Element of health technology assessment	Reference case	EAG comment on company's submission
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.	**Appropriate** The company submission reports cost per QALY estimates as the base-case.
Source of data for measurement of health-related quality of life	Reported directly by patients, carers or both	**Some concerns** The base-case analysis in the company submission was informed by utility data from the latest NICE technology appraisal (TA882).[22] The pivotal REGENCY trial collected EQ-5D-5L data that was not used in the base-case due to face validity concerns.[3] The EAG considered the reporting of the methods for analysing EQ-5D data from REGENCY lacked clarity.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	**Appropriate** The base-case analysis in the company submission was informed by values form TA882.[22]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the people having the health benefit, except in specific circumstances	**Appropriate** No additional weights to the QALY due to severity were deemed appropriate for this submission.
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	**Key issues** The EAG noted differences in concomitant treatment costs across for voclosporin, belimumab, and rituximab that were not clearly reported in the company submission

Element of health technology assessment	Reference case	EAG comment on company's submission
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	**Appropriate** Both costs and health outcomes are discounted at an annual rate of 3.5%.

4.2.2 Model structure

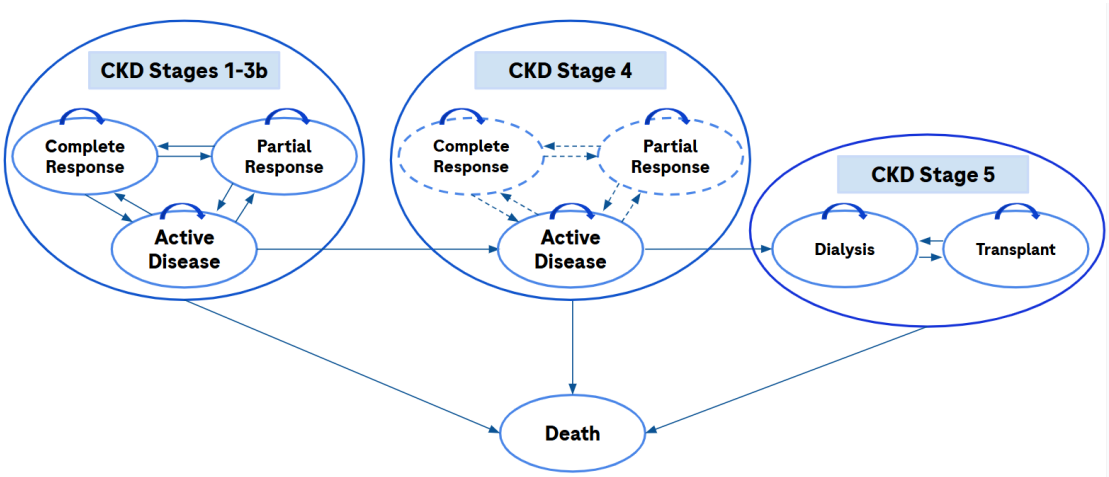
The structure presented for the decision analytic model in the company submission was directly influenced by the submissions for VOC to UK HTA bodies (NICE TA882 and SMC2570).[3,22,50] This structure followed a Markov state transition model that in the company base-case included seven health-states using a six-month cycle duration for a 70-year time horizon; these health-states were validated by clinical experts.[3]

Based on information from REGENCY,[3] patients enter the model receiving therapy with CKD disease stage ranging from 1 to 3b (defined as having eGFR ≥ 30 ml/min/1.73 m^2). Patients with CKD stage 1-3b start in the active disease (AD) health-state and can move to CRR, PRR, stay in AD, or have a disease progression to CKD stage 4. Patients in the CRR health state can move to the PRR health state, move to the active disease health state, or stay in CRR. Patients in the PRR health state either move to CRR, move to active disease, or stay in PRR. Once patients' disease progresses to CKD stage 4, they are assumed not to recover. Instead, they stay in CKD stage 4 or progress to CKD stage 5 (ESRD). Patients progressing to CKD stage 5 are assumed to receive dialysis and can stay receiving dialysis or move to the transplant state, where they can remain in the transplant state or move back to dialysis.

Figure 1 presents the model structure in the company submission. The model structure also includes the option of CKD stage 4 patients to move to a CRR and PRR state within CKD stage 4. Nonetheless, this was only explored as a scenario analysis. The reason given for this was that there were few patients

in REGENCY that progressed to CKD stage 4 and could be assessed as complete or partial responders.[3]

Figure 1: Model structure in the company submission



Source: CS Figure 17[3]

Abbreviations: CKD = chronic kidney disease

This model structure assumes there is no progression to CKD stage 4 from CRR or PRR. The reasoning behind this assumption was the small number of patients moving to CKD stage 4 in REGENCY, meaning there was little data to accurately inform transitions to CKD stage 4. Moreover, no transitions were observed from CRR or PRR to CKD stage 4 leading to this simplifying assumption. Similarly, the company base-case assumed patients at CKD stage 4 cannot transition back to a less severe CKD stage.

EAG comment: The EAG considers the model structure to represent disease progression to an appropriate degree. However, the EAG are concerned about how renal flares were included in the model structure. This is an area of the disease that is of relevance to patients and where the intervention is expected to have an impact relative to some of the comparators. Although the company model assumes the impact on the risk of renal flares translates directly into impacting the risk of progression to CKD 4 (see Section 2.3.3 and Section 4.2.5), the EAG considers the current structure may not appropriately capture the impact that renal flares may have on patient HRQoL and health care resource use.

Regarding the transplant state, the EAG is concerned that having the costs and impact of kidney transplant and post-transplant recovery modelled as a single health state rather than as two separate health states (with transplant as the tunnel state) may cause the cost of transplant to be wrongly estimated, leading to more structural uncertainty in the model. The EAG expects that this structural uncertainty increases the more patients progress to the transplant state.

The EAG is concerned that TA752 was not considered to be an informative resource, despite being included in the NICE scope.[49,76] Although the submission focuses on BEL for active autoantibody-positive SLE rather than LN, the EAG considers a discussion of the limitations of alternative model structures compared to the structure chosen for the company base-case would have been informative for the NICE committee.

4.2.3 Population

The base-case analysis submitted by the company focused on adult patients with LN active class III or IV LN, with or without concomitant class V disease. Patient age at baseline was 33 years old, with an average weight of 67 kg and average body surface area of 1.72m^2; 15.5% were male. All patients entering the model were assumed to be between CKD stage 1 (no kidney disease) and CKD stage 3b and have AD. Patient characteristics were based on the baseline characteristics of the REGENCY trial.[3,77]

EAG comment: The population characteristics for the economic model were considered appropriate for the decision problem.

4.2.4 Interventions and comparators

Intervention: OBI + MMF: OBI (1000 mg) in combination with MMF (2 g per day) and low-dose corticosteroid (0.5 mg/kg per day until day 15, then tapered to a target dose of 5 mg per day by week 24 and maintaining this dosage until week 80). A three-year stopping rule was applied to the intervention and across all comparator therapies.

Comparators: The cost-effectiveness analysis in the CS included the following comparators: MMF; VOC + MMF; and RTX + MMF.

The following therapies in the NICE scope were excluded as comparators in the cost-effectiveness analysis of the initial company submission: BEL + MMF; cyclophosphamide; cyclosporin with or without MMF; and tacrolimus with or without MMF. BEL + MMF was excluded as it is currently not reimbursed for LN in the UK. Cyclophosphamide was considered as effective as MMF with potentially higher adverse events in the company submission, as cyclophosphamide is typically used when MMF is discontinued. Clinical experts indicated to the company that tacrolimus was rarely used in practice, while it was not possible to generate comparative evidence connect to OBI for either tacrolimus nor cyclophosphamide in the NMA. The reasons for excluding cyclosporin were less clear. The company submission assumes that conclusions around the cost-effectiveness of OBI + MMF compared to VOC + MMF can be extrapolated to comparisons between OBI + MMF and tacrolimus or cyclosporin and, therefore, its inclusion is redundant. In addition, it is possible that no comparative evidence could be generated for cyclosporin, which was not clear in the text of the company submission. For further critique of how comparators were presented in the submission, see Section 2.3.2.

EAG comment: The definition of stopping rules was considered incomplete as the economic model assumed that alive patients continued receiving treatment regardless of their kidney disease status, which may stand in contradiction with the SmPC for OBI in LN that recommends stopping treatment given disease progression.[78] Moreover, data from REGENCY regarding treatment discontinuation and the use of rescue therapies was not used to assess the impact that these can have on the effectiveness of OBI and the comparator interventions in the company base-case.[3]

In the response to question B5b of the PfCs, the company presented a scenario using discontinuation data from the OBI arm in REGENCY to model the impact of discontinuation of therapy costs on OBI alone, and the impact of assuming equivalent discontinuation rates across MMF combination

therapies.[7] However, this analysis did not clearly specify the assumptions used to cost subsequent therapies (as either MMF alone or a proportion of other MMF combination therapies) or the assumed impact that treatment discontinuation had on effectiveness.

As detailed in section 2.3.2, the EAG is concerned that the economic analysis only included three of the seven comparators listed in the NICE scope as relevant for this appraisal.[49] Of particular concern was the absence of BEL, as clinical advice to the EAG noted it is used by clinicians, even when not reimbursed for LN specifically (though it is still reimbursed for SLE). Furthermore, BEL features both in the KDIGO 2024 and EULAR 2025 guidelines, as well as the forthcoming BSR 2025 guidelines, according to the submission to NICE from the BSR for this submission, which are likely to continuously shape clinical practice.[10,20,79,80]

Due to the considerations above, the EAG requested BEL therapy to be included in the economic analysis within the PfCs.[7] The company acceded to include BEL as a comparator with the caveat that this therapy is only reimbursed in England for SLE. Given its potential use off-label and the current changes in practice based on recent clinical guidelines, the inclusion of BEL is considered an informative comparator and improves the adherence of the economic analysis to the NICE scope.[49]

Clinical advice to the EAG highlighted that RTX is typically used off-label, even when not recommended for use for LN, and noted that tacrolimus is rarely used in current clinical practice (although clinical practice is continuously changing to adapt to international guidelines). Regarding the use of VOC + MMF, clinical advice to the EAG noted that low-dose VOC was more relevant to current clinical practice. Clinicians consulted by the EAG acknowledged that VOC + MMF is still used in a smaller proportion of patients with more severe disease, reflecting the fact that this is an evolving field where changes to standard of care in the UK have only occurred recently and are influenced by recommendations from international clinical guidelines.[49]

4.2.5 Treatment effectiveness and extrapolation

The decision model derives transition probabilities between active disease (AD), complete response (CRR), and partial response (PRR) for each comparator using data from REGENCY and the NMA.[3] Transition probabilities from AD to CKD stage 4 were informed by expert opinion from TA882 and surrogate outcome data on renal flares.[22] Survival data were informed by the REGENCY trial, and advanced disease risks were informed by TA882 and the published literature.[3,22] Finally, assumptions of treatment effect duration and waning after stopping treatment delivery were informed by clinical expert opinion. The following sections review the company's reporting and methods used in the CS, respectively.

Transitions of complete and partial response in CKD stage 1-3b: transitions for renal response in the MMF alone arm

Baseline probabilities for moving between AD, PRR, and CRR for MMF alone were based on patient data from the placebo arm in REGENCY fitted into a multi-state-model.[3] However, the economic model used the primary and secondary efficacy endpoints from the placebo arm of REGENCY,[3] estimating the probability of PRR ([redacted]) and CRR ([redacted]) at week 76, assumed these corresponded to a three-year timepoint and transformed them to six-month probabilities using a Weibull distribution, then replaced the estimates from the multi-state model with the newly calculated probabilities based on trial endpoints. Table 4.3 reports the six-monthly probabilities of response to therapy for the MMF alone arm used in the company base-case analysis.

Table 4.3: 6-monthly probabilities of response to therapy for MMF alone

From / To	AD	PRR	CRR
AD (MSM)*	#	[redacted]	[redacted]
AD	#	[redacted]	[redacted]
PRR	[redacted]	#	[redacted]
CRR	[redacted]	[redacted]	#

Source: Produced by the EAG based on Appendix H, Table 36[21]
Note: # refers to 1 minus sum of PRR and CRR probabilities
*Values derived from the multi-state-model approach only used in a scenario analysis
Abbreviations: AD = active disease; CRR = complete renal response; PRR = partial renal response; MSM = multi-state-model

EAG comment: The EAG considers the use of a multi-state-model to fit data from each arm of REGENCY to be appropriate.[3] However, it was unclear from the CS whether multiple models with different covariates were tested, how goodness of fit was assessed, and how results from the multi-state-model compared to results from the primary efficacy analysis for CRR.

The base-case approach by the company combined parameters estimated from the primary and secondary endpoints of REGENCY,[3] with parameters estimated through a multi-state-model approach. As the decision model incorporates values estimated from two different methodologies, this is likely to introduce additional parameter uncertainty into the results. Furthermore, it was not from the CS what was the impact of including parameters from the REGENCY endpoints into the results of the multi-state-model compared to relying on the multi-state-model parameters only, and why this was deemed the better approach.

In assuming that primary and secondary endpoints from REGENCY corresponded to a three-year (157 week) timepoint, the analysis fails to represent the actual follow-up timepoint of 76 weeks for the primary analysis from the REGENCY trial.[3] It was also unclear from the CS why using the Weibull distribution to transform probabilities from three years into six months was considered the most appropriate approach, and whether other approaches (such as using an exponential function as suggested by Gidwani and Russell, 2020[81]) were considered. Regarding this, the company specified in the response to question B16 in the PfCs that this approach was preferred over using an exponential function, as the model predictions over three years are closer to the three-year results of the ITC using the Weibull function.[7] As the EAG rejects the assumption that results from the ITC correspond to three-year estimates, it is unclear whether using the Weibull function improves the predictive ability of the model compared to the exponential function.[81]

The approach adopted in the EAG's base-case analysis assumed a follow-up time of 1.5 years (76 weeks) rather than three years, as it aligns with the

follow-up time in REGENCY.[3] In addition, the exponential function was used to transform probabilities to the 6-month cycle duration in the model.[81]

Transitions between renal response rates for the OBI + MMF, VOC + MMF and RTX + MMF arms

The baseline probabilities for moving between the AD, PRR, and CRR states for OBI + MMF, VOC + MMF and RTX + MMF were based on IPD data from the OBI arm of REGENCY fitted into a multi-state-model.[3] Six-month probabilities estimated for OBI + MMF are reported in Table 4.4.

Table 4.4: 6-month probabilities of response to therapy for the OBI + MMF arm

From / To	AD	PRR	CRR
AD (MSM)*	#	[redacted]	[redacted]
AD	#	[redacted]	[redacted]
PRR	[redacted]	#	[redacted]
CRR	[redacted]	[redacted]	#

Source: Produced by the EAG based on CS Appendix H, Table 36[21]
Note: # refers to 1 minus sum of probabilities in the left and right-side columns
*Values derived from the multi-state-model approach only used in a scenario analysis
Abbreviations: AD = active disease; CRR = complete renal response; CS = company submission; PRR = partial renal response

To derive the transition probability of moving from AD to CRR in the OBI + MMF arm, the company estimated the OR for CRR between OBI + MMF and MMF alone from the NMA, and used the proportion of patients with CRR at week 76 in the MMF alone arm of REGENCY as the baseline probability to calculate the respective probability of reaching CRR for the OBI + MMF arm.[3] Using this method, the company assumed the probability from REGENCY corresponded to a three-year timepoint and used a Weibull distribution to transform three-year probabilities into six-month probabilities (corresponding to one model cycle).[3] The same approach was followed to calculate the probability of moving from AD to PRR for OBI + MMF, using the OBI + MMF estimates of the OR for PRR from the NMA, the probability of PRR from the MMF alone arm of REGENCY,[3] and using a Weibull distribution to transform three-year probabilities to six-month probabilities.

To estimate the probability of moving from AD to CRR in the VOC + MMF arm, BEL + MMF arm, and the RTX + MMF arm, the company used the approach described above of using the OR estimates for CRR from the NMA for the VOC + MFF arm and the RTX + MMF arm respectively, and the baseline probability of CRR response from the MMF alone arm of REGENCY, transforming three-year probabilities into six-month probabilities using the Weibull function.[3] The same approach was used to derive the probability of moving from AD to PRR for VOC + MMF and RTX + MMF respectively, using OR estimates for PRR response from the NMA, and the probability of PRR response from REGENCY as the baseline.[3] OR estimates used to derive the CRR and PRR transition probabilities for OBI + MMF, VOC + MMF, and RTX + MMF are reported in Table 4.5.

Table 4.5: Odds ratios of interventions compared to MMF alone from the NMA used in the decision model

OR for CRR response				
Therapy	**Mean**	**LL**	**UL**	**Distribution**
OBI + MMF	[redacted]	[redacted]	[redacted]	NR
VOC + MMF	[redacted]	[redacted]	[redacted]	NR
BEL + MMF	[redacted]	[redacted]	[redacted]	NR
RTX + MMF	[redacted]	[redacted]	[redacted]	NR
OR for PRR response				
Therapy	**Mean**	**LL**	**UL**	**Distribution**
OBI + MMF	[redacted]	[redacted]	[redacted]	NR
VOC + MMF	[redacted]	[redacted]	[redacted]	NR
BEL + MMF	[redacted]	[redacted]	[redacted]	NR
RTX + MMF	[redacted]	[redacted]	[redacted]	NR

Source: Produced by the EAG based on the cost-effectiveness model by the company
Timepoints not specified, the company base-case assumes 3 years
Abbreviations: LL = lower limit; NR = not reported; BEL + MMF = belimumab + mycophenolate; OBI + MMF = obinutuzumab with mycophenolate; RTX + MMF = rituximab + mycophenolate; VOC + MMF = voclosporin + mycophenolate; UL = upper limit

EAG comment: As with the approach to derive transitions for the MMF alone arm, the EAG do not consider the assumption that timepoints from REGENCY nor the NMA correspond to a three-year (157 weeks) timepoint to be appropriate, given the primary follow-up time of REGENCY.[3] The timepoint

corresponding to the other studies included in the network of the NMA was not clearly reported in the CS. In the response to question B4 in the PfCs, the company reported primary endpoints of 52 weeks for AURORA-1, 104 weeks for BLISS-LN, and 52 weeks for LUNAR.[7] Given that the varying study endpoints in the NMA were at or below two years, unless the probabilities of reaching CRR and PRR are unlikely to change over time between week 76 (1.5 years) and week 157 (three years) of receiving treatment, the approach used by the company is likely to be inappropriate to calculate the effectiveness estimates in the economic model.

The CS considered the assumption that probabilities for returning to AD from the OBI + MMF arm of REGENCY also applied to VOC + MMF and RTX + MMF was a conservative assumption.[3] Although this was justified based on clinical opinion around the mechanism of action of OBI, the EAG considers this to be a speculative assumption under the evidence provided, as it is unclear whether therapies with better or worse efficacy in achieving CRR or PRR meant that the risk of returning to AD was also lowered.

The EAG also found small differences between all NMA estimates reported in the CS for CRR and PRR, and those used in the executable model reported in Table 4.5. Although the direction of the estimates did not change, the EAG note an upward bias in the estimates used in the decision model. Moreover, the distribution used to model uncertainty around the NMA estimates for the probabilistic analysis was not specified in the company's economic model.

