Dear Janet,

Many thanks to the NICE technical team and the Liverpool Review and Implementation Group for the opportunity to respond to the requests for clarification with regard to our submission for the Single Technology Appraisal of edoxaban tosylate for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation [ID624].

Written responses to the questions are provided on the following pages; academic-/commercial-in-confidence information has been marked as requested.

A number of supporting documents accompany this written response. Where required, they are referred to in the response text; as requested, they have been emailed separately as attachments.

In addition to this written response, we have provided an updated submission document, based on the clarifications discussed in the following pages. For each question which has resulted in an amendment to the submission, details of the amendment are noted in the response. The updated submission also includes a correction to the figures in Table 87; this correction has been previously discussed with the NICE project team on 04 Feb 2015 (and, as we understand it, shared with the ERG prior to the receipt of clarification questions). In developing this clarification response, we additionally notice a small error in Table 79, in which two headings (for apixaban and dabigatran 110mg) had been swapped. This has also now been corrected.

We hope that our responses provide sufficient clarity; however, if any further information is required throughout the course of this appraisal, please don't hesitate to contact us.

Yours sincerely,

Whitney Longstaff

Health Economics & Outcomes Research Manager, UK & Ireland
Daiichi Sankyo

Section A: Clarification on effectiveness data

A1. **Priority question:** Please provide the data inputs for the network meta-analysis.

These data are provided in four Excel files which accompany this response. Please note that these data are provided in confidence.

A2. **Priority question:** Figure 7 of the company submission (page 77) reports the p-values for interaction for subgroup analyses of the primary efficacy endpoint. In relation to the analysis of CHADS2 scores:

a) Please clarify whether the p-value for $CHADS_2$ score is for the comparison of patients with $CHADS_2$ score ≤ 3 versus patients with $CHADS_2$ score > 3, or for the comparison of patients with $CHADS_2$ score = 2 versus patients with $CHADS_2$ score ≥ 3.

The p-value is for the comparison of patients with $CHADS_2$ score ≤ 3 versus patients with $CHADS_2$ score > 3.

b) Please clarify whether the subgroup analysis of patients with $CHADS_2$ score=2 versus patients with $CHADS_2$ score ≥ 3 was a pre-specified or post-hoc analysis.

This was a pre-specified analysis.

A3. **Priority question:** Please provide the following Kaplan-Meier analyses (listed in a to j below) to the following specification:

Population: Use the ITT population including all patients lost to follow-up or withdrawing from trial.

Censoring: Censor lost to follow-up and withdrawn patients at the time recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off, and not when last seen. Please use the format of the table provided.

All analyses are provided in a PDF which accompanies this response (titled to correspond with the question number), using the table format specified in the clarification request. Results for both the ITT and mITT populations are presented. Please note these data are confidential. If there is anything about the presentation format that requires adjustment, please let us know.

The attached PDF labels the requested analyses according the headings specified below.

a) ENGAGE AF-TIMI 48 trial data. Time to death from any cause Kaplan-Meier analysis, stratified by treatment arm and by index event type.

Please see Analyses 1-1.1 (ITT) & 1-1.2 (mITT) in the associated PDF.

b) ENGAGE AF-TIMI 48 trial data. Time to ischaemic stroke Kaplan-Meier analysis, stratified by treatment arm and by index event type.

Please see Analyses 1-2.1 (ITT) & 1-2.2 (mITT) in the associated PDF.

c) ENGAGE AF-TIMI 48 trial data. Time to haemorrhagic stroke Kaplan-Meier analysis, stratified by treatment arm and by index event type.

Please see Analyses 1-3.1 (ITT) & 1-3.2 (mITT) in the associated PDF.

d) ENGAGE AF-TIMI 48 trial data. Time to systemic embolism Kaplan-Meier analysis, stratified by treatment arm and by index event type.

Please see Analyses 1-4.1 (ITT) & 1-4.2 (mITT) in the