Transitions to advanced disease: CKD stage 4

[redacted]. Appendix H in the CS presents spaghetti plots showing a high variation in eGFR levels during follow-up,

[redacted]. Figure 2 presents the eGFR values over 76 weeks, stratified by REGENCY treatment arm.[21]

Figure 2: eGFR values over 76 weeks stratified by REGENCY treatment arm

Source: Company submission, Appendix H, Figure 11[21] Abbreviations: eGFR = estimated glomerular filtration rate

The company base-case presented in the economic model adopted a baseline risk estimate for the six-month transition to CKD stage 4 of 3.05%, based on NICE TA882.[22] The evidence base for the estimate in TA882 was clinical expert opinion, highlighting the lack of published evidence around progression to AD. Following the model structure from TA882,[22] once patients transition to CKD stage 4 in the company model, their disease cannot recover to CKD stage 3b or below. Therefore, improvements in the probability of achieving CRR or PRR from therapy reduced the number of patients at risk of progressing to CKD stage 4 and AD.

The CS made the case that renal flares are a key driver in kidney disease progression and simultaneously presented results from REGENCY and NOBILITY showing that OBI + MMF has the potential to reduce renal flares compared with MMF alone. The company base-case then assumed that OBI + MMF reduces the probability of transitioning to CKD stage 4 by the same magnitude as it reduces the risk of a renal flare event, using the time to event

hazard ratio (HR) from REGENCY of 0.44 (95% CI 0.24 to 0.82). This assumption is extended to VOC + MMF by using the OR estimate in AURORA-2 and transforming it to an estimated HR of 0.88 (95% CI 0.49 to 1.45).[3] The six-monthly transition probabilities from AD to CKD stage 4 used in the company base-case are presented in Table 4.6.

Table 4.6: 6-monthly transition probabilities from AD to CKD stage 4 by therapy arm

Treatment	Transition probability
MMF and RTX + MMF	3.05%
OBI + MMF	[redacted]
VOC + MMF	2.70%
BEL + MMF	1.56%

Source: Produced by the EAG based on the company submission, Table 47[3]
Abbreviations: MMF = mycophenolate; OBI + MMF = obinutuzumab with mycophenolate; RTX + MMF = rituximab + mycophenolate; VOC + MMF = voclosporin + mycophenolate; UL = upper limit

EAG comment: The EAG acknowledges the scarcity of published data surrounding transitions to CKD stage 4 as a gap in the evidence and a limitation in the economic model structure attempting to capture advanced kidney disease. The EAG considers the approach of using the estimate for the baseline risk of progression from TA882 to be mostly appropriate, as estimates from the whole sample of the safety-evaluable population show a similar probability of progression using a calculation using approximations by the EAG of the 6-month probability of progression to CKD stage 4 using the count method (3.05% assumed in the company model compared to [redacted]).[22]

The EAG considers that the model structure based on TA882 already accounted for the impact that achieving CRR or PRR has on reducing the risk of progressing to advanced disease, as fewer patients in the AD state mean less transitions to the advanced kidney disease stage.[22] Therefore, including an additional reduction to the probability of progression from advanced disease to CKD stage 4 based on time-to-renal flare data risks double-counting the effectiveness of the drug in the decision model structure.

The EAG further questions the base-case assumption that the impact the therapy has on renal flares is equivalent to the impact on transitions to CKD stage 4, as the evidence presented in the CS does not directly support the assumption that this is a one-to-one relationship. The company addressed some of these uncertainties in the PfC response to questions B7 and B8.[7] The study by Perez-Arias et al (2022) was referenced in the company response to justify this approach.[1] However, this study showed variations in flare presentation, including number of previous flares, duration and intensity of renal flares as having a very different impact on eGFR or achieving CRR through therapy.[1]

An additional point of concern to the EAG was the evidence used for the effectiveness data on renal flares, as methods did not rely on the NMA results reported in the clinical effectiveness section to estimate relative effectiveness. Instead, the analysis relied on a Bucher ITC using available data from REGENCY, AURORA-2, and BLISS-LN. The methods used to conduct the Bucher ITC were not reported in full within the CS.[3]

Furthermore, the EAG questions why the AURORA-2 study was used in the Bucher analysis when this study had been excluded from their clinical NMA (see Section 3.4.2). In their reporting of the Updated Clinical SLR (Table 18), the company state that AURORA-2 was excluded from the clinical NMA because it "is based on complete response of patients in AURORA-1 and other patients removed and not followed all the way through AURORA-1 and AURORA-2."[5] The company did not provide a rationale, either in the original CS or in PfCs, as to why estimates on renal flares have been derived from AURORA-2 given its exclusion in the NMA.[5,7] The company's rationale for excluding AURORA-2 from the NMA also suggests a lack of clinical comparability to the participants in REGENCY, given that AURORA-2 only included participants that had achieved complete response. This clinical heterogeneity would likely violate the transitivity assumption, which is required for all ITCs including Bucher analyses.[82] The EAG therefore has concerns that the Bucher analysis assessing renal flares comparing REGENCY and AURORA-2 is open to substantial uncertainty.

The one-way sensitivity analysis of the company base-case showed differences in progression to CKD stage 4 (from differences in HRs of time-to-renal flare) had a potentially larger impact on cost-effectiveness than improvements in reaching CRR, which was the primary outcome of the studies presented. Given the weaker evidence base underscoring this assumption, the EAG questions the appropriateness of assuming differences in progression to CKD stage 4 in the base-case analysis, rather than as a scenario analysis.

In the PfCs, question B3, the EAG questioned the appropriateness of not including the short-term impact of renal flares separately, to which the company responded that this approach misses the impact that persistent flares have on kidney disease progression.[7] The company explored a scenario which assumed that renal flares had a health-state related impact at CRR and affected the transitions from CRR to AD rather than AD to CKD stage 4 directly, based on TA882, but considered this approach would not fully capture the short- and long-term impact of renal flares on progression to late-stage CKD, therefore maintaining the base-case approach.[22]

In the EAG base-case analysis, it was assumed that the model structure accounts for improvements in kidney disease progression via improvements in CRR and has removed the different HRs of time-to-renal flare used between OBI, VOC, or BEL and MMF alone. The EAG considers this is a conservative assumption, as the prevention of renal flares likely has an impact on long-term disease, even if the size of the impact is uncertain. Furthermore, the evidence base for the differences between OBI, VOC and BEL was weak and not transparently reported. The preferred assumption for the EAG base-case would be to include an additional health-state capturing the impact of the first (and subsequent) renal flare. However, this would involve changing the model structure and would require further validation from clinical experts.

The EAG has explored a scenario analysis of including the HR of time to renal flare for the estimate of progression to CKD stage 4 for OBI, and assumed an equivalent estimate for VOC, BEL and RTX. In addition, the EAG has explored a separate scenario of its base-case analysis assuming the risk of

progressing from PR to CKD stage 4 is not zero but half the risk of progressing from AD to CKD stage 4.

Transitions to advanced disease: CKD stage 5 or ESRD

Patients in the CKD stage 4 state in the company base-case are assumed to have AD and can either remain in stage 4 or move to CKD stage 5 (ESRD). The per-cycle probability of progressing to CKD stage 5 was informed by Sugrue et al (2019) and was assumed to be constant over time.[83] Patients progressing to CKD stage 5 are assumed to receive dialysis and either stay in dialysis or progress to the kidney transplant health state. Once a patient progresses to CKD stage 5, they are assumed not to recover back to CKD stage 4 or below. The probability of moving from dialysis to transplant is informed by EAG feedback to NICE TA882,[22] where patients are assumed to stay in the transplant state or return to dialysis. The probability of patients returning from transplant to dialysis was informed by Sugrue et al (2019).[83]

EAG comment: The EAG considers the approach to modelling progressive disease to be generally appropriate.

Risk of mortality

The company's approach to calculating the risk of mortality for patients starting therapy with CKD 1 to 3b, as presented in the CS, employed an approach where the total number of deaths ([redacted]) was divided by the number of patient observations every six months ([redacted]) over the 76-month REGENCY follow-up to derive the six-month mortality rate.[3] These rates were transformed into probabilities using an exponential function. Furthermore, the mortality risk calculation used for the base-case stratified mortality rates by response status (i.e. AD, PRR or CRR). The risk of mortality at the CKD stage 4, CKD stage 5 (dialysis) and transplant health states, respectively, were informed by Sugrue et al (2019).[83]

EAG comment: In the response to PfCs regarding a request from the EAG to perform a parametric survival analysis (question B9), the company argued that in the data covering the period up to the 76-week data cut only four deaths occurred. Given the low number of events, a survival analysis was not

presented but the company reported Kaplan-Meier estimates of OS for the 76-week data cut.[7] These are presented in Figure 3 below.

Figure 3: Kaplan Meier data of time to death up to week 76, efficacy-evaluable population of the REGENCY trial

Source: PfC response, supporting files[7]

Moreover, the text in the CS risks being misleading, as Appendix H describes how mortality risks were calculated from the multi-state-model approach used to derive transition probabilities across response status above.[21] This may be at odds with the 'count' method for calculating the risk of mortality presented in CS Section 3.3.2.5.[3] If a multi-state-model was used, it was unclear why data from both arms of REGENCY were pooled together, and whether the company tested using the intervention arm as a covariate or stratifying factor.[3] Mortality risks for a six-month model cycle were assumed to be [redacted] for AD, [redacted] for PRR, and [redacted] for CRR in the base-case analysis.

It was also unclear how survival risks compared to UK population lifetables, and the clinical mechanism of how a lack of renal response leads to an increase in the mortality risk from LN for causes other than kidney disease progression (already accounted for in the model structure).

The approach used to model mortality risks in the advanced disease stage from CKD stage 4 onwards was consistent with TA882, as both were informed by Sugrue et al (2019) and was considered appropriate for the decision problem.[22,83]

Treatment effect duration and waning

The company base-case assumed a stopping rule of 36 months for all therapies assessed (i.e. OBI + MMF, VOC + MMF, RTX + MMF, BEL + MMF and MMF alone). This assumption was in line with NICE TA882, which based this assumption on the follow-up of the AURORA trials and clinical guidelines.[20,22,79,80]

After the three-year stopping rule, the model assumes a temporary maintenance of treatment effect post-stoppage, followed by a linear decline of treatment-related effectiveness (treatment waning), which varies by therapy as follows:

- For OBI + MMF, improvements in the probability of CRR and PRR are expected to last 12 months, after which probabilities converge with MMF alone probabilities over 12 months. This assumption was justified by the mechanism of action of OBI being based on B-cell depletion and its potential for a longer duration of response.

- For VOC + MMF, no post-stoppage effect is assumed and treatment waning to MMF alone risks occurs over six months after stopping treatment. The company cited clinical opinion indicating that VOC needs to be administered daily and that treatment response was expected to be similar to MMF alone after three months.

- For RTX + MMF and BEL + MMF, the model assumes a maintenance of treatment effects over six months, followed by a linear waning to MMF alone risks over six months. The reasoning for this assumption was that RTX has a B-cell depletion mechanism similar to OBI but is unable to maintain B-cell depletion for as long as OBI.

No additional treatment effect post-stoppage or treatment waning assumption were applied to the MMF alone arm.

EAG comment: Although the company adopted a three-year stopping rule for all treatments, recent guidelines suggest a duration ranging between 2.5 and 5 years, with treatment duration dependent on disease management and treatment-related adverse events.[20,79,80] As the decision model allows the exploration of a treatment duration beyond three years, the EAG has considered scenario analysis from its base-case assuming a 4-year and a 5-year stopping rule.

The EAG considers the maintenance of treatment effectiveness beyond the stopping rule and subsequent treatment waning assumptions to be highly speculative, as the evidence base relies on studies with a follow-up below the three-year stopping rule assumed in the model. The company presented evidence from Gomez Mendez et al (2018) on the association between complete cell depletion and CRR, yet this is based on the LUNAR study, which has a primary endpoint at week 78.[4] Therefore, much of the evidence base still rests on clinical expert opinion.

Due to the speculative nature and high uncertainty around treatment waning assumptions after 3 years, the EAG's approach to its base-case analysis was to assume no treatment waning, and a treatment effect duration after 3 years of 1 year for OBI, 6 months for BEL and RTX, and no treatment effect after 3 years for VOC, based on clinical expert opinion around the mechanisms of action of each therapy. The EAG recognises this presents a conservative assumption compared to the company base-case, but believes it is a better reflection of the absence of long-term evidence. A scenario analysis was also presented by the EAG assuming no treatment efficacy or waning beyond 3 years for any of the treatments assessed, to test the size of the impact this assumption had on overall cost-effectiveness.

4.2.6 Health-related quality of life

Health-related quality of life values used in the economic model

The REGENCY study collected EQ-5D-5L data for the population with CKD stage 1-3b;[3] however, utility estimates were deemed to lack face validity (see below). The company instead informed the utility values for the CRR, PRR and AD health states based on the preferred approach used by the EAG appraising NICE TA882.[22] These values were sourced from the 36-month datapoint in the AURORA-2 trial, where the EAG applied a weighted average approach.

For utility values related to advanced disease from CKD stage 4, the CS adopted the disutility estimates used in NICE TA882, which had been adopted from Jesky et al (2016), a UK observational study.[84]

For utility values of patients in the CKD stage 5 dialysis state, the company weighted the proportions of patients receiving haemodialysis and peritoneal dialysis in the UK using 2024 registry data,[85] and utility estimates from TA882 based on Lee et al. (2005).[22,86] Estimates for the CKD stage 5 transplant state were also extracted from Lee et al. (2005).[86] Patient utility values used in the base-case economic model are presented in Table 4.7.

Table 4.7: Patient health state utility values used in the base-case model from the company submission

Health state	Mean	SE
CKD1-3b: Complete Response	0.814	0.155
CKD1-3b: Partial Response	0.8	0.181
CKD1-3b: Active disease	0.749	0.192
CKD4: Active Disease	0.694	0.131
CKD5: Dialysis	0.458	0.33
CKD5: Transplant	0.71	0.27

Source: Reproduced from the CS, Table 56[3]
Abbreviations: CKD = chronic kidney disease; CS = company submission; SE = standard error

EAG comment: The overall approach of informing utility values of advanced disease patients based on the published literature and precedence from the

latest NICE appraisal of LN was considered appropriate. It is also worth noting that, compared to other economic evaluations presented that consider disease at CKD stage 4 and ESRD,[53,71,72] the estimates at these states are lower in this model. Therefore, the model structure presented by the company potentially rewards therapies that prevent transitions to CKD stage 4 and beyond.

EQ-5D-5L values collected from REGENCY

According to the company submission, the REGENCY trial collected EQ-5D-5L questionnaire and visual analogue scale (VAS) data at weeks 0, 24, 50 and 76.[3] Responses to the EQ-5D-5L questionnaires were scored using UK tariffs to obtain utility estimates. A linear mixed-effects model was used to generate health-state specific utilities for CRR, PRR and AD using the pooled sample of REGENCY and stratifying by treatment arm.[3]

Results showed no statistically significant difference between the different levels of response for the pooled sample nor by treatment arm.[3] Results also suggested that utility values were higher for the OBI + MMF arm compared to MMF alone and that utility increased with lower levels of response, with the highest utility at active disease and the lowest at complete response, with no statistical significance. These results were considered counterintuitive by both the company and experts advising the company and, therefore, were deemed to lack face validity. Utilities estimated in both approaches were used as scenario analyses in the model and are reported in Table 4.8.

Table 4.8: Utilities modelled as scenario analyses

Response status	Pooled REGENCY Mean (SD)	OBI + MMF Mean (SD)	MMF alone Mean (SD)
Complete response	[redacted]	[redacted]	[redacted]
Partial response	[redacted]	[redacted]	[redacted]
Active disease	[redacted]	[redacted]	[redacted]

Source: Produced by the EAG based on the company submission, Table 51 and Table 52[3]
Abbreviations: MMF = mycophenolate mofetil; OBI = obinutuzumab; SD = standard deviation

EAG comment: In the response to question B10 in the PfCs, the company further clarified the algorithm used to convert 5L values to 3L was chosen in line with the latest guidance from NICE TSD 22.[7,87] The company further clarified in the response to question B10 in the PfCs that the analysis of EQ-5D-5L utilities from the REGENCY trial relied on a linear mixed-effects model controlling for baseline utility and disease state (CRR, PRR, or AD).[3] It was unclear from the information provided in the submission what the linear specification used was; whether additional covariates were included and, if so, which additional covariates; and how significance and goodness-of fit were assessed. Considering the lack of face validity in the EQ-5D-5L utility values obtained in REGENCY, the EAG has concerns as to whether the EQ-5D was an appropriately sensitive instrument to capture patient HRQoL or whether response status (i.e. complete, partial, or no renal response) is the primary driver of patient HRQoL compared to other areas of the disease such as renal flares, fatigue and treatment-related SAEs.

4.2.7 Resources and costs

Intervention and comparators' resource use and costs

In the CS, Section 3.5 provides detailed information about costs and resource use in the company economic model; this is detailed in Table 4.9 below.[3] The dosing regimen for OBI + MMF + MPDL + PDS, MMF + MPDL + PDS, VOC + MMF + MPDL + PDS and RTX + MMF + MPDL + PDS were included in Sections 1.3.2 and 3.2.3 of the CS.[3] All first-line treatment regimens included in the evaluation followed a 36-month (three-year) stopping rule, informed by the REGENCY trial.[77] The drug acquisition cost of OBI was calculated by applying a PAS discount of [redacted]% on its list price, £3312, which resulted in a net price of £[redacted]. The list prices of all other drugs were used to calculate the treatment costs for LN patients in the economic model. The different treatment costs were calculated by multiplying the drug acquisition cost with their respective dosages.

EAG comment: The EAG have validated the unit costs of drugs and their sources. The treatment end point in the REGENCY trial was 76 weeks (1.5

years),[77] while the NMA adopted a minimum of 48-week time-point for all the included studies to extract treatment effectiveness data.[6] However, the economic model implemented a 36-month stopping rule for all the included treatments.[88] Hence, the EAG has concerns around how reflective this model assumption is of the real-world evidence. In their response to the PfCs, the company provided a scenario analysis with a time-point of 1.5 years upon request from the EAG (see Section 5.1.2).[7]

The company assumed vial sharing (no drug wastage) as their base-case.[88]. However, the updated model had the option to change the model setting to no vial sharing with respect to IV and subcutaenous drugs. As such, the EAG explored a no vial sharing setting in the updated model and observed that there was very little decrease in the ICERs, thus making the vial sharing a conservative assumption. It should be noted that the preferred assumption in the NICE reference case, which is also reflective of the UK clinical setting, is to assume no vial sharing for IV drugs (OBI, methylprednisolone, BEL and RTX).[89] As such, the EAG requested in the PfCs that the company to change their base-case to no vial sharing. In response, the company justified that vial sharing was a conservative assumption and maintained the original assumption for their base-case.[7] However, the EAG is of the opinion that no vial sharing should be the base-case, as it is the preferred assumption by NICE.

Table 4.9: Drug acquisition costs per week for intervention and comparators

	Cost per vial/ pack	Vial size/ tablets per pack	Dosing regimen	Vials/ tablets per admin	Total cost per admin	Source (cost, regimen)
Obinutuzumab	£3312.00 (£[redacted])	1 x 1,000 mg	IV: 1000 mg on weeks 0, 2, 24, 26 and 52. Subsequent infusions every 6 months starting at Week 80	1	£3312.00 (£[redacted])	Schedule & dosing: REGENCY[77] Price: BNF[90]
Mycophenolate mofetil	£6.45	50 x 500 mg	Oral: 2500 mg/day	5	£0.65 / day	Schedule & dosing: REGENCY study (patients could receive 2 to 2.5 g per day)[77] Price: eMIT National[91]
Voclosporin	£1000.00	180 x 7.9 mg	Oral: 23.7 mg twice daily	6	£33.33 / day	Schedule & dosing: AURORA 1 study[45] Price: BNF[90]
Rituximab	£349.25	2 x 100 mg	IV: 1,000 mg on weeks 0, 2, 24, 26, and 52. Subsequent infusions every 6 months starting at Week 80 (assume same schedule as OBI)	5	£1746.30	Schedule & dosing: Assumed same schedule as OBI, obtained from REGENCY[77]; Dosing based on the LUNAR study Price: BNF[90]
	£873.15	1 x 500 mg		2		
Methylprednisolone	£4.77	1 x 125 mg	IV: 1 to 3 administrations of 500 to 1000 mg each. Assume average of 2 admins of 750 mg each.	6	£20.79	Schedule & dosing: REGENCY study[77] Price: eMIT National[91]
	£6.93	1 x 500 mg		1.5		

	Cost per vial/ pack	Vial size/ tablets per pack	Dosing regimen	Vials/ tablets per admin	Total cost per admin	Source (cost, regimen)
Prednisone	£1.20	150 mg	0.5 to 1.0 mg/kg/day; total daily dose ≤ 60 mg. Assume average dose of 0.75 mg/kg/day, maximum 60 mg. After week 24, 10 mg/day	5	£6.00	Schedule & dosing: REGENCY study (tapering from day 15 until week 24 is not considered, for simplicity)[77] Price: eMIT National[91]
	£1.60	400 mg		2		
Source: CS document, Section 3.5.1.1, Table 58[21] Abbreviations: BNF = British National Formulary; eMIT = electronic market information tool; g = gram; IV = intravenous; kg = kilogram; mg = milligram						

Administration cost

CS Section 3.5.1.3 provided information about the administration costs incurred for drugs administered intravenously and subcutaneously in the economic model.[3] In this section, company stated that: "In the economic model, drug administration costs are accrued for the duration of treatment. OBI, RTX and some background corticosteroids are applied intravenously." However, in the economic model, there are some inconsistencies in the application of administration costs when compared to what was being stated in the CS. Table 4.10 provides information about the different first-line treatments, their route of administration, and initial and subsequent administration costs per drug administration.

Table 4.10: Drug administration costs

Drug	Route of administration	Initial administration cost	Subsequent administration cost
Obinutuzumab	IV	£418.29	£426.15
Mycophenolate mofetil	Oral	£0	£0
Voclosporin	Oral	£0	£0
Rituximab	IV	£418.29	£426.15
Methylprednisolone	IV	£418.29	£426.15
Prednisone	Oral	£0	£0

Source: CS Section 3.5.1.3[3]
Abbreviations: CS = company submission; IV = intravenous

EAG Comment: The EAG finds the company's approach to including the administration cost of drugs in the economic evaluation appropriate. However, the information surrounding the frequency of administration of drugs is not transparent in the CS, especially for methylprednisolone and prednisone. The frequency of administration of corticosteroids were different among the various treatment regimens (intervention and comparators) in the company's base-case. However, in the CS it was stated that the dosing schedule for methylprednisolone and prednisone were sourced from the REGENCY trial and it did not specify that there were any variations in the dosing schedule of corticosteroids for different treatment regimens. Additionally, in the OBI +

MMF and RTX + MMF treatment arms, administration unit costs were included corresponding to the administration of methylprednisolone, but not OBI and RTX respectively, which deviates from the company base-case assumption.

A further issue with the administration cost in the model is that, for all drug administrations (initial and subsequent), the unit cost of administration is £426.15 in the company base-case. As such, the EAG has some concerns around implementation of administration costs in the updated company base-case.

Rescue therapy cost

The considerations and assumptions on rescue therapy in the cost-effectiveness analysis were discussed in CS Section 3.1.5.4.[3] LN patients in the company's economic model received rescue therapy or subsequent treatment after discontinuation of the first-line treatment regimen (36 months from the induction of patients into the model).[88] The proportion of patients receiving subsequent treatments in the company base-case was informed by REGENCY for OBI + MMF and MMF alone.[77] The same proportion as OBI + MMF was assumed for the other comparators as rescue or subsequent therapy. The subsequent treatments for each treatment arm were informed by the REGENCY trial for OBI + MMF and MMF.[3] However, there was not enough clarity around the evidence used to inform subsequent treatments for VOC, BEL and RTX. The total drug cost and administration costs of treatments were assumed to be the same as the first-line treatment.

For other subsequent treatments not included as first-line treatment in the model, the drug costs were calculated using list prices. All subsequent regimens follow a 36-month stopping period, except tacrolimus, which has a 12-month stopping period in the model.[88] The proportion of patients and the associated costs of subsequent treatments are given in Table 4.11. It was assumed that patients cannot continue to receive the same first-line treatment as subsequent therapy (e.g. a patient who was initially treated with OBI + MMF cannot be given OBI as a subsequent treatment).[88]

EAG comment: The EAG has some concerns around how the proportion of patients who received rescue therapy in each treatment arm as well as distribution of patients receiving different rescue treatments, were informed to be modelled in the CS. The total proportion of rescue therapy in the company base case was [redacted] in the MMF treatment arm (because some of the patients receive more than one rescue therapy), whereas the reported proportion of patients who received rescue therapy in the REGENCY trial was [redacted].[77,88] To maintain consistency across the treatment arms, EAG is of the opinion that the total proportion of patients who receive rescue therapy in the MMF arm should be [redacted]%, even though this change would have negligible effect on the ICER. Despite the assumption that all other comparator arms except the MMF arm have the same subsequent treatment proportion as the OBI arm ([redacted]), the subsequent treatment proportion for the VOC arm was [redacted] in the company economic model.[88]

The company has used rescue therapy and subsequent treatment as synonymous terms, but according to the clinical experts' opinion, it is not the same. The company had modelled rescue therapy, informed by the REGENCY trial, as subsequent treatment but the trial endpoint was not long enough to inform subsequent treatment. There was no clear evidence about the rescue therapy distributions in the treatment arms from REGENCY trial that informed the same in the CS model.

Anifrolumab is not recommended by NICE for reimbursement in the treatment of LN and clinical advice to the EAG noted that this is not a relevant treatment used in LN patients. As such, the EAG has some concerns over including anifrolumab as a relevant subsequent treatment.

Clinical advice to the EAG suggested that corticosteroids are used for longer durations to treat symptoms in LN patients. Long-term use of corticosteroids can accumulate toxicity and cause serious adverse events, which can be a severe burden on the patient in terms of costs incurred and quality of life. The EAG has some concerns on whether the effect of long-term corticosteroids use have been captured to the appropriate extent in the model.

Table 4.11: Subsequent treatment proportion and associated cost

Treatment regimen	Total costs per treatment (£)			Proportion of patients				Source
	Total drug costs	Total admin costs	Total	OBI	MMF	VOC	RTX	
ANIFROLUMAB	0.00	0.00	0	[redacted]	[redacted]	[redacted]	[redacted]	Assumed no reimbursement
BELIMUMAB			39,833	[redacted]	[redacted]	[redacted]	[redacted]	Assumed no reimbursement
CYCLOSPORIN	139.83		140	[redacted]	[redacted]	[redacted]	[redacted]	BNF Cyclosporin 100 mg x 30 capsules; assumed maximum treatment duration of 3 months (BNF Nephrotic Syndrome)[90]
CYCLOPHOSPHAMIDE	78.64	2,556.90	2,636	[redacted]	[redacted]	[redacted]	[redacted]	eMIT National cyclophosphamide 1g powder for solution for injection vials; dose per month assumed per maximum 6 months[91]
OBI			13,813	[redacted]	[redacted]	[redacted]	[redacted]	Assumed consistent with treatment duration at first line
RTX			8,191	[redacted]	[redacted]	[redacted]	[redacted]	Assumed consistent with treatment duration at first line
TACROLIMUS	2,878.17		2,878	[redacted]	[redacted]	[redacted]	[redacted]	BNF Envarsus 4 mg modified release x 30 tablets; 4mg daily for a maximum of 1 year[90]
VOC			17,294	[redacted]	[redacted]	[redacted]	[redacted]	Assumed consistent with treatment duration at first line
TOTAL				[redacted]	[redacted]	[redacted]	[redacted]	

Source: CS document, Section 3.5.1.4, Table 60[21]
Abbreviations: BNF = British National Formulary; eMIT = electronic market information tool; mg = milligram; MMF = mycophenolate mofetil; OBI = obinutuzumab; RTX = rituximab; VOC = voclosporin.

Health state unit costs and resource use

CS Section 3.5.2 discusses health care resource use and cost in the economic evaluation.[21] In the company base-case,[88] the resource use and costs inputs were informed by TA882,[22] which was sourced from the NHS reference costs and the Personal Social Service Research Unit (PSSRU).[92] The supportive care costs were assumed to be health-state dependent and consistent for all comparators. The kidney biopsy, which is the diagnostic test for LN, is one of the most expensive procedures for CKD-4 patients at £1044.53. In CKD-5 patients, costs related to dialysis and kidney transplant are the most expensive procedures. These frequencies and costs were validated by the company with clinical expert opinion. There was a one-off cost for each health state and a subsequent recurrent six-month cost for resource use. CKD-5 T had the highest one-off health state resource use cost of £39,110, while the six-month recurrent cost for CKD-5 D with £27,956 was the highest recurrent health state cost.

Table 4.12: Health-state related costs

Health state	One-off cost (£)	Recurrent cost per 6-monthly model cycle (£)
CKD Stage 1-3b AD	843.80	465.00
CKD Stage 1-3b PR	513.61	324.21
CKD Stage 1-3b CR	183.42	183.42
CKD Stage 4 AD	2,113.17	622.59
CKD Stage 4 PR	714.98	525.58
CKD Stage 4 CR	428.57	428.57
CKD Stage 5 D	32,379.84	27,955.78
CKD Stage 5 T	39,109.54	6,005.31

Source: CS Document, Section 3.5.2, Table 63
Abbreviations: AD, active disease; CKD, chronic kidney disease; CR, complete response; D, dialysis; PR, partial response; T, transplant

EAG comment: The EAG is of the opinion that the sources that informed resource use costs and frequencies are appropriate.

End-of-life costs

In the CS (Section 3.5.4.1), an end-of-life cost was incurred to all mortality in the model.[3] The company adopted the approach followed in TA882 to model the end-of-life cost.[22] This analysis captured the cost of death associated with LN (related to transition to death from CKD 5 health states) and the non-disease related cost of death (related to transitions from any other health states to death).

The cost of an LN-related death was £14,922, which included the hospital care costs associated with renal failure (sourced from PSSRU 2024) inflated to the 2025 cost-year.[88,92] Similarly, the non-disease related mortality cost was based on the cost of hospital care for any diagnosis from Table 7.2.2 of the latest PSSRU 2024 report, inflated to the 2025 cost-year using Consumer Price Index inflation indices for health, giving £14,922.[88,92]

EAG comment: The EAG find the calculation and adaptation of end-of-life costs in the company submission to be appropriate.

4.2.8 Adverse events

Patient health-related quality of life

The base-case analysis in the CS assumed that the utility estimates for each health state in the economic model captured the impact of treatment-related adverse events. Therefore, no additional differences in treatment-related adverse events were assumed in the base-case, though this scenario was explored in the sensitivity analysis.

The scenario analysis assessed adverse events as utility decrements (disutilities) outside the health state utilities implemented in the base-case model. In this scenario, adverse events are applied as a one-off occurrence during the first six months of starting therapy. Disutilities and duration of adverse events were informed by TA882, TA942 and Kim et al (2019).[22,69,93] When this data was not available, the CS assumed a 0.5 disutility with a 10-day duration.

The frequency of adverse events was informed by arm-specific treatment-related adverse events Grade 3 or above from the REGENCY trial.[3] Due to the lack of data on Grade 3 or above adverse events for comparator therapies that were not part of REGENCY, the economic model assumed MMF in combination therapies (VOC and RTX) have the same adverse events profile as the MMF alone arm in REGENCY.[3] The disutility estimates and assumed duration of the adverse events in the scenario analysis are presented in Table 4.13.

Table 4.13: Disutility and duration of adverse events in the economic model

Adverse event	Disutility	Duration (days)	Reference
Acute kidney injury	0.38	10	TA942,[93] Table 36; duration assumption
COVID-19	0.31	3.5	TA882: Table B.3-12
COVID-19 pneumonia	0.31	3.5	TA882: Table B.3-12
Gastroenteritis	0.01	8	TA882: Table B.3-12
Gastroenteritis viral	0.01	8	TA882: Table B.3-12
Hypertension	0.15	8	TA882: Table B.3-12
Infusion related reaction	0.2	3.5	TA882: Table B.3-12
Intervertebral disc disorder	0.5	10	Assumption
Large intestinal stenosis	0.006	10	Kim (2019),[69] duration assumption
Nephrotic syndrome	0.5	10	Assumption
Neutropenia	0.09	15.1	TA882: Table B.3-12
Pneumonia	0.31	3.5	TA882: Table B.3-12
Small intestinal obstruction	0.006	10	Kim (2019),[69] duration assumption
Urinary tract infection	0.2	3.5	TA882: Table B.3-12
Cholecystitis	0.2	3.5	TA882: Table B.3-12
Pain in extremity	0.5	10	TA942,[93] Table 36; duration assumption

Source: Reproduced from the company submission, Table 57[3]
Abbreviations: TA = technology appraisal

Healthcare costs and resource use

In CS Section 3.5.3, the average number of treatment emergent adverse events (any adverse events that occur after the start of a treatment up until the point of rescue) of Grade 3 and higher were included to calculate the costs incurred for the OBI and MMF arms (see Table 4.14).[3] The evidence that informed the adverse events were sourced from the REGENCY trial,[77] while all other associated costs were adopted from NHS reference costs.[94] The other comparator treatment regimens, which included MMF, were assumed to have the same adverse event profile as the MMF treatment arm.

In the company model, the lifetime cost of adverse events in a treatment arm was calculated by multiplying the average cost of that adverse event per patient week with the rate of adverse events.[88] The total cost incurred by adverse reactions for each treatment arm was applied at the beginning of Cycle 1. The adverse event-associated total costs were [redacted] and [redacted] for OBI + MMF and MMF alone treatment arms, respectively.

Table 4.14: Grade 3+ adverse events costs and frequencies

Adverse event	Cost (£)	OBI + MMF N=136	MMF N=132	Source
Acute kidney injury	670.65	[redacted]	[redacted]	NHS National Cost Collection data 2023/24; LA07L-P - Acute Kidney Injury without Interventions, weighted by CC Score - Non-Elective Inpatient - Short Stay[94]
COVID-19	654.52	[redacted]	[redacted]	NHS National Cost Collection data 2023/24; DX21A - COVID-19 Infection, 19 years and over - Non-Elective Inpatient - Short Stay[94]
COVID-19 pneumonia	742.95	[redacted]	[redacted]	NHS National Cost Collection data 2023/24; DX11A - COVID-19 Infection, with Pneumonia, 19 years and over - Non-Elective Inpatient - Short Stay[94]
Gastroenteritis	1,451.94	[redacted]	[redacted]	NICE TA882; NHS National Cost Collection data 2023/24; FD01C - Gastrointestinal Infections with Single Intervention, with CC Score 5+ - Non-Elective Inpatient - Short Stay[94], [22]
Gastroenteritis viral	1451.94	[redacted]	[redacted]	NICE TA882; NHS National Cost Collection data 2023/24; FD01C - Gastrointestinal Infections with Single Intervention, with CC Score 5+ - Non-Elective Inpatient - Short Stay[94], [22]
Hypertension	404.67	[redacted]	[redacted]	NICE TA882; NHS National Cost Collection data 2023/24; EB04Z - Hypertension - Day Case[94], [22]
Infusion related reaction	1.16	[redacted]	[redacted]	NICE TA809; infusion-related reactions determined to be allergies and treated with an antihistaminic (fexofenadine); eMIT National Database 2023/24[94]
Intervertebral disc disorder	752.11	[redacted]	[redacted]	NHS National Cost Collection data 2023/24; HC20J-M - Vertebral Column Injury without Interventions, weighted by CC score - Non-Elective Inpatient - Short Stay[94]
Large intestinal stenosis	436.65	[redacted]	[redacted]	NHS National Cost Collection data 2023/24; FD05B - Abdominal Pain without Interventions - Non-Elective Inpatient - Short Stay[94]

Adverse event	Cost (£)	OBI + MMF N=136	MMF N=132	Source
Nephrotic syndrome	196.88	[redacted]	[redacted]	NHS National Cost Collection data 2023/24; Nephrologist visits: – NHS trust and NHS foundation trusts. Total Outpatient Attendance – Service code 361[94]
Neutropenia	618.04	[redacted]	[redacted]	NICE TA882; NHS National Cost Collection data 2023/24; WJ11Z - Other Disorders of Immunity - Regular Day or Night Admissions[94], [22]
Pneumonia	1452.50	[redacted]	[redacted]	NICE TA882; NHS National Cost Collection data 2023/24; DZ11P - Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 8-12 - Day Case[94], [22]
Small intestinal obstruction	436.65	[redacted]	[redacted]	NHS National Cost Collection data 2023/24; FD05B - Abdominal Pain without Interventions - Non-Elective Inpatient - Short Stay[94]
Urinary tract infection	578.98	[redacted]	[redacted]	NHS National Cost Collection data 2023/24; LA04N-S - Kidney or Urinary Tract Infections, without Interventions, weighted by CC Score - Non-Elective Inpatient - Short Stay[94]
Cholecystitis	593.80	[redacted]	[redacted]	NHS National Cost Collection data 2023/24; FD01F-J - Gastrointestinal Infections without Interventions, with CC Score 0-1 - Non-Elective Inpatient - Short Stay[94]
Pain in extremity	0.26	[redacted]	[redacted]	eMIT National Database 2023/24; Paracetamol 500mg tablets / Packsize 16[94]

Source: CS Document, Section 3.5.3, Table 64[3]
Abbreviations: BNF = British National Formulary; CC = complication/comorbidity; COVID = coronavirus disease; eMIT = electronic market information tool; MMF = mycophenolate mofetil; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OBI = obinutuzumab; TA = technology appraisal; PSSRU = personal social services research unit.

EAG comment: The EAG is concerned about the company's approach of not including treatment-related differences of AE in patient utilities in the company's base-case, while the healthcare and resource use impact of AE differences was included. The EAG considers a more appropriate approach would be to include Grade 3+ treatment-related AEs in both patient HRQoL and healthcare resource use, as not including the impact of treatment-relate adverse events on HRQoL is likely to present a favourable scenario to the intervention.

Furthermore, the EAG is concerned about the one-off approach used to include the impact of treatment-related AEs, as no evidence was provided to justify that most adverse events resolve within the first six months of starting therapy, or whether patients remain at risk of adverse events as they continue therapy. Relevant to this is the shorter follow-up of the REGENCY data used (up to 76 weeks) compared with the stopping rule assumption of three years (157 weeks). The EAG also notes additional uncertainties around the disutility and the assumed 3.5-day duration of COVID-19 and COVID-19 pneumonia, as the sources informing these assumptions in TA882 (i.e. Kim et al 2019) do not mention COVID-19.[22,69] Since clinical advice to the EAG highlighted the role that treatment-related AEs can have on patient HRQoL, the EAG's base-case analysis included the impact of treatment-related AE disutilities using the approach from the company base-case. In addition, the EAG's base-case analysis further assumed that the impact of treatment-related adverse events in patient HRQoL and costs extends to the full duration of therapy.

5 Cost-effectiveness results

Section 5.1 summarises the company's cost-effectiveness results, Section 5.2 presents the EAG's additional work and preferred assumptions and Section 5.3 explores decision modifiers including the company's and EAG's preferred QALY weighting for severity.

5.1 Company's cost-effectiveness results

5.1.1 Company's base case

In the response to the PfCs, the company included belimumab as a comparator in the economic model.[7] Table 5.1 presents the updated pairwise cost-effectiveness results for OBI + MMF with BEL + MMF as one of the relevant comparators, using the OBI PAS price. The OBI + MMF treatment incurred an incremental cost of £[redacted] and incremental QALY of [redacted], resulting in an ICER of £[redacted]/QALY when compared to MMF.

Table 5.2 provides the company base-case deterministic results of net monetary benefit (NMB) and net health benefit (NHB) at willingness to pay thresholds of £20,000 and £30,000. OBI + MMF had NMB of £31,132 and £42,981 versus VOC + MMF and RTX + MMF, respectively.

Table 5.3 provides the full incremental analysis results of the updated cost-effectiveness analysis post-clarification provided by the company. RTX + MMF and BEL + MMF were dominated by OBI + MMF, while VOC + MMF was extendedly dominated by obinutuzumab treatment regimen. The incremental analysis of OBI + MMF vs MMF was £[redacted]/QALY.

Table 5.1: Deterministic incremental results for company base-case with pair-wise cost-effectiveness analysis post-clarification

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
OBI + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	-	-	-	-
MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VOC + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
BEL + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
RTX + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Source: CS Clarification response document[7]
Abbreviations: MMF = mycophenolate mofetil; MPDL = methyl prednisolone; NHB = net health benefit; NMB = net monetary benefit; OBI = obinutzumab; PDS = prednisolone; RTX = rituximab; VOC = voclosporin, BEL = belimumab

Table 5.2: Deterministic company base-case results for NMB and NHB post-clarification

Treatment	NMB at £20,000	NHB at £20,000	NMB at £30,000	NHB at £30,000
OBI + MMF + MPDL + PDS	-	-	-	-
MMF + MPDL + PDS	18,714	28,804	0.936	0.960
VOC + MMF + MPDL + PDS	31,353	35,658	1.568	1.189
BEL + MMF + MPDL + PDS	31,147	33,123	1.557	1.104
RTX + MMF + MPDL + PDS	42,777	50,002	2.139	1.667

Source: CS Clarification response document[7]
Abbreviations: MMF = mycophenolate mofetil; MPDL = methyl prednisolone; NHB = net health benefit; NMB = net monetary benefit; OBI = obinutzumab; PDS = prednisolone; RTX = rituximab; VOC = voclosporin, BEL = belimumab

Table 5.3: Deterministic results for company base-case with fully incremental analysis post-clarification

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]				
RTX + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
VOC + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
BEL + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
OBI + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS Clarification response document[7]
Abbreviations: MMF = mycophenolate mofetil; MPDL = methyl prednisolone; NHB = net health benefit; NMB = net monetary benefit; OBI = obinutzumab; PDS = prednisolone; RTX = rituximab; VOC = voclosporin, BEL = belimumab

EAG Comment: The EAG has verified the deterministic results with the company base-case model.[8] The incremental cost-effectiveness ratios (ICERs) of OBI treatment regimen against its comparators are lower than the NICE guidance threshold of £20,000/QALY.[95] The addition of BEL + MMF as a comparator in the post-clarification CS economic model changed the total costs of all the included treatments by a small margin.[8] As a result, the ICERs in the post-clarification cost-effectiveness model decreased compared with the original CS economic model. However, these changes showed a low degree of variation from the initial results, hence did not affect the original decision of the cost-effectiveness analysis.

5.1.2 Company's sensitivity and scenario analyses

The company conducted various sensitivity and scenario analyses on the base-case economic model. CS Section 3.11 provides information on the company base-case sensitivity and scenario analyses results.

Probabilistic sensitivity analysis (PSA)

In their response to PfCs, the company provided PSA results with 5000 iterations in the updated company base-case and these results are provided in Table 5.4, Figure 4 and Figure 5.[7] OBI + MMF had an incremental cost of £[redacted] and incremental QALY of [redacted] when compared to MMF, which resulted in an ICER of £[redacted]. It was dominant against VOC + MMF and RTX + MMF. OBI + MMF was [redacted] and [redacted] cost-effective at willingness to pay thresholds of £20,000 and £30,000, respectively.

Table 5.4: Probabilistic sensitivity analysis of 5000 iterations on the company base-case, post-clarification

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
OBI + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	-	-	-	-
MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VOC + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
BEL + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
RTX + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Source: CS Clarification response document[7]
Abbreviations: MMF = mycophenolate mofetil; MPDL = methyl prednisolone; NHB = net health benefit; NMB = net monetary benefit; OBI = obinutuzumab; PDS = prednisone; RTX = rituximab; VOC = voclosporin, BEL = belimumab

Figure 4: Cost-effectiveness plane of company base-case post-clarification

Source: Company updated economic model post-clarification[8]

Abbreviations: MMF = mycophenolate mofetil; MPDL = methyl prednisone; OBI = obinutuzumab; PDS = prednisone; QALY = quality-adjusted life year; RTX = rituximab; VOC = voclosporin; BEL = belimumab

Figure 5: Cost-effectiveness acceptability curve (CEAC) of company base-case post-clarification

Source: Company updated economic model post-clarification[8]

Abbreviations: MMF = mycophenolate mofetil; MPDL = methyl prednisone; OBI = obinutuzumab; PDS = prednisone; QALY = quality-adjusted life year; RTX = rituximab; VOC = voclosporin; BEL = belimumab

EAG Comment: The EAG re-ran the probabilistic sensitivity analysis (PSA) for the decision model submitted by the company after the points for clarification response. Our results showed that the ICER for OBI + MMF versus MMF was £[redacted]/QALY, while OBI + MFF was dominant compared to

VOC + MMF, BEL + MMF and RTX + MMF. Although the PSA ICER results reported by the company were correctly estimated, the PSA ICER results in the decision model file were based on average ICERs which is a skewed estimation of the ICER.

One-way sensitivity analysis

The univariate deterministic sensitivity analysis (USDA) results on the updated company base-case are provided in Figure 6, Figure 7, Figure 8 and Figure 9.[8] The percentage of USDA input for lower range was 10%, while for the higher range it was 90%.

EAG Comment: In OBI + MMF versus MMF, transition probabilities from CKD13bAD to CKD4AD for OBI had the highest impact on the ICER. For OBI + MMF versus VOC + MMF, variation in transition probabilities from CKD13bAD to CKD4AD for VOC had the highest impact while for OBI + MMF versus RTX + MMF variation in transition probabilities from CKD13bAD to CKD4AD for RTX had the highest impact on the incremental analysis. The company did not provide the univariate deterministic sensitivity analysis for the updated company base-case. Hence, the EAG re-ran the scenarios in the updated company base-case.

Figure 6: Tornado diagram showing OWSA results, OBI versus MMF – NMB at WTP threshold of £30,000 – OBI PAS price, post-clarification

Source: Company economic model post-clarification[8]
Abbreviations: MMF = mycophenolate mofetil; MPDL = methyl prednisone; OBI = obinutuzumab; PDS = prednisone; QALY = quality-adjusted life year; RTX = rituximab; VOC = voclosporin; BEL = belimumab; CKD = chronic kidney disease

Figure 7: Tornado diagram showing OWSA results, OBI versus VOC – NMB at WTP threshold of £30,000 – OBI PAS price, post-clarification

Source: Company economic model post-clarification[8]
Abbreviations: MMF = mycophenolate mofetil; MPDL = methyl prednisone; OBI = obinutuzumab; PDS = prednisone; QALY = quality-adjusted life year; RTX = rituximab; VOC = voclosporin; BEL = belimumab; CKD = chronic kidney disease

Figure 8: Tornado diagram showing OWSA results, OBI versus BEL – NMB at WTP threshold of £30,000 – OBI PAS price, post-clarification

Source: Company economic model post-clarification

Abbreviations: Abbreviations: MMF = mycophenolate mofetil; MPDL = methyl prednisone; OBI = obinutuzumab; PDS = prednisone; QALY = quality-adjusted life year; RTX = rituximab; VOC = voclosporin

Figure 9: Tornado diagram showing OWSA results, OBI versus RTX– NMB at WTP threshold of £30,000 – OBI PAS price, post-clarification

Source: Company economic model post-clarification[8]
Abbreviations: MMF = mycophenolate mofetil; MPDL = methyl prednisone; OBI = obinutuzumab; PDS = prednisone; QALY = quality-adjusted life year; RTX = rituximab; VOC = voclosporin; BEL = belimumab; CKD = chronic kidney disease

Scenario analyses

The company undertook several scenario analyses on the original base-case model.[3] The scenarios were modelled as a VBA-coded run, which could only be executed together. In their responses to the PfCs, the company did not provide the scenario analysis results on the updated company base-case. To provide clarity on some of the questions in the PfCs, the company provided additional scenarios. All scenarios after the PfC update are presented in Table 5.5 and Table 5.6.[7]

EAG comment: In the PfCs, the EAG requested that the company add an additional parameter sheet in the model, which enables the user to manually change the scenarios in the model, for improved transparency. In their response, the company corrected the error in their original model while calculating the scenario results for treatment effect equivalence. They also added another scenario of cost comparison analysis where the QALYs become equal between OBI + MMF, VOC + MMF, BEL + MMF and RTX + MMF. OBI + MMF remain cost-effective in these scenarios.[7] The company provided additional scenario analysis on treatment time-points, time to treatment discontinuation, use of median CRR odds ratio in calculating transition probabilities and deriving CRR probabilities using the exponential method. The additional scenario analysis did not exhibit a significant degree of variation from the updated company base-case results. The company did not provide an updated scenario analysis result for the updated company base-case that included BEL + MMF.

Even though the post-clarification company economic model had a 'Parameters' sheet, it did not include the functionality required to enable the user to change the settings manually. This could have been useful for checking individual scenarios manually and improve the transparency of the economic evaluation. The EAG conducted the scenario run on the updated company model and have requested the results from the company to verify the EAG produced results.

Table 5.5: Scenario analysis on updated company base-case post-clarification

		ICER			
Base case assumption	**Scenario**	**vs MMF**	**vs VOC**	**vs RTX**	**vs BEL**
Base case		**1454**	**Dominant**	**Dominant**	**Dominant**
Treatment duration – 6 cycles	12	3822	Dominant	Dominant	Dominant
	18	5173	Dominant	Dominant	Dominant
Response transitions – ITC	REGENCY	3557	Dominant	Dominant	Dominant
Loss of response transitions – by treatment	Pooled	2122	Dominant	Dominant	Dominant
Loss of response transitions (other comparators) – Equal to OBI+MMF	Midpoint of OBI+MMF and MMF	1454	Dominant	Dominant	Dominant
	Equal to MMF	1454	Dominant	Dominant	Dominant
Impact of renal flares – applied to transition to CKD Stage 4	No	12,097	SW 2,100,748	Dominant	Dominant
	Response to active disease	5758	Dominant	Dominant	Dominant
	Active disease and CKD stage 4	87	Dominant	Dominant	Dominant
Duration of effect wanes to MMF transition probabilities	OBI+MMF effect is maintained over time	Dominant	Dominant	Dominant	Dominant
	VOC+MMF effect is maintained over time	1454	SW 16,952	Dominant	Dominant
	RTX+MMF effect is maintained over time	1454	Dominant	SW 339,188	Dominant
	BEL+MMF effect is	1454	Dominant	Dominant	SW 8625

		ICER			
Base case assumption	**Scenario**	**vs MMF**	**vs VOC**	**vs RTX**	**vs BEL**
	maintained over time				
Utility source – TA882 EAG approach	REGENCY - Mixed Model - per treatment arm	1537	Dominant	Dominant	Dominant
	REGENCY - Mixed Model - pooled	1557	Dominant	Dominant	Dominant
	NICE TA882 - company submitted	1405	Dominant	Dominant	Dominant
AE disutility – FALSE	TRUE	1452	Dominant	Dominant	Dominant
Exclude COVID AEs – FALSE	TRUE	1402	Dominant	Dominant	Dominant
Include oral administration cost – FALSE	TRUE	1454	Dominant	Dominant	Dominant
REGENCY subsequent treatment proportions	Multiplier: x 2	128	Dominant	Dominant	Dominant
	Multiplier: x 3	Dominant	Dominant	Dominant	Dominant
Time horizon – 70 years	60	1379	Dominant	Dominant	Dominant
	80	1468	Dominant	Dominant	Dominant
Discount rate costs – 3.5%	0	2167	Dominant	Dominant	Dominant
	0.015	1305	Dominant	Dominant	Dominant
Discount rate outcomes – 3.5%	0	669	Dominant	Dominant	Dominant
	0.015	965	Dominant	Dominant	Dominant

Source: Company clarification response[7]
Abbreviations: AE = adverse event; BEL = belimumab; CKD = chronic kidney disease; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; OBI = obinutuzumab; RTX = rituximab; TA = technology appraisal; VOC = voclosporin

Table 5.6: Additional scenario analysis provided by the company post-clarification

		ICER			
Base case assumption	**Scenario**	**versus MMF**	**versus VOC + MMF**	**versus BEL + MMF**	**versus RTX + MMF**
Base case		**1454**	**Dominant**	**Dominant**	**Dominant**
Treatment effectiveness – no equivalence	Transitions assumed equivalent to OBI	1452	Dominant	Dominant	Dominant
	Transitions and treatment waning assumed equivalent to OBI	1452	Dominant	Dominant	Dominant
OBI time to discontinuation – 3 years	Probabilities from REGENCY applied to OBI arm only	826	Dominant	Dominant	Dominant
	Probabilities from REGENCY applied to all add-on treatments	880	Dominant	Dominant	Dominant
CRR odds ratio estimates - mean	Median	1649	Dominant	Dominant	Dominant
ITC time-point (3 years)	1.5 years	201	Dominant	Dominant	Dominant
CRR transition – Weibull function	Exponential function	1593	Dominant	Dominant	Dominant
CRR transition – Weibull function; time-point 3 years	Exponential function, 1.5 years	Dominant	Dominant	Dominant	Dominant

Source: Company clarification response[7]
Abbreviations: CRR = complete renal response; ITC = indirect treatment comparison; OBI = obinutuzumab; MMF = mycophenolate mofetil; RTX = rituximab; VOC = voclosporin

5.2 EAG's additional analyses

5.2.1 Model validation and face validity check

Errors: In the response to PfC questions B1 and B17, the company highlighted correcting two errors and included BEL as a comparator.[7]

The following errors were corrected by the EAG and based on the executable decision model submitted after the company response to the PfCs.[7]

- There was an error in the sheet "Transition matrices" (cell AF110) for the transition probability of RTX from AD to CKD 4 being 3% rather than 3.05%, which was corrected to align with the submission documents.

- The unit cost of IV administration was £426.15 throughout the model cycles, whereas the initial cost of administration was £418.29 (see Section 4.2.7). In the sheet "Treatment Costs", columns BG, CW, EX, GY and IZ (rows 222 to 5465), the formula for input of administration cost was changed so that initial IV administration cost became £418.29.

- The dose of methylprednisolone in the sheet "Treatment Costs" (cell HZ224) was changed from 100 to 1000. The EAG is of the opinion that this was an error, since the weekly dose of methylprednisolone would not be as low as 100 mg. As such, this was changed to a 1000 mg dose, similar to other cycles in the treatment arm.

- The percentage of rescue therapy for MMF alone in the sheet "Rescue Therapy" (cell H34; [redacted]) did not correspond to the value of total proportion of patients reported in the REGENCY trial ([redacted]). The EAG is of the opinion that the total proportion of patients receiving rescue therapy should be [redacted] in the MMF arm, to maintain consistency in assumption across the different treatment arms (refer section 4.2.7)The EAG has reweighted treatment distribution values in the company

base-case to align with the rescue therapy rates in the submission documents.

Table 5.7: Treatment distribution of rescue therapy used on the company base-case normalised to 100%

Treatment regimen	OBI + MMF + MPDL + PDS	MMF + MPDL + PDS	VOC + MMF + MPDL + PDS	BEL_IV + MMF + MPDL + PDS	RTX + MMF + MPDL + PDS
Anifrolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Belimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cyclosporin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obinutuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rituximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tacrolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Voclosporin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Produced by the EAG based on the executable model file
*Values in bold shows that patients were not allowed to receive their 1st line therapy as a 2nd line therapy.
Abbreviations: BEL = belimumab; EAG = External Assessment Group; IV = intravenous; MMF = mycophenolate mofetil; MPDL = methylprednisolone; OBI = obinutuzumab; PDS = prednisone; RTX = rituximab; VOC = voclosporin

Matters of judgement

1. Challenges validating parameters informing deterministic and probabilistic analyses: The EAG requested in the PfCs (question B2) for the company to include a "Parameters" sheet in the decision model reporting the parameter estimates used in the model for the deterministic analysis, the parameters and distributions used for the probabilistic analysis, and the intervals used for the sensitivity analyses.[7] The EAG considers that the company only partially complied with this request, as many of the parameters reported in the "Parameters" sheet were not linked to the Markov trace in the model. As a result, it was difficult for the EAG to validate the parametric assumptions going into the probabilistic analysis and ensure that any parametric assumptions implemented in the EAG's base-case were reflected in the probabilistic and one-way sensitivity analyses.

2. The methods used to include NMA estimates as model inputs for CRR and PRR: As reported in Section 4.2.5, it was unclear to the EAG why there were small variations between the NMA parameters reported in the submission documents and those used in the economic model, as well as the distributions used to sample parameters from the NMA and the HRs used for renal flares, as these were not presented in the "Parameters" sheet. The EAG has explored using the estimates from the NMA directly in the company model. The EAG has also attempted to validate the calculations used to extrapolate ITC values into six-month model cycles and was unable to replicate the estimates used in the company base-case.

3. Dosage and administration of concomitant therapies: In the scenario of equivalent effectiveness, it was noted there were noticeable differences in treatment administration costs, likely related to concomitant therapies given in combination with MMF. This may not be an issue with the executable file of the decision model, but rather an issue of transparency in reporting the assumptions used to model the delivery of concomitant therapy. Assumed differences in concomitant treatment doses and number of deliveries between the comparators were not presented in the CS, and it was challenging to extract this information from the model file. Preferred assumptions used in the EAG base-case are presented in Section 5.2.3.

5.2.2 EAG's exploratory analyses using company's base case

Table 5.8 presents a list of the EAG's exploratory analyses using the company's base-case model, including justifications for these assumptions.

Results are presented separately using pairwise comparisons of OBI + MMF versus, MMF alone, VOC + MMF, belimumab + MMF and RTX + MMF, respectively. Table 5.9 showed that compared to MMF, the assumptions with the largest impact related to removing the hazard ratio of time to renal flare and changing the costs of concomitant treatment delivery. Table 5.10 showed that, compared to VOC + MMF, the assumption with the largest impact was removing the HR of time to renal flare. Table 5.11 and Table 5.12 showed that

OBI remained the dominant intervention compared to BEL + MMF and RTX + MMF across all exploratory analyses.

Table 5.8: List of EAG's exploratory analyses using the company's base case

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
0	Company decision model submitted with the points for clarifications response	Company decision model with corrections to errors found by the EAG	Several minor errors were spotted in the company's executable model file	Section 5.2.1
1	Hazard ratio of time to renal flare applied to the probability of progressing from active disease to CKD stage 4. Data from REGENCY applied to obinutuzumab, ITC results from AURORA-2 and BLISS-LN applied to voclosporin and belimumab.	Removing the hazard ratios of time to renal flare from the probability of progressing from active disease to CKD stage 4. Instead assume that improvements in response lead to a reduction of patients at risk of CKD stage 4.	The EAG considers the model structure accounts for improvements in renal response leading to lower kidney disease progression. The approach of estimating differences in kidney disease progression based on the hazard ratio of time-to-renal flare was considered too strong an assumption given the evidence base supporting it.	Section 4.2.5
2	CRR and PRR timepoints	CRR and PRR	Better alignment	Section 4.2.5

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
	from the NMA assumed to correspond to 3 years of treatment. Weibull function used to transform probabilities to 6-month cycles.	timepoints from the NMA assumed to correspond to 1.5 years of treatment. Exponential function used to transform probabilities to 6-month cycles.	with the follow-up of the key clinical studies used in the NMA.	
3	Treatment effect duration, and waning after 3 years: OBI: 1 year, 1 year VOC: 0, 6 months BEL: 6 months, 6 months RTX: 6 months, 6 months	No treatment waning, treatment effect duration after 3 years: OBI: 1 year VOC: 0 BEL: 6 months RTX: 6 months	Assumptions of treatment effect duration and waning after 3 years were considered highly speculative given the absence of trial data beyond 2 years of treatment.	Section 4.2.5
4	Assumption of vial sharing for IV delivery	No vial sharing assumed for IV delivery	Better alignment with NICE methods guidance.	Section 4.2.7
5	Baseline patient HRQoL estimates include the impact of adverse events. Cumulative impact of adverse events on costs applied in the first 6-month cycle	Cumulative impacts of treatment-related adverse events applied to patient HRQoL and costs. Impact of adverse events applied for the 3-year	Differences in treatment-related adverse events were highlighted as one of the primary concerns to patients.	Section 4.2.8

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
		duration of treatment		
6	CRR and PRR timepoints from the NMA assumed to correspond to 3 years. Weibull function used to transform probabilities. Estimates from company calculations.	CRR and PRR timepoints from the NMA assumed to correspond to 1.5 years. Exponential function used to transform probabilities. Estimates from EAG's own calculations	CRR and PRR estimates in the economic model showed small differences to the values reported from the NMA results in the submission documents. The EAG presented our own estimations of treatment effect based on values from the submission.	Section 5.2.1
7	Treatment distribution for rescue therapy in the company base-case included treatment not reimbursed in the NHS	Alternative treatment distribution for rescue therapy based on the MMF arm of REGENCY and therapies reimbursed in the NHS	The alternative proposed approach to the rescue therapy costs has a better alignment with the care delivered for LN in the English NHS	Section 4.2.7
8	Treatment drug and delivery costs for interventions and concomitant therapies based on the executable model	Treatment drug and delivery costs for interventions and concomitant therapies based on EAG assumptions	Assumptions around doses, deliveries, and concomitant treatment costs were not clearly laid out in the company	Section 4.2.7

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
	submitted by the company	informed by REGENCY, TA882, and BLISS-LN	submission. The EAG has attempted to replicate these costs based on the available literature.	

Abbreviations: BEL = belimumab; CKD = chronic kidney disease; CRR = complete renal response; EAG = External Assessment Group; HRQoL = health-related quality of life; ITC = indirect treatment comparison; IV = intravenous; LN = lupus nephritis; MMF = mycophenelate mofetil; NHS = National Health Service; NMA = network meta-analysis; OBI = obinutuzumab; PRR = partial renal response; RTX = rituximab; TA = technology appraisal; VOC = voclosporin

Table 5.9: Deterministic results of EAG's exploratory analyses using company's base case – versus MMF alone

Exploratory analysis number	MMF alone		
	Incremental costs (£)	Incremental QALYs	ICER £/QALY
-	[redacted]	[redacted]	£1,454
0	[redacted]	[redacted]	£5,096
1	[redacted]	[redacted]	£19,669
2	[redacted]	[redacted]	£2,434
3	[redacted]	[redacted]	£6,353
4	[redacted]	[redacted]	£5,084
5	[redacted]	[redacted]	£5,703
6	[redacted]	[redacted]	£4,006
7	[redacted]	[redacted]	£1,884
8	[redacted]	[redacted]	£7,582
EAG's base-case	[redacted]	[redacted]	£23,943

Abbreviations: EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; QALY = quality-adjusted life year

Table 5.10: Deterministic results of EAG's exploratory analyses using company's base case – versus VOC + MMF

Exploratory analysis number	Voclosporin + MMF		
	Incremental costs (£)	Incremental QALYs	ICER £/QALY
-	[redacted]	[redacted]	*Dominant
0	[redacted]	[redacted]	*Dominant
1	[redacted]	[redacted]	**£1,819,600

Exploratory analysis number	Voclosporin + MMF		
	Incremental costs (£)	Incremental QALYs	ICER £/QALY
2	[redacted]	[redacted]	*Dominant
3	[redacted]	[redacted]	*Dominant
4	[redacted]	[redacted]	*Dominant
5	[redacted]	[redacted]	*Dominant
6	[redacted]	[redacted]	*Dominant
7	[redacted]	[redacted]	*Dominant
8	[redacted]	[redacted]	*Dominant
EAG's base-case	[redacted]	[redacted]	**£705,549

*Obinutuzumab dominant (more effective and less costly)
**ICER for voclosporin vs obinutuzumab is above the £20,000/QALY threshold
Abbreviations: EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; QALY = quality-adjusted life year; VOC = voclosporin

Table 5.11: Deterministic results of EAG's exploratory analyses using company's base case – versus BEL + MMF

Exploratory analysis number	Belimumab + MMF		
	Incremental costs (£)	Incremental QALYs	ICER £/QALY
-	[redacted]	[redacted]	*Dominant
0	[redacted]	[redacted]	*Dominant
1	[redacted]	[redacted]	*Dominant
2	[redacted]	[redacted]	*Dominant
3	[redacted]	[redacted]	*Dominant
4	[redacted]	[redacted]	*Dominant
5	[redacted]	[redacted]	*Dominant
6	[redacted]	[redacted]	*Dominant
7	[redacted]	[redacted]	*Dominant
8	[redacted]	[redacted]	*Dominant
EAG's base-case	[redacted]	[redacted]	*Dominant

*Obinutuzumab dominant (more effective and less costly)
Abbreviations: BEL = belimumab; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; QALY = quality-adjusted life year

Table 5.12: Deterministic results of EAG's exploratory analyses using company's base case – versus RTX + MMF

Exploratory analysis number	Rituximab + MMF		
	Incremental costs (£)	Incremental QALYs	ICER £/QALY
-	[redacted]	[redacted]	*Dominant
0	[redacted]	[redacted]	*Dominant
1	[redacted]	[redacted]	*Dominant

Exploratory analysis number	Rituximab + MMF		
	Incremental costs (£)	Incremental QALYs	ICER £/QALY
2	[redacted]	[redacted]	*Dominant
3	[redacted]	[redacted]	*Dominant
4	[redacted]	[redacted]	*Dominant
5	[redacted]	[redacted]	*Dominant
6	[redacted]	[redacted]	*Dominant
7	[redacted]	[redacted]	*Dominant
8	[redacted]	[redacted]	*Dominant
EAG's base-case	[redacted]	[redacted]	*Dominant

*Obinutuzumab dominant (more effective and less costly)
Abbreviations: EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; QALY = quality-adjusted life year; RTX = rituximab

5.2.3 EAG's preferred assumptions

The following section presents the EAG's base-case analysis based on the executable model filed submitted by the company in response to the PfCs.[7]

1. Removing the HR of time-to-renal flare from the probability of transitioning from active disease to CKD stage 4: The EAG acknowledges the lack of long-term data regarding transitions to advanced kidney disease from clinical trials of LN and, therefore, the need to rely on expert opinion. Most of the expert opinion submitted and clinical advice received by the EAG acknowledges the role that preventing renal flares has on reducing progression to advanced kidney disease. The EAG considers that the current model structure reflects this relationship, where only patients with AD are at risk of progressing to CKD stage 4 and, thus, improvements in renal response (particularly complete response), mean that fewer patients are at risk of kidney disease progression.

This approach indirectly assumes that improvements in response are likely to lead to reductions on renal flares and, hence, reduce kidney disease progression. As this might be a conservative assumption, the EAG considers that the ideal approach is to have additional health states in the model for the first renal flare (and, if data is available, subsequent flares), which captures their short-term impact on patients. This approach would also require

comparative data on renal flares for the comparator interventions (particularly VOC, BEL and RTX).

The EAG considers the approach used by the company to obtain comparative evidence on time to renal flares was based on a surrogate outcome; not transparently presented; relied on data from heterogenous populations; and failed to establish effectiveness differences between OBI, VOC and BEL. The EAG considers this to be a key issue and has described a critique surrounding the approach taken by the company to model the transition to CKD 4 in Section 4.2.5.

Considering the uncertainty in the evidence base and the large impact this assumption has on cost-effectiveness, the EAG removed this assumption from its base-case and explored a scenario using the estimated HR of OBI (compared to MMF alone) in REGENCY across all the combination therapies in the risk of progressing to CKD stage 4.

2. Follow-up timepoints from the NMA for CRR and PRR assumed to be 76 weeks (18 months): Although current guidelines recommend a duration of therapy close to three years, the clinical studies informing the NMA had respective follow-up timepoints of: 52 weeks for AURORA-1; 104 weeks for BLISS-LN; and 76 weeks for REGENCY.[3,44,45] The EAG considers that 76 weeks matches the follow-up data from REGENCY and, therefore, allows for a more appropriate representation of the evidence submitted.

In addition, the EAG has adopted the approach presented Gidwani and Russell (2020),[81] using probability-rate conversions with the exponential function to transform probabilities to the six-month cycle in the decision model. On one hand, the EAG recognises the limitations of this approach, as its use in models with more than two health state transitions leads to less accurate extrapolations. Nonetheless, it was unclear to the EAG how the company's approach using a Weibull function to transform rates to probabilities improved the accuracy of extrapolations within the model.

3. No treatment waning: Given the shorter duration in follow-up from clinical trials relative to the expected three-year treatment duration of therapy as

described above, assumptions around treatment effectiveness beyond the three-year stopping rule remain highly speculative until data with longer follow-up becomes available. The EAG has taken a more conservative assumption of removing the treatment waning assumption and (based on clinical expert opinion from the company and sought by the EAG around the mechanisms of action of each intervention compared), has kept the assumption of differences in treatment effect duration after three years. This assumes that after stopping treatment the decision model assumes the effectiveness of OBI is maintained for a further two cycles (one year), and the effectiveness of BEL and RTX is maintained for one cycle (six months).

4. No vial sharing: To align the decision model with the latest costing methodology, the EAG removed the assumption of vial sharing from the company's base-case.

5. Treatment-related adverse events disutilities and costs included for the duration of therapy: As the impact of treatment-related adverse events is one of the biggest concerns to patients, based on clinical advice sought by the EAG, the EAG has included the impact of disutilites on patient HRQoL using the information available in the decision model. It was unclear to the EAG whether some of the adverse events tended to be one-off occurrences or whether patients continue to be at risk of further occurrences during the three-year duration of therapy.

The EAG still has outstanding concerns regarding the company's approach to include treatment-related adverse events. First, it was unclear which events are likely to reoccur over the duration of treatment; moreover, most events such as acute kidney injury and COVID-19 pneumonia were assumed to resolve in less than two weeks. Second, there was little evidence of the impact of COVID-19-related adverse events on reducing patient utility values from the literature presented in the CS.

6. Effectiveness estimates of CRR and PRR based on NMA reported results: The EAG note minor discrepancies between the NMA results reported in the CS and the values used in the decision model. Moreover, the

EAG attempted to validate the calculations transforming OR into six-month probabilities in the company's executable model but was unable to generate the same results. For these reasons, the EAG has added an additional sheet in the economic model presenting our approach to calculating the effectiveness estimates in the economic model, based on the mean values reported in the NMA results, and has used these values for the EAG's base-case analysis.

7. Treatment distribution of rescue therapy costs based on the placebo arm of REGENCY: After consultation with clinical experts, the EAG has removed anifrolumab from distribution of rescue therapy treatment regimens. Furthermore, BEL and OBI have also been removed, as BEL and OBI do not have an indication for use as rescue therapy, despite their off-label use (i.e. the EAG are assuming they are only used as first-line therapy). As the treatment distribution of MMF alone informed by REGENCY had a better resemblance to clinical practice in England, the same distribution was used for VOC, BEL and RTX. Furthermore, it was assumed that patients receiving therapies that are not reimbursed would receive cyclosphosphamide instead; the treatment distribution is presented in Table 5.13. Assumptions surrounding the probabilities of rescue therapy by treatment arm in the company submission were maintained in the EAG's base-case.

Table 5.13: Treatment distribution of rescue therapy used on the company base-case

Treatment regimen	OBI + MMF + MPDL + PDS	MMF + MPDL + PDS	VOC + MMF + MPDL + PDS	BEL_IV + MMF + MPDL + PDS	RTX + MMF + MPDL + PDS
Anifrolumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BEL*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cyclosporin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OBI*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tacrolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment regimen	OBI + MMF + MPDL + PDS	MMF + MPDL + PDS	VOC + MMF + MPDL + PDS	BEL_IV + MMF + MPDL + PDS	RTX + MMF + MPDL + PDS
Source: Produced by the EAG based on the executable model file *Currently not being reimbursed in the English NHS for lupus nephritis Abbreviations: BEL = belimumab; EAG = External Assessment Group; IV = intravenous; MMF = mycophenolate mofetil; MPDL = methylprednisolone; OBI = obinutuzumab; PDS = prednisone; RTX = rituximab; VOC = voclosporin					

8. Concomitant treatment dosing and delivery assumptions based on REGENCY, TA882 and BLISS-LN: The EAG are concerned that assumptions of dosing and delivery around MMF and concomitant treatment delivered alongside MMF (methylprednisolone and prednisone) were not transparently reported in the CS and this information was difficult to extract from the executable decision model. As a validation exercise, the EAG has created the additional sheet in the decision model "EAG Tx costs", the treatment delivery assumptions used in the EAG base-case are reported in Table 5.14. Assumptions surrounding MMF, methylprednisolone, and prednisone were applied consistently across the comparator arms.

Table 5.14: Treatment delivery assumptions in the EAG base-case

Intervention	Delivery method	Induction	Body weight (kg)*	Source
OBI	IV	1000 mg. 4 doses given in the first 6 months (including an induction dose), then 1 dose every 6 months.		REGENCY
VOC	Pills	47.4 mg/day.		TA882[22]
RTX	IV	Assumed same as OBI		Assumption
BEL	IV	10 mg/kg. 3 doses given in the first month (including induction dose),	[redacted]	BLISS-LN[44]

Intervention	Delivery method	Induction	Body weight (kg)*	Source
		then one dose every 28 days.		
MMF	Pills	1500 mg/day titration to week 4 to 2000 mg/day (assumed 1750 mg/day) then 2000 mg/day thereafter.		REGENCY
Methylprednisolone	IV	80 mg. 4 doses given in the first 6 months (including an induction dose), then 1 dose every 6 months. Delivered until dose 6 of OBI		REGENCY
Prednisone	Pills	0.75 mg/kg/day.	[redacted]	REGENCY

Source: Produced by the EAG
*Based on baseline patient characteristics from REGENCY
Abbreviations: BEL = belimumab; EAG = External Assessment Group; IV = intravenous; kg = kilogram; mg = milligram; MMF = mycophenolate mofetil; OBI = obinutuzumab; RTX = rituximab; TA = Technology Appraisal; VOC = voclosporin

EAG's base-case analysis results

The following section presents the deterministic and probabilistic results for the EAG's proposed base-case analysis. Table 5.15 reports the deterministic results and Table 5.16 reports the probabilistic results based on pairwise comparisons between obinutuzumab and each comparator. Caveats about the probabilistic analysis presented in Section 5.2.1 still apply.

- Deterministic results showed that OBI + MMF compared to MMF alone was more costly and more effective, increasing costs by [redacted] and QALYs by [redacted] for a total ICER of £23,943/QALY, above NICE's cost-effectiveness threshold of £20,000/QALY. Probabilistic results showed that OBI increased QALYs by [redacted] and increased costs by [redacted], leading to a probabilistic ICER of £43,430/QALY.

- Deterministic results showed that OBI + MMF compared to VOC + MMF was less costly and less effective, decreasing costs by [redacted] and decreasing QALYs by [redacted]. Based on these results, VOC + MMF had an ICER of £705,549/QALY, above NICE's cost-effectiveness threshold of £20,000/QALY. Probabilistic results showed that OBI + MMF decreased QALYs by [redacted] and decreased costs by [redacted], leading to a probabilistic ICER of £919,282/QALY.

- Deterministic results showed that OBI + MMF compared to BEL + MMF was less costly and more effective, decreasing costs by [redacted] and increasing QALYs by [redacted]. Probabilistic results showed that OBI + MMF increased QALYs by [redacted] and decreased costs by [redacted].

- Deterministic results showed that OBI + MMF compared to RTX + MMF was less costly and more effective, decreasing costs by [redacted] and increasing QALYs by [redacted]. Probabilistic results showed that OBI + MMF increased QALYs by [redacted] and decreased costs by [redacted].

Further results presenting a fully incremental comparison based on the deterministic EAG base-case results, reported in Table 5.17, showed that OBI + MMF extendedly dominated RTX + MMF and BEL + MMF compared to MMF alone, with an ICER of £23,943/QALY compared to MMF alone; furthermore, VOC + MMF was more costly and effective than OBI + MMF, with and ICER of £705,549/QALY, with both ICERs above NICE's willingness to pay threshold of £20,000.

Table 5.15: Deterministic results using EAG's preferred model assumptions

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
OBI + MMF	[redacted]	[redacted]	[redacted]				

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
MMF alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,943
VOC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*£705,549
BEL + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	OBI dominant
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	OBI dominant

Source: CS Clarification response document[7]
*OBI + MMF is less costly and less effective, the ICER reported is for VOC + MMF (vs obinutuzumab + MMF)
Abbreviations: MMF = mycophenolate mofetil; MPDL = methyl prednisolone; NHB = net health benefit; NMB = net monetary benefit; OBI = obinutuzumab; PDS = prednisolone; RTX = rituximab; VOC = voclosporin, BEL = belimumab

Table 5.16: Probabilistic results using EAG's preferred model assumptions

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
OBI + MMF	[redacted]	[redacted]	[redacted]				
MMF alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,430
VOC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*£919,282
BEL + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	OBI dominant
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	OBI dominant

Source: CS Clarification response document[7]
*OBI + MMF is less costly and less effective, the ICER reported is for VOC + MMF (vs OBI + MMF)
Abbreviations: MMF = mycophenolate mofetil; MPDL = methylprednisolone; NHB = net health benefit; NMB = net monetary benefit; OBI = obinutuzumab; PDS = prednisolone; RTX = rituximab; VOC = voclosporin; BEL = belimumab

Table 5.17: Deterministic incremental comparison

Treatment	Total		Incremental		Incremental ICER (£/QALY)	Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs		
MMF alone	[redacted]	[redacted]	[redacted]	[redacted]		

Treatment	Total		Incremental		Incremental ICER (£/QALY)	Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs		
RTX + MMF	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	
BEL + MMF	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	
OBI + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£23,943	£23,943
VOC + MMF	[redacted]	[redacted]	[redacted]	[redacted]	£705,549	£66,480

Source: Produced by the EAG
Abbreviations: MMF = mycophenolate mofetil; MPDL = methylprednisolone; NHB = net health benefit; NMB = net monetary benefit; OBI = obinutzumab; PDS = prednisolone; RTX = rituximab; VOC = voclosporin; BEL = belimumab

5.2.4 Scenario analyses using EAG's preferred assumptions

The following section reports on the additional scenarios conducted by the EAG on the EAG's base-case model. Table 5.18 presents the EAG's base-case assumptions and the 10 additional scenarios testing additional assumptions. Results were primarily deterministic and are based on pairwise comparisons between OBI + MMF versus, MMF alone, VOC + MMF, belimumab + MMF, and RTX + MMF, respectively.

Compared to MMF alone, the scenarios that had the biggest impact were extending the stopping rule to five years (OBI less cost-effective), assuming no treatment duration after stopping treatment at three years (OBI less cost-effective), and including the HR of time to renal flare (OBI more cost-effective); results are reported in Table 5.19.

Compared to VOC, the scenarios that had the biggest impact were assuming no treatment duration after stopping treatment at three years (OBI less cost-effective), including the hazard ratio of time to renal flare (OBI dominant), and including a risk of progression at PRR (OBI more cost-effective); results are reported in Table 5.20.

Compared to BEL and RTX, OBI was the dominant intervention across all scenarios, results are reported in Table 5.21 and Table 5.22, respectively.

Table 5.18: Summary of EAG's scenario analyses using EAG's preferred assumptions

-	EAG's base-case assumption	EAG's scenario
1	3-year stopping rule for all treatments	4-year stopping rule
2	3-year stopping rule for all treatments	5-year stopping rule
3	No risk of progression from PRR to CKD stage 4.	Risk progression from PRR to CKD stage 4 is non-zero, but half the risk or progression from AD to CKD 4.
4	Treatment effect duration after 3 years	No treatment effect duration after 3 years
5	Excluding the impact of the hazard ratio of time to renal flare from REGENCY on the risk of progression to CKD 4	Hazard ratio of time to renal flare from REGENCY on the risk of progression to CKD 4 included, assumed equal for obinutuzumab, voclosporin, belimumab, and rituximab.
6	Differences in patient HRQoL based on CRR, PRR, or AD	No differences in patient HRQoL based on CRR, PRR, or AD. Mean patient HRQoL estimated from REGENCY.
7	NMA estimates for CRR and PRR for obinutuzumab and MMF alone	MSM estimates for CRR and PRR for obinutuzumab and MMF alone from REGENCY.
8	Transition probabilities for CRR, PRR and AD stratified by treatment arm in REGENCY	Transition probabilities for CRR, PRR and AD pooled across treatment arms in REGENCY
9	Different rescue therapy costs	Equivalent rescue therapy costs across treatment arms
10	Treatment-related adverse event costs applied for the treatment duration	Treatment-related adverse event costs applied only in the first cycle

Abbreviations: AD = active disease; CKD = chronic kidney disease; CRR = complete renal response; EAG = External Assessment Group; HRQoL = health-related quality of life; NMA = network meta-analysis; MMF = mycophenolate mofetil; PRR = partial renal response

Table 5.19: Deterministic results of EAG's scenario analyses using EAG's preferred assumptions – versus MMF alone

Scenario analysis number	MMF alone		
	Incremental costs (£)	Incremental QALYs	ICER £/QALY
-	[redacted]	[redacted]	**23,943**
1	[redacted]	[redacted]	26,786
2	[redacted]	[redacted]	28,946
3	[redacted]	[redacted]	23,898
4	[redacted]	[redacted]	30,082
5	[redacted]	[redacted]	6209
6	[redacted]	[redacted]	26,520
7	[redacted]	[redacted]	23,943
8	[redacted]	[redacted]	23,943
9	[redacted]	[redacted]	26,416
10	[redacted]	[redacted]	22,623

Abbreviations: EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; QALY = quality-adjusted life year

Table 5.20: Deterministic results of EAG's scenario analyses using EAG's preferred assumptions – versus VOC + MMF

Scenario analysis number	Voclosporin + MMF		
	Incremental costs (£)	Incremental QALYs	ICER £/QALY
-	[redacted]	[redacted]	**705,549***
1	[redacted]	[redacted]	557,333*
2	[redacted]	[redacted]	514,283*
3	[redacted]	[redacted]	1,222,825*
4	[redacted]	[redacted]	189,789*
5	[redacted]	[redacted]	OBI dominant
6	[redacted]	[redacted]	796,173*
7	[redacted]	[redacted]	705,549*
8	[redacted]	[redacted]	705,549*
9	[redacted]	[redacted]	714,647*
10	[redacted]	[redacted]	726,084*

*ICER for voclosporin vs obinutuzumab is above the £20,000/QALY threshold
Abbreviations: EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; QALY = quality-adjusted life year; VOC = voclosporin

Table 5.21: Deterministic results of EAG's scenario analyses using EAG's preferred assumptions – versus BEL + MMF

Scenario analysis number	Belimumab + MMF		
	Incremental costs (£)	Incremental QALYs	ICER £/QALY*
-	[redacted]	[redacted]	**OBI dominant**
1	[redacted]	[redacted]	OBI dominant
2	[redacted]	[redacted]	OBI dominant
3	[redacted]	[redacted]	OBI dominant
4	[redacted]	[redacted]	OBI dominant
5	[redacted]	[redacted]	OBI dominant
6	[redacted]	[redacted]	OBI dominant
7	[redacted]	[redacted]	OBI dominant
8	[redacted]	[redacted]	OBI dominant
9	[redacted]	[redacted]	OBI dominant
10	[redacted]	[redacted]	OBI dominant

*Dominant means more effective and less costly
Abbreviations: BEL = belimumab; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; QALY = quality-adjusted life year

Table 5.22: Deterministic results of EAG's scenario analyses using EAG's preferred assumptions – versus RTX + MMF

Scenario analysis number	Rituximab + MMF		
	Incremental costs (£)	Incremental QALYs	ICER £/QALY*
-	[redacted]	[redacted]	**OBI dominant**
1	[redacted]	[redacted]	OBI dominant
2	[redacted]	[redacted]	OBI dominant
3	[redacted]	[redacted]	OBI dominant
4	[redacted]	[redacted]	OBI dominant
5	[redacted]	[redacted]	OBI dominant
6	[redacted]	[redacted]	OBI dominant
7	[redacted]	[redacted]	OBI dominant
8	[redacted]	[redacted]	OBI dominant
9	[redacted]	[redacted]	OBI dominant
10	[redacted]	[redacted]	OBI dominant

*Dominant means more effective and less costly
Abbreviations: EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; QALY = quality-adjusted life year; RTX = rituximab

5.3 Decision modifiers

5.3.1 QALY weighting for severity

The company has not presented a case for a QALY weighting for severity; the EAG considers this approach to be appropriate given the decision problem and the evidence submitted by the company.

5.3.2 Uncaptured benefits

The EAG believes there may be two potential uncaptured benefits within the CS. The first relates to the short-term impact of renal flares; the issues surrounding the current clinical assessment of renal flares and how this has been modelled within the CS have been extensively critiqued by the EAG in Sections 2.3.3 and 4.2.5. Further data surrounding renal flare incidence, reported in a standardised manner across clinical trials and different treatments, would be required to more appropriately model the impact of reducing renal flares on LN and progression to CKD stage 4.

Furthermore, the EAG believe that the potential impact of the different treatments for LN (including OBI, VOC, BEL and RTX) on fatigue has not been captured within the CS. The submission from Lupus UK drew attention to how fatigue negatively impacts on HRQoL for people with LN.[9] Fatigue was not directly measured within the REGENCY and NOBILITY trials or considered within the company's economic model. As such, the impact of treatments for LN on fatigue is currently uncaptured and unknown.

5.3.3 Health inequalities

The EAG's critique surrounding the company's discussion of health inequalities has been presented in Section 2.2.4.

In the CS (Section 1.4), the company only considered the potential equality considerations relating to ethnicity.[3] Related to this, and as described in Section 3.2.2, the REGENCY and NOBILITY trials may not be comparable to the LN population within the UK. The EAG have noted there are differences in the proportions of Black and Asian populations in the REGENCY and NOBILITY trials compared with the UK population.[14] This is of concern to the

EAG, given that there is evidence suggesting that ethnicity is a potential effect modifier for treatment response in LN.[33,34] Although the company provided a subgroup analysis by race for CRR at 76 weeks in the REGENCY trial (CS Section 2.8, Figure 7), this is split by 'Black' and 'Other.' However, there were only 32 participants in the 'Black' subgroup compared with 239 in the 'Other' subgroup.[3] These issues mean it is challenging to quantify the impact of OBI on people from different ethnic groups.

Furthermore, as discussed in Section 2.2.4, there are several other potential factors that may lead to health inequalities surrounding the treatment of LN. These include: the exclusion of paediatric patients and patients with pure class V LN from the CS, despite inclusion in the NICE scope (see Section 2.3.1); and LN treatments being incompatible with pregnancy and for those looking to conceive (see Section 2.2.4). As paediatric patients and pregnant women were not eligible for the REGENCY and NOBILITY trials, the EAG are unable to comment on the potential impact of OBI for these populations.[3]

Finally, the EAG note that there are potential issues surrounding the need to attend hospital to be administered OBI through IV infusion, which may affect those who work or who are less able to afford travel costs. These issues were particularly highlighted in the submission to NICE by Lupus UK, where some patients had expressed concern surrounding the need to travel to receive IV infusion and the potential impact on the NHS.[9] Although the potential for OBI to reduce pill burden and improve adherence to treatment was discussed by the company (CS Section 1.3.1.7), the company did not consider these other potential impacts relating to the need to attend hospital.[3]

5.4 Confidential comparator and subsequent treatment prices

A confidential appendix was included as part of the EAG report using confidential prices for the following therapies used in the comparator and rescue therapy costs using prices from the Medicines Procurement and Supply Chain (MPSC; formerly known as the Commercial Medicines Unit,

CMU) and the Patient Access Scheme (PAS) for: VOC, RTX, tacrolimus, BEL and cyclosporin.

5.5 Conclusions of the cost-effectiveness section

The company presented an economic model structure based on NICE TA882, the latest TA submission to NICE for treating LN.[22] This structure was tailored to the population of the REGENCY trial, where patients with CKD stages 0 to 3b and AD are eligible to receive therapy and have CRR, PRR or remain at AD.[3] Patients who remain at AD are at risk of progression to CKD stage 4, where they are assumed not to recover and instead are at risk of progressing further to CKD stage 5 (ESRD) with dialysis, where patients stay until they receive a kidney transplant or die. This structure allowed that improvements in either CRR or PRR led to patients being at a reduced risk of kidney disease progression. The EAG considered the model structure to be mostly appropriate. However, reflecting on the role that renal flares can play in disease progression, the EAG considers a more appropriate and transparent approach would be to include one or multiple flares as health states in addition to AD and response status, provided that they are informed with appropriate data for the number of flares and their impact on kidney disease progression.

Baseline population characteristics were based on the REGENCY trial.[3] The primary intervention was OBI + MMF. The comparators included in the decision model were MMF alone, VOC + MMF, RTX + MMF, and BEL + MMF, the latter of which was included following the PfCs.[7] The following comparators outlined in the NICE scope were not included due to limited comparative evidence available: cyclophosphamide; cyclosporin with or without MMF; and tacrolimus with or without MMF.

Transitions between AD, CRR and PRR were derived from a multi-state-model using independent patient data from the 76-week follow-up data of the REGENCY trial, stratified by the intervention arm (OBI + MMF) and placebo arm (MMF alone).[3] Relative effectiveness estimates were based on the NMA estimates of CRR and PRR from REGENCY, NOBILITY, AURORA-1, LUNAR

and BLISS-LN.[3,44,45] The EAG raised concerns that the estimates from the NMA used in the executable model presented minor differences compared to the values reported in the NMA within the CS, as well as the methods used to generate six-month cycle probabilities, which relied on the assumption that NMA timepoints reflected outcomes at 3 years.

Due to the longer-term progression to CKD stage 4 compared to the shorter trial follow-up (1.5 years), there is an absence of data on the risk of progression, which was filled with the estimate used in NICE TA882 informed by clinical expert opinion.[22] The company then combined the HR of time to renal flare for OBI + MMF versus MMF alone from REGENCY, and similarly used OR estimates from AURORA-2 and BLISS-LN to generate differences in the risk of progression to CKD stage 4.[3] This approach has been heavily criticised by the EAG, as the comparisons of differences in the risk of renal flares between OBI + MMF, VOC + MMF and BEL + MMF were not adjusted by population differences in the studies, as this analysis was presented separately from the NMA. The EAG also has concerns surrounding the appropriateness of using a Bucher analysis to compare the OBI + MMF trials with AURORA-2 (VOC + MMF), due to heterogeneity in the patient populations. Furthermore, there was little evidence to suggest a one-to-one relationship between a reduction on time to renal flare and an equivalent reduction in the risk of progression to CKD stage 4, as this misses additional key factors, such as the number of renal flares a person has prior to the first flare, the number of subsequent flares, and the duration of the flare.[1] Finally, this approach risked double-counting the effectiveness of the therapies, as improvements in CRR may reduce the risk of further renal flares and in turn reduce the risk of kidney disease progression, which is already accounted for by the model structure.

Due to the low number of deaths, a survival analysis of mortality from the REGENCY trial was not feasible at 76 weeks follow-up.[3] The risk of mortality was derived from a multi-state-model using the pooled sample of REGENCY; therefore, mortality risk varied by response status (AD, CRR, PRR).

Given the short follow-up duration of the published trial evidence in LN relative to the proposed three-year treatment duration, assumptions around continuous treatment efficacy and waning of efficacy beyond three years remain highly uncertain. Due to the absence of data, these assumptions were based on expert opinion regarding the mechanisms of action of the therapies included in the economic analysis. Therapies with B-cell depletion as a mechanism of action were assumed to have a longer treatment duration after stopping delivery, with OBI + MMF having the longest duration of one year followed by six months of waning efficacy due to improvements in B-cell depletion. RTX + MMF also offers B-cell depletion, so it was assumed to have a shorter six-month duration and six months of waning efficacy. As VOC + MMF has a different mechanism of action, efficacy was assumed to wane in the six months after stopping treatment. Considering the high uncertainty in the evidence underpinning these assumptions, the EAG took the more conservative approach of assuming no treatment waning but maintained the assumed differences in duration of efficacy after three years.

Patient health-related quality of life (HRQoL) in the decision model was informed by the EAG preferred assumptions in NICE TA882 using utility values based on AURORA-2 for AD, CRR and PRR states, respectively.[22] HRQoL was recorded from REGENCY using the EQ-5D-5L; these data were assessed by the company and results presented as part of the submission showing no statistical difference between response status (CRR or PRR) across both arms of the trial. Point estimates of patient utility were higher for AD than for PRR or CRR and, therefore, the company considered that they lacked face validity. However, it was not clear whether this represented a clinically significant difference. The EAG considers this a potential gap in the evidence, as this could mean that either the EQ-5D is not sensitive enough to pick up differences in HRQoL from response status, or that response status does not play a major role in patient HRQoL over the short-term compared to other areas of the disease, such as treatment-related AEs, renal flares and fatigue.

Assumptions of treatment costs around drug dosage, delivery and number of deliveries and concomitant therapy for OBI + MMF were based on REGENCY. However, the EAG noticed differences in the dosage and delivery assumptions of concomitant treatment for the comparator therapies in the executable model, which were not clearly reported in the main submission, including the cost of BEL, which was only included after the PfCs.[7] In the absence of this information, the EAG attempted to replicate the treatment cost calculations from the company base-case, assuming the same concomitant treatment costs from REGENCY were applied for the comparator arms.[3]

The resource use section seemed to conflate subsequent treatment with rescue therapy. As the follow-up of REGENCY is shorter than the stopping rule of OBI, there was no data on subsequent treatment costs[3]; instead, the decision model applied the cost of rescue therapy as a one-off cost based on the proportion of patients who received rescue therapy (excluding corticosteroid-only therapy) in each arm of REGENCY.[3] The cost of this pay-off was based on the distribution of therapies patients received in each trial arm in RECENCY, with the assumption that the risk of rescue therapy in the OBI + MMF arm was equivalent for VOC + MMF, BEL + MMF, and RTX + MMF. The EAG removed anifrolumab from the rescue therapy distribution, as it is not reimbursed in the English NHS, and made a conservative assumption that BEL and OBI are also not reimbursed as rescue therapy despite knowledge of their use off-label. In addition, the EAG was concerned that the decision model did not capture differences in long-term corticosteroid use and its burden on patients. Health care resource use related to the condition for each model health-state was informed by NICE TA882.[22] The model also included palliative care costs for patients at the end of life and renal failure-related costs.

The company's base-case analysis assumed that the impact of treatment-related AEs on patient HRQoL was captured in the baseline utility values for LN. The EAG considered this to be a conservative assumption that potentially ignored important differences in treatment-related AEs, which play an important role in patient quality of life. The company base-case included the

impact of Grade 3+ AEs on health care resource use, based on treatment-related AE data in REGENCY.[3] These were included as a one-off cost under the assumption that most events resolve in less than six months and do not reoccur. The EAG questioned the implied assumption that most AEs do not reoccur during the three-year duration of therapy, opting to include costs and quality of life impacts of treatment-related AEs across the duration of therapy in the decision model.

After correcting for errors, the pairwise results from the company's base-case analysis showed that OBI + MMF was: more effective ([redacted] QALY increment) and more costly ([redacted] cost increment) compared to MMF alone (with an ICER of £5096/QALY), and more effective and less costly compared to VOC + MMF, RTX + MMF, and BEL + MMF. Deterministic sensitivity analysis showed that differences in the probability of progression from AD to CKD stage 4 had the largest impact on cost-effectiveness, followed by differences in the probability of moving from AD to CR. Scenario analyses with the largest impact on cost-effectiveness included removing the HR of time to renal flare from the probability of progression from AD, and assuming no loss of treatment efficacy after three years.

The alternative base-case proposed by the EAG included: removing the HR of time to renal flare and assumed differences in the risk of progression from AD to CKD stage 4 for OBI + MMF, VOC + MMF, and RTX + MMF; assuming a follow-up time for outcomes aligned with the follow-up of REGENCY; assuming no treatment waning beyond three years; assuming no vial sharing; including the impact of treatment-related adverse events on costs and QALYs for the duration of therapy; using the effectiveness estimates reported for the NMA results in the company submission; and assuming an alternative treatment distribution for the cost of rescue therapy.

Deterministic pairwise results from the EAG's base-showed that OBI + MMF, compared to MMF alone, was more costly and more effective, increasing costs by [redacted] and QALYs by [redacted] for a total ICER of £23,943/QALY, above NICE's cost-effectiveness threshold of £20,000/QALY. Compared to VOC + MMF, OBI + MMF was less costly and less effective, decreasing costs by

[redacted] and decreasing QALYs by [redacted]. Based on these results, VOC + MMF had an ICER of £705,549/QALY, above NICE's cost-effectiveness threshold of £20,000/QALY. Compared to BEL + MMF and RTX + MMF, OBI + MMF was the dominant intervention (more effective and less costly). Scenarios run by the EAG showed that decreasing the probability of progressing from AD to CKD stage 4 (by introducing the REGENCY HR), differences in the effectiveness duration after stopping treatment, and changing the duration of therapy had the largest impact on cost-effectiveness. However, OBI + MMF remained dominant over BEL + MMF and RTX + MMF.

The EAG therefore considers that the current decision model presented a cost-effectiveness analysis that was favourable to OBI + MMF, as it relied primarily on (all else being equal): reducing the probability of moving from AD to CKD stage 4; having an improved treatment effect duration beyond the end of therapy (which relied on clinical opinion in the absence of longer follow-up data); and delivering improvements in CRR. Furthermore, the model did not account for differences in the short-term impact of renal flares (due to a lack of comparative evidence) and may underestimate the impact of treatment-related adverse event differences and differences in rescue therapy and subsequent treatment costs. The decision model was further unable to quantify issues related to treatment adherence and the "pill burden" due to the design of the clinical trials, as well as the personal patient burden of IV therapy delivered at a medical centre.

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7 Appendix

7.1 Original company base-case cost-effectiveness result

7.1.1 Original company bae-case deterministic result

CS Section 3.10.1 (Table 66) provides the deterministic base-case results.[3]. Table 7.1 provides the company's base-case incremental results for pairwise cost-effectiveness analysis, initially given in the CS document using the PAS price for OBI, before the clarification response.[3] The OBI + MMF treatment incurred an incremental cost of £[redacted] and an additional QALY of [redacted] when compared to MMF. The incremental cost-effectiveness ratio (ICER) of the OBI + MMF treatment arm versus the MMF treatment arm was £[redacted] per QALY. The OBI treatment regimen remained dominant over the VOC and RTX treatment regimens in the incremental analysis.

Table 7.1: Deterministic incremental results for company base-case with pair-wise cost-effectiveness analysis pre-clarification

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
OBI + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	-	-	-	-
MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VOC + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
RTX + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Source: CS Document Section 3.10.1, Table 66[3]
Abbreviations: ICER = incremental cost-effectiveness ratio; LY = life year; MMF = mycophenolate mofetil; MPDL = methyl prednisolone; OBI = obinutzumab; PDS = prednisolone; QALY = quality-adjusted life year; RTX = rituximab; VOC = voclosporin

Table 7.2: Deterministic company base-case results for NMB and NHB pre-clarification

Treatment	NMB at £20,000	NHB at £20,000	NMB at £30,000	NHB at £30,000
OBI + MMF + MPDL + PDS	-	-	-	-
MMF + MPDL + PDS	18,419	28,508	0.921	0.950
VOC + MMF + MPDL + PDS	31,132	35,407	1.557	1.180
RTX + MMF + MPDL + PDS	42,981	50,349	2.149	1.678

Source: CS Document Section 3.10.1, Table 66[3]
Abbreviations: MMF = mycophenolate mofetil; MPDL = methyl prednisolone NHB = net health benefit; NMB = net monetary benefit; OBI = obinutzumab; PDS = prednisone ; RTX = rituximab; VOC = voclosporin

7.1.2 Original company base-case sensitivity and scenario analysis

Original company base-case probabilistic sensitivity analysis

The company conducted probabilistic sensitivity analysis (PSA) of 1000 iterations on the original company base-case economic model to explore the uncertainty in the economic evaluation. Figure 10 and Figure 11 provide the PSA results for the company base-case, given in CS Section 3.11.1.[3] The EAG conducted a re-run of the PSA in the company model and the incremental results are given in Table 7.4.

Since there was a high degree of variation between the PSA results provided in the CS and the EAG re-run of the model, the EAG explored PSA analysis with 10,000 iterations in the company base-case and its incremental results are given in Table 7.5 and Table 7.6.

Table 7.3: Probabilistic sensitivity analysis on the company base-case, provided in the company submission document pre-clarification

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
OBI+MMF+MPDL+PDS	[redacted]	[redacted]	[redacted]				
MMF+MPDL+PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VOC+MMF+MPDL+PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
RTX+MMF+MPDL+PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Source: CS document Section 3.11.1[3]
Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; MMF = mycophenolate mofetil; NHB = net health benefit; NMB = net monetary benefit; OBI = obinutuzumab; PAS = patient access scheme; QALYs = quality-adjusted life years; RTX = rituximab; VOC = voclosporin; MPDL = methyl prednisolone; PDS = Prednisone.

Figure 10: Incremental cost-effectiveness plane pre-clarification

[redacted]

Source: CS original economic model[88]

Abbreviations: MMF = mycophenolate mofetil; MPDL = ; OBI = obinutzumab; PDS = ; QALY = quality-adjusted life year; RTX = rituximab; VOC = voclosporin

Figure 11: Cost-effectiveness acceptability curve pre-clarification

[redacted]

Source: CS original economic model[88]

Abbreviations: GBP = British pounds; MMF = mycophenolate mofetil; MPDL = methylprednisolone; OBI = obinutzumab; PDS = prenisone; QALY = quality-adjusted life year; RTX = rituximab; VOC = voclosporin; WTP = willingness to pay

Table 7.4: PSA with 1000 iterations on the original company base-case pre-clarification, re-run by EAG

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
OBI + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]				
MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VOC + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
RTX + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Source: Based on CS section 3.10, Table 66[88]
Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; MMF = mycophenolate mofetil; NHB = net health benefit; NMB = net monetary benefit; OBI = obinutuzumab; PAS = patient access scheme; QALYs = quality-adjusted life years; RTX = rituximab; VOC = voclosporin; MPDL = methylprednisolone; PDS = prednisone.

Table 7.5: PSA with 10,000 iterations on the original company base-case pre-clarification, re-run 1 by EAG

Treatment	Total			Incremental			ICER (£ /QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
OBI + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]				
MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VOC + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
RTX + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Treatment	Total			Incremental			ICER (£ /QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Source: Based on CS section 3.10, Table 66[88] Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; MMF = mycophenolate mofetil; NHB = net health benefit; NMB = net monetary benefit; OBI = obinutuzumab; PAS = patient access scheme; QALYs = quality-adjusted life years; RTX = rituximab; VOC = voclosporin; MPDL = methylprednisolone; PDS = prednisone.							

Table 7.6: PSA with 10,000 iterations on the original company base-case pre-clarification, re-run 2 by EAG

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
OBI + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]				
MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VOC + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
RTX + MMF + MPDL + PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Source: Based on CS section 3.10, Table 66[88] Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; MMF = mycophenolate mofetil; NHB = net health benefit; NMB = net monetary benefit; OBI = obinutuzumab; PAS = patient access scheme; QALYs = quality-adjusted life years; RTX = rituximab; VOC = voclosporin.							

EAG Comment: In the CS (Section 3.11.1, Table 68), the incremental PSA results for OBI + MMF vs MMF was £[redacted]/QALY, and VOC + MMF and RTX + MMF was dominated by OBI + MMF.[3] According to the company submission OBI + MMF was [redacted] and [redacted] cost-effective at willingness to pay thresholds of £20,000 and £30,000, respectively.[3] The EAG conducted a re-run of the PSA with 1000 iterations to verify the results but the results showed a very high degree of variation from the company's submitted results. The ICER for OBI + MMF against comparators MMF was £[redacted]/ QALY and, VOC + MMF and RTX + MMF were dominant. In the case of OBI + MMF versus MMF, this would change the decision on cost-effectiveness to 'dominant' in the PSA result, as opposed to £[redacted]/QALY in the deterministic result.

Hence, the EAG undertook exploratory PSA analyses with 10,000 iterations and the results are reported in Table .5 and Table .6. The increased number of iterations did not reduce the degree of variations of the PSA incremental results. On further investigation of the company model, the EAG identified an error in the method used to calculate the ICER from PSA results. The ICER for each iteration in the PSA was calculated and the mean value of all the ICERs were reported as the result. However, conventionally, the mean total cost and mean total QALY of the PSA iterations would be calculated and, from that, the ICER would be calculated by dividing the mean total cost by mean total QALY. When this method was adopted, the EAG found that the PSA result (Table 7.4) for OBI + MMF vs MMF would become [redacted].

One-way sensitivity analysis on the original company base-case

The univariate deterministic sensitivity analysis on the original company submission economic model is provided in Figure 12, Figure 13 and Figure 14.[3]

Figure 12: Tornado diagram showing OWSA results, OBI versus MMF – NMB at WTP threshold of £30,000 – OBI PAS price

Source: CS original economic model[88]
Abbreviations: MMF = mycophenolate mofetil; MPDL = methylprednisone; OBI = obinutuzumab; PDS = prednisone; QALY = quality-adjusted life year; RTX = rituximab; VOC = voclosporin; BEL = belimumab; CKD = chronic kidney disease

Figure 13: Tornado diagram showing OWSA results, OBI versus VOC+MMF – NMB at WTP threshold of £30,000 – OBI PAS price

Source: CS original economic model[88]
Abbreviations: MMF = mycophenolate mofetil; MPDL = methylprednisone; OBI = obinutuzumab; PDS = prednisone; QALY = quality-adjusted life year; RTX = rituximab; VOC = voclosporin; BEL = belimumab; CKD = chronic kidney disease

Figure 14: Tornado diagram showing OWSA results, OBI versus RTX+MMF – NMB at WTP threshold of £30,000 – OBI PAS price

Source: CS original economic model[88]
Abbreviations: MMF = mycophenolate mofetil; MPDL = methyl prednisone; OBI = obinutuzumab; PDS = prednisone; QALY = quality-adjusted life year; RTX = rituximab; VOC = voclosporin; BEL = belimumab; CKD = chronic kidney disease

Scenario analysis on original company base-case

Table 7.7: Scenario analysis results on the original company base-case pre-clarification

		ICER			NMB			NHB		
Base case assumption	**Scenario**	**vs MMF**	**vs VOC + MMF**	**vs RTX + MMF**	**vs MMF**	**vs VOC + MMF**	**vs RTX + MMF**	**vs MMF**	**vs VOC + MMF**	**vs RTX + MMF**
Base case		**1,743**	**Dominant**	**Dominant**	**£28,508**	**£35,407**	**£50,349**	**0.95**	**1.18**	**1.68**
Treatment duration – 6 cycles	12	4,237	Dominant	Dominant	£35,139	£60,045	£61,534	1.17	2.00	2.05
	18	5,655	Dominant	Dominant	£40,405	£81,428	£70,597	1.35	2.71	2.35
Equivalence – FALSE	TRUE	NA	-52,825	NA	£28,508	£35,407	£50,349	0.95	1.18	1.68
Response transitions – ITC	REGENCY	3,935	Dominant	Dominant	£20,220	£44,860	£59,177	0.67	1.50	1.97
Loss of response transitions – by treatment	Pooled	2,431	Dominant	Dominant	£25,966	£34,883	£50,770	0.87	1.16	1.69
Loss of response transitions (other comparators) – Equal to OBI+MMF	Midpoint of OBI+MMF and MMF	1,743	Dominant	Dominant	£28,508	£36,586	£52,422	0.95	1.22	1.75
	Equal to MMF	1,743	Dominant	Dominant	£28,508	£37,811	£54,520	0.95	1.26	1.82
Impact of renal flares – applied	No	12,706	SW 1,536,062	Dominant	£8,387	£18,520	£30,228	0.28	0.62	1.01

		ICER			NMB			NHB		
Base case assumption	**Scenario**	**vs MMF**	**vs VOC + MMF**	**vs RTX + MMF**	**vs MMF**	**vs VOC + MMF**	**vs RTX + MMF**	**vs MMF**	**vs VOC + MMF**	**vs RTX + MMF**
to transition to CKD Stage 4	Response to active disease	6,165	Dominant	Dominant	£17,253	£27,953	£39,094	0.58	0.93	1.30
	Active disease and CKD stage 4	329	Dominant	Dominant	£35,768	£43,224	£57,608	1.19	1.44	1.92
Duration of effect wanes to MMF transition probabilities	OBI+MMF effect is maintained over time	Dominant	Dominant	Dominant	£99,226	£106,125	£121,067	3.31	3.54	4.04
	VOC+MMF effect is maintained over time	1,743	SW 16,543	Dominant	£28,508	-£11,311	£50,349	0.95	-0.38	1.68
	RTX+MMF effect is maintained over time	1,743	Dominant	SW 593,817	£28,508	£35,407	£28,528	0.95	1.18	0.95
Utility source – TA882 EAG approach	REGENCY - Mixed Model - per treatment arm	1,539	Dominant	Dominant	£32,502	£35,464	£49,746	1.08	1.18	1.66
	REGENCY - Mixed Model - pooled	1,866	Dominant	Dominant	£26,498	£35,284	£49,469	0.88	1.18	1.65
	NICE TA882 - company submitted	1,684	Dominant	Dominant	£29,564	£35,302	£50,635	0.99	1.18	1.69
AE disutility – FALSE	TRUE	1,743	Dominant	Dominant	£28,533	£35,432	£50,373	0.95	1.18	1.68
Exclude COVID AEs – FALSE	TRUE	1,691	Dominant	Dominant	£28,560	£35,460	£50,401	0.95	1.18	1.68
Include oral administration cost – FALSE	TRUE	1,403	Dominant	Dominant	£28,850	£81,937	£50,236	0.96	2.73	1.67

		ICER			NMB			NHB		
Base case assumption	**Scenario**	**vs MMF**	**vs VOC + MMF**	**vs RTX + MMF**	**vs MMF**	**vs VOC + MMF**	**vs RTX + MMF**	**vs MMF**	**vs VOC + MMF**	**vs RTX + MMF**
REGENCY subsequent treatment proportions	Multiplier: x 2	708	Dominant	Dominant	£29,552	£35,086	£50,212	0.99	1.17	1.67
	Multiplier: x 3	-327	Dominant	Dominant	£30,596	£34,766	£50,075	1.02	1.16	1.67
Time horizon – 70 years	60	1,670	Dominant	Dominant	£28,391	£35,353	£50,157	0.95	1.18	1.67
	80	1,756	Dominant	Dominant	£28,518	£35,412	£50,369	0.95	1.18	1.68
Discount rate costs – 3.5%	0	2,463	Dominant	Dominant	£28,654	£35,979	£58,770	0.96	1.20	1.96
	0.015	1,598	Dominant	Dominant	£64,037	£51,718	£76,378	2.13	1.72	2.55
Discount rate outcomes – 3.5%	0	802	Dominant	Dominant	£43,851	£42,427	£61,580	1.46	1.41	2.05
	0.015	1,156	Dominant	Dominant	£28,508	£35,407	£50,349	0.95	1.18	1.68

Source: CD document 3.11.3 Table 69[88]
Abbreviations: MMF = mycophenolate mofetil; MPDL = methyl prednisolone; NHB = net health benefit; NMB = net monetary benefit; OBI = obinutzumab; PDS = prednisolone; RTX = rituximab; VOC = voclosporin, BEL = belimumab

Threshold analysis on original company base-case

Table 7.8: Threshold analysis results for original company base-case, pre-clarification

Discount rate	versus VOC+MMF			versus RTX+MMF		
	ICER	NMB	NHB	ICER	NMB	NHB
0%	Dominant	£35,407	1.18	Dominant	£50,349	1.68
10%	Dominant	£32,251	1.08	Dominant	£49,095	1.64
20%	Dominant	£29,095	0.97	Dominant	£47,842	1.59
30%	Dominant	£25,940	0.86	Dominant	£46,588	1.55
40%	Dominant	£22,784	0.76	Dominant	£45,335	1.51
50%	Dominant	£19,628	0.65	Dominant	£44,081	1.47
60%	Dominant	£16,472	0.55	Dominant	£42,828	1.43
70%	Dominant	£13,316	0.44	Dominant	£41,575	1.39
80%	6,235	£10,160	0.34	Dominant	£40,321	1.34
90%	13,617	£7,004	0.23	Dominant	£39,068	1.30
100%	20,999	£3,848	0.13	Dominant	£37,814	1.26

Source: CS document, table 70[3]
Abbreviations: ICER, incremental cost-effectiveness ratio; MMF, mycophenolate mofetil; NHB, net health benefit; NMB, net monetary benefit; OBI, obinutuzumab; PAS, patient access scheme; RTX, rituximab; VOC, voclosporin.

Threshold analysis on updated company base-case

In the CS (Section 3.11.4), a threshold analysis was conducted on the original company base-case to simulate a range of discount rates on the price of drugs.[3] In the CS, the rationale for a threshold analysis was that VOC was available to NHS with a confidential PAS price while RTX was available through biosimilars.[3]

EAG comment: In their response to the PfCs, the company provided the threshold analysis on the updated company base-case.[7] In the threshold analysis, OBI + MMF was dominant against both comparators (BEL + MMF and RTX + MMF). Similar to the original company model, OBI treatment against VOC + MMF, except at a 100% discount rate on VOC acquisition cost.

Table 7.9: Threshold analysis results for updated company base-case, post-clarification

Discount rate	Versus VOC + MMF			Versus BEL + MMF			Versus RTX + MMF		
	ICER	NMB	NHB	ICER	NMB	NHB	ICER	NMB	NHB
0%	Dominant	£35,658	1.19	Dominant	£33,123	1.10	Dominant	£50,002	1.67
10%	Dominant	£32,502	1.08	Dominant	£30,717	1.02	Dominant	£48,749	1.62
20%	Dominant	£29,346	0.98	Dominant	£28,311	0.94	Dominant	£47,495	1.58
30%	Dominant	£26,190	0.87	Dominant	£25,906	0.86	Dominant	£46,242	1.54
40%	Dominant	£23,034	0.77	Dominant	£23,500	0.78	Dominant	£44,988	1.50
50%	Dominant	£19,878	0.66	Dominant	£21,094	0.70	Dominant	£43,734	1.46
60%	Dominant	£16,722	0.56	Dominant	£18,689	0.62	Dominant	£42,481	1.42
70%	Dominant	£13,566	0.45	Dominant	£16,283	0.54	Dominant	£41,227	1.37
80%	5,817	£10,410	0.35	Dominant	£13,877	0.46	Dominant	£39,974	1.33
90%	13,148	£7,254	0.24	Dominant	£11,472	0.38	Dominant	£38,720	1.29
100%	20,479	£4,098	0.14	Dominant	£9,066	0.30	Dominant	£37,467	1.25

Source: Response to PfCs, Table 3[7]
Abbreviations: ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; NHB = net health benefit; NMB = net monetary benefit; OBI = obinutuzumab; PAS = patient access scheme; RTX = rituximab; VOC = voclosporin.

Single Technology Appraisal

Obinutuzumab with immunosuppressive therapies for treating lupus nephritis

EAG report – factual accuracy check and confidential information check

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Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 20, Section 1.3 “Furthermore, there needs to be evidence from clinical trials or rea-world evidence that measures the incidence of renal flares instead of time to renal flare.”	“Furthermore, there needs to be evidence from clinical trials or **real-world** evidence that measures the incidence of renal flares instead of time to renal flare.”	Typographical error.	The EAG accepts this change and has amended the text accordingly.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 20, Section 1.3 “However, this was based on the LUNAR study, which had a primary endpoint of 76 weeks.”	“This was a post-hoc analysis of the LUNAR study, and had a follow-up time of 52 and 78 weeks.”	Incorrect information used for referenced study - the primary endpoint of the LUNAR trial (NCT00282347) was at week 52, but the Gomez Mendel post-hoc study utilised data from LUNAR taken at weeks 52 and 78 for their b-cell depletion/CRR correlation analysis	The EAG has accepted this change and has corrected the text as follows: “However, this was a post-hoc analysis of the LUNAR study, with a primary endpoint at 78 weeks. (…)”

		This was a post-hoc analysis of the LUNAR study, and had a follow-up time of 52 and 78 weeks.	

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 20, Section 1.3 "Additional analyses by the EAG suggest that the length of treatment duration after stopping treatment is an important determinant of cost-effectiveness; this is a key concern given the weak evidence base for these assumptions."	"Additional analyses by the EAG suggest that the length of treatment effect after stopping treatment is an important determinant of cost-effectiveness; this is a key concern given the weak evidence base for these assumptions."	Clarification.	The EAG accepts this change and has amended the text accordingly.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 56/57, Section 3.2, Table 3.2. “[redacted]”	“After screening, eligible patients were randomised to receive obinutuzumab or placebo in a 1:1 ratio. Randomisation was managed by a central interactive voice/Web response system vendor by use of a block design. The factors for balancing between the treatment groups were Region (Afro Caribbean/African American vs. Others) and	Randomisation section text for NOBILITY study marked as ‘confidential’, however, data is published. Therefore, no confidential marking required.	The EAG accepts this changed and has removed the confidential mark-up from the text describing randomisation in NOBILITY accordingly.

	United States vs. non-United States sites. The EAG are satisfied that this is an appropriate method of randomisation."		

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 59, Section 3.2.2 "Only 16 (5.9%) participants were Asian". This is true of the total REGENCY population, but the EAG then claim "Patients of Black or African American ethnicity and American Indian or Alaska Native ethnicity accounted for 20 (14.8%) and 25 (18.5%) respectively of patients in the REGENCY trial".	"Patients of Black or African American ethnicity and American Indian or Alaska Native ethnicity accounted for 40 (14.8%) and 51 (18.8%) respectively of patients in the REGENCY trial."	Incorrect data references.	The EAG accepts this change and has updated the data references in the text.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 60, Section 3.2.2 “In the response to PfCs, the company provided baseline characteristics and demographic data for the [redacted] UK/EU participants out of the total 271 randomised.[7] In these data, there were [redacted] patients from the EU, and ethnicity data from the EU patients was similar to that reported in UK patients. However, data was only available [redacted] UK patients which was too low for the EAG to assess similarity to the UK LN patient population.”	“In the response to PfCs, the company provided baseline characteristics and demographic data for the [redacted] UK/EU participants out of the total 271 randomised.[7] In these data, there were [redacted] patients from the EU, and ethnicity data from the EU patients was similar to that reported in UK patients. However, data was only available [redacted] UK patients which was too low for the EAG to assess similarity to the UK LN patient population.”	The EAG presents data provided in the company response to PfCs which should be marked as confidential.	The EAG accepts this change and has marked the data obtained from the PfCs document as confidential

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 60, Section 3.2.2 “In NOBILITY, only 3 (5.9%) participants were Asian”.	“In NOBILITY, only 5 (4.0%) participants were Asian”	Incorrect data references.	The EAG accepts this change and has updated the data reference in section 3.2.2

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 62, Section 3.3 “REGENCY met its primary endpoint, achieving statistically significant difference between proportion of patients achieving CRR at Week 76 in the obinutuzumab group (42.0%) and the placebo group (31.1%).”	“REGENCY met its primary endpoint, achieving statistically significant difference between proportion of patients achieving CRR at Week 76 in the obinutuzumab group (46.4%) and the placebo group (33.1%).”	Incorrect data references.	The EAG accepts this change and has updated the data references in section 3.3

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 62, Section 3.3 “REGENCY met its primary endpoint, achieving statistically significant difference between proportion of patients achieving CRR at Week 76 in the obinutuzumab group (42.0%) and the placebo group (31.1%).”	“REGENCY met its primary endpoint, achieving statistically significant difference between proportion of patients achieving CRR at Week 76 in the obinutuzumab group (46.4%) and the placebo group (33.1%).”	Incorrect data references.	This amendment was previously accepted and updated by the EAG in response to issue 8.

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 62, Section 3.3 “NOBILITY also met its primary endpoint achieving statistically significant difference between treatment groups of proportion of patients achieving CRR with	“The same primary efficacy endpoint was also met in NOBILITY with a statistically significant difference reported between proportion of patients who achieved CRR at week 52 within the obinutuzumab group (34.9%) versus the placebo group (22.6%).”	Incorrect (and duplicate) detail around NOBILITY primary endpoint. The primary endpoint was only CRR at week 52 and did not include “successful prednisone taper” as stated.	The EAG has accepted this change and removed the text “NOBILITY also met its primary endpoint achieving statistically significant difference between treatment

successful prednisone taper at Week 52. The same primary efficacy endpoint was also met in NOBILITY with a statistically significant difference reported between proportion of patients who achieved CRR at week 52 between the obinutuzumab group (34.9%) versus the placebo group (22.6%)."			groups of proportion of patients achieving CRR with successful prednisone taper at week 52" from section 3.3.

Issue 11

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 63, Section 3.3 "The proportion of patients achieving ORR at week 50 in REGENCY was 74.4% in the obinutuzumab arm and 56.5% in the placebo arm, an adjusted mean difference of 18.0% (95% CI: 8.1 to 28.0; nominal p=0.0005)."	"The proportion of patients achieving ORR at week 50 in REGENCY was 59.1% in the obinutuzumab arm and 50.7% in the placebo arm, an adjusted mean difference of 8.36% (95% CI: -3.41 to 20.12; nominal p=0.1670)."	Incorrect data references.	The EAG accepts this change and has updated section 3.3

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 67, Section 3.4 “The outcomes evaluated in the NMA were CRR, PRR, eGFR (mean change from baseline), ORR (mean change from baseline) and AEs.”	"The outcomes evaluated in the NMA were CRR, PRR, eGFR (mean change from baseline), ORR (either CRR or PRR) and AEs."	ORR is a binary renal response outcome, defined as either CRR or PRR, and should not be described as a 'change from baseline'.	The EAG accepts this change and has amended accordingly.

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 73, Section 3.4.4, Table 3.5. The results for comparing OBI +	[redacted]	Incorrect values.	The EAG has amended the data for the base case

MMF versus Low-dose VOC + MMF and High-dose VOC + MMF have been reversed			and sensitivity analysis.

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 97, Section 4.2.4 “As detailed in section , the EAG is concerned that the economic analysis only included three of the seven comparators listed in the NICE scope as relevant for this appraisal.”	“As detailed in section 2.3.2, the EAG is concerned that the economic analysis only included three of the seven comparators listed in the NICE scope as relevant for this appraisal.”	Missing section number.	The EAG has amended this typo as proposed by the company.

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 98, Section 4.2.5 “Finally, assumptions of treatment effect duration and waning after stopping treatment delivery were informed by clinical expert opinion”	“Finally, assumptions of treatment effect duration and waning after stopping treatment delivery were informed by data from REGENCY, NOBILITY, available literature and clinical expert opinion”	The current text does not explain that the company used available evidence that was then validated with clinical opinion.	The EAG considers this a matter of judgement and not a factual inaccuracy, as the primary evidence informing the assumptions of treatment duration and waning was clinical expert opinion, as the follow-up from the pivotal clinical trials in this submission were shorter than 3 years, as detailed in section 4.2.5, Treatment effect duration and waning.

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 105, Section 4.2.5 “Furthermore, the EAG	To confirm, the renal flare outcomes from the AURORA trials were sourced	As explained in the company submission, renal flares are	The EAG considers this is a matter of judgement

questions why the AURORA-2 study was used in the Bucher analysis when this study had been excluded from their clinical NMA (see Section 3.4.2). In their reporting of the Updated Clinical SLR (Table 18), the company state that AURORA-2 was excluded from the clinical NMA because it "is based on complete response of patients in AURORA-1 and other patients removed and not followed all the way through AURORA-1 and AURORA-2."5 The company did not provide a rationale, either in the original CS or in PfCs, as to why estimates on renal flares have been derived from AURORA-2 given its exclusion in the NMA.5,7 The company's rationale for excluding AURORA-2 from the NMA also suggests a lack of clinical comparability to the participants in	from an analysis of pooled data from AURORA 1 and AURORA 2. These data were the only reported evidence for renal flares associated with voclosporin treatment, so the company utilised it in the base case.	an important clinical endpoint. They are associated with short-term impacts to patient health-related quality of life and healthcare resource use associated with resolving renal flares. However, there is a multitude of published evidence on the link between short-term renal flares and long-term impacts on progression to end-stage renal disease and expensive, high-burden complications like dialysis and transplant (1-5). Literature also highlights that even with strong initial complete renal response, renal flares can occur and have long-term implications. This highlights the importance of capturing the effect of both response and flares on long-term clinical outcomes (6). This is well accepted and supported by the clinical community (7).	rather than a factual inaccuracy. The EAG acknowledged the impact of renal flares as an important outcome for patients and clinicians. However, the EAG has multiple concerns regarding the sources of the evidence presented, the methodology reported to analyse the evidence, and the significant impact that assumptions have on cost-effectiveness relative to this uncertain evidence base. See Key Issue 1, and sections 2.3.2, and 4.2.5 in the EAG report for further details.

REGENCY, given that AURORA-2 only included participants that had achieved complete response. This clinical heterogeneity would likely violate the transitivity assumption, which is required for all ITCs including Bucher analyses.[82] The EAG therefore has concerns that the Bucher analysis assessing renal flares comparing REGENCY and AURORA-2 is open to substantial uncertainty."			

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 106, Section 4.2.5 "The company also rejected alternative approaches to include the impact of flares, such as those presented in TA882, (which assumed that renal flares had a	"The company proposed alternative approaches to include the impact of flares, such as those presented in TA882, (which assumed that renal flares had a health-state related impact at CRR and affected the transitions from CRR to AD rather than AD to	This is incorrect. The company did not reject alternative approaches, but highlighted that alternative approaches would not fully capture the downstream impacts sustained, frequent	The EAG accepts this change and has updated the text in section 4.2.5, Page 106 to: "The company explored a scenario which assumed that renal flares had a

health-state related impact at CRR and affected the transitions from CRR to AD rather than AD to CKD stage 4 directly).[22]"	CKD stage 4 directly), would not fully capture the short- and long-term impact of renal flares on progression to late-stage CKD."	flares have on long-term prognosis. The company also included a scenario investigating the impact of applying renal flare HRs on transitions between Stage 1-3b CRR and AD. The company argue that these approaches would better reflect differences in long-term outcomes between treatments than arbitrarily applying the OBI renal flare outcomes from REGENCY to other treatments as in the EAG scenario. As noted in the company submission, response to clarification, clinical opinion to the company, clinical opinion to the EAG, and the wider literature, renal flares impact progression. The EAG's choice to ignore that is as equally strong an assumption as the company's attempts to capture it, however uncertain.	health-state related impact at CRR and affected the transitions from CRR to AD rather than AD to CKD stage 4 directly, based on TA882, but considered this approach would not fully capture the short- and long-term impact of renal flares on progression to late-stage CKD, therefore maintaining the base-case approach.

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 124, Section 4.2.8 "The adverse event-associated total costs were [redacted] and [redacted] for OBI + MMF and OBI treatment arms, respectively"	"The adverse event-associated total costs were [redacted] and [redacted] for OBI + MMF and MMF treatment arms, respectively."	Incorrect treatment.	The EAG accepts this change and has amended the text in section 4.2.8 as suggested by the company.

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 127, Section 4.2.8 "The EAG is concerned about the lack of consistency in the application of treatment-related AE assumptions in patient HRQoL and healthcare costs and resource use in the base-case analysis presented in the CS. The EAG considers a more appropriate	"The EAG disagreed with the company approach to capture the impact of treatment-related AEs on patient HRQoL in the base-case analysis presented in the CS. The EAG considers a more appropriate approach would be to consistently include Grade 3+ treatment-related AEs in both patient HRQoL and healthcare resource use, as not including the impact of treatment-relate adverse events on HRQoL is	Misrepresentation of company methods. The company disagrees that the approach was inconsistent. The company considered that, as in many cost-effectiveness analyses, reactions to adverse reactions to treatment were captured within health state utility values. The company tested this assumption in scenario analysis. The	Although the EAG considers the company's approach of not including the impact of AE on patient utilities a matter of judgement, the text in section 4.2.8, page 127 has been updated as follows: "The EAG is concerned about the company's approach of not including

approach would be to consistently include Grade 3+ treatment-related AEs in both patient HRQoL and healthcare resource use, as not including the impact of treatment-relate adverse events on HRQoL is likely to present a favourable scenario to the intervention.”	likely to present a favourable scenario to the intervention.”	methods used in the scenario analysis uses Grade 3+ treatment-related AEs in both HRQoL and healthcare resource use. The company is happy for the base case to consider adverse utility decrements, but rejects that its original methods were not appropriate or consistent.	treatment-related differences of AE in patient utilities in the company’s base-case, while the healthcare and resource use impact of AE differences was included. The EAG considers a more appropriate approach would be to include Grade 3+ treatment-related AEs in both patient HRQoL and healthcare resource use, as not including the impact of treatment-relate adverse events on HRQoL is likely to present a favourable scenario to the intervention.”

Issue 20

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 153, Section 5.2.3 "For these reasons, the EAG has added an additional sheet in the economic model presenting our approach to calculating the utility estimates in the economic model, based on the mean values reported in the NMA results, and has used these values for the EAG's base-case analysis."	"For these reasons, the EAG has added an additional sheet in the economic model presenting our approach to calculating the efficacy estimates in the economic model, based on the mean values reported in the NMA results, and has used these values for the EAG's base-case analysis."	Clarification. Assumption 6 does not relate to utility.	The EAG accepts this change and has amended the text in section 5.2.3, page 153 as follows: "For these reasons, the EAG has added an additional sheet in the economic model presenting our approach to calculating the effectiveness estimates in the economic model (…)"

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 149, Section 5.2.3 "**1. Removing the HR of time-to-renal flare from the probability of transitioning from active disease to**	"**1. Removing the HR of time-to-renal flare from the probability of transitioning from active disease to CKD stage 4:** The EAG acknowledges the lack of long-term data regarding	The EAG fail to highlight the use of clinical trial evidence and the available evidence in the literature, only highlighting the additional	The EAG does not consider this to be a factual inaccuracy but a matter of judgement. Furthermore the EAG

CKD stage 4: The EAG acknowledges the lack of long-term data regarding transitions to advanced kidney disease from clinical trials of LN and, therefore, the need to rely on expert opinion. Most of the expert opinion submitted and clinical advice received by the EAG acknowledges the role that preventing renal flares has on reducing progression to advanced kidney disease. The EAG considers that the current model structure reflects this relationship, where only patients with AD are at risk of progressing to CKD stage 4 and, thus, improvements in renal response (particularly complete response), mean that fewer patients are at risk or kidney disease progression."	transitions to advanced kidney disease from clinical trials of LN and, therefore, the need to rely on expert opinion. Most of the expert opinion submitted and clinical advice received by the EAG acknowledges the role that preventing renal flares has on reducing progression to advanced kidney disease. The EAG considers that the current model structure reflects this relationship, where only patients with AD are at risk of progressing to CKD stage 4 and, thus, improvements in renal response (particularly complete response), mean that fewer patients are at risk of kidney disease progression."	validation of these data with clinical experts performed by the company. The EAG acknowledge the role that preventing renal flares has on reducing progression to advanced kidney disease but choose to exclude this impact in their base case. This is an equally strong assumption that hasn't been sufficiently recognised. The EAG justification here does not relate to renal flares, rather they use other outcomes to justify the exclusion of the well-accepted impact of renal flares. This is inappropriate.	presented in its scenario analysis the assumption that time-to-renal flare data had an impact on transitions from CKD stage 4 to AD (assuming no differences between obinutuzumab, voclosporin, belimumab, and rituximab MMF combinations given the absence of evidence to reject this assumption).

Issue 22

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 160, Section 5.2.4, Table 5.20. "*Dominant means more effective and less costly"	"*ICER for voclosporin vs obinutuzumab is above the £20,000/QALY threshold"	Wrong descriptor for * footnote in Table 5.20	The EAG accepts this change and has amended the text accordingly.

Issue 23

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 161, Section 5.2.4, Table 5.21. "ICER £/QALY"	"ICER £/QALY*"	* symbol missing from ICER subheading in table to link to descriptor in footnote (see Table 5.22 as an example)	The EAG accepts this change and has amended the text accordingly.

References

1. Panagiotopoulos A, Kapsia E, El Michelakis I, Boletis J, Marinaki S, Sfikakis PP, et al. Immunosuppressives discontinuation after renal response in lupus nephritis: predictors of flares, time to withdrawal and long-term outcomes. Rheumatology (Oxford, England). 2024.
2. Gibson KL, Gipson DS, Massengill SA, Dooley MA, Primack WA, Ferris MA, et al. Predictors of relapse and end stage kidney disease in proliferative lupus nephritis: focus on children, adolescents, and young adults. Clinical journal of the American Society of Nephrology : CJASN. 2009;4(12):1962-7.
3. Moroni G, Quaglini S, Gallelli B, Banfi G, Messa P, Ponticelli C. The long-term outcome of 93 patients with proliferative lupus nephritis. Nephrology Dialysis Transplantation. 2007;22(9):2531-9.
4. Perez-Arias AA, Márquez-Macedo SE, Pena-Vizcarra OR, Zavala-Miranda MF, Romero-Díaz J, Morales-Buenrostro LE, et al. The influence of repeated flares in response to therapy and prognosis in lupus nephritis. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2023;38(4):884-93.
5. Anders H-J, Saxena R, Zhao M-h, Parodis I, Salmon JE, Mohan C. Lupus nephritis. Nature Reviews Disease Primers. 2020;6(1):7.
6. Banos A, Bertsias G. Flares in Lupus Nephritis: Risk Factors and Strategies for Their Prevention. Current rheumatology reports. 2023;25(10):183-91.
7. Roche Products Ltd. Roche UK Clinical Expert Advisory meeting in 2025 to substantiate statements made within the Gazyvaro NICE submission for Lupus Nephritis (TA11478) [Confidential]. 2025.

Single Technology Appraisal

Obinutuzumab with immunosuppressive therapies for treating lupus nephritis

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Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG has some concerns around how the proportion of patients who received rescue therapy in each treatment arm as well as distribution of patients receiving different rescue treatments, were informed to be modelled in the CS. The total proportion of patients that receive subsequent treatment was [redacted]% in the MMF treatment arm, whereas the reported subsequent treatment proportion according to the REGENCY trial was [redacted]%.[77,88] Despite the assumption that all other comparator arms except the MMF arm have the same subsequent treatment proportion as the OBI arm ([redacted]%), the subsequent treatment proportion for the	The total proportion of patients that receive subsequent treatment was [redacted]% in the MMF treatment arm, whereas the reported subsequent treatment proportion according to the REGENCY trial was [redacted]%.[77,88] The proportion of subsequent treatments included in the cost-effectiveness model are presented in Table 51. The proportion of patients as treated with subsequent rescue therapy in the MMF arm of the cost-effectiveness model and captured in EAR 4.11 is higher than [redacted]% as some patients received more than one subsequent therapy. Despite the assumption that all other comparator arms except the MMF arm have the same subsequent treatment proportion as the OBI arm ([redacted]%), the subsequent treatment proportion for the VOC arm was [redacted]% in the company economic model.[88]	Incorrect data reference for the total proportion of patients that receive subsequent treatment in the MMF treatment arm. The EAG interpretation that the proportions of rescue therapy included in the MMF arm of the analysis is an error is incorrect. The company explained the rationale for this in CS Section 3.5.1.4. The text has been updated to reflect this. This change should also be reflected in the cost-effectiveness model to avoid underestimating subsequent treatment costs on the MMF arm. The company agree with the EAG updates of reweighting	The EAG does not consider this to be a factual inaccuracy but a matter of judgement. The [redacted]% parameter used in the EAG's cost-effectiveness model was considered to be a more transparent estimate as it is based on data from the REGENCY trial, therefore this is still part of our base-case analysis. To address the proposed amendment, the EAG has updated the text of the report, section 4.2.7, page 119, as follows: "The total proportion of rescue therapy in the company base case was [redacted]% in the MMF

VOC arm was [redacted]% in the company economic model.[88]		the subsequent treatment proportions and the fix to the proportion for the VOC arm.	treatment arm (because some of the patients receive more than one rescue therapy), whereas the reported proportion of patients who received rescue therapy in the REGENCY trial was [redacted]%.[77,88] To maintain consistency across the treatment arms, EAG is of the opinion that the total proportion of patients who receive rescue therapy in the MMF arm should be [redacted]%, even though this change would have negligible effect on the ICER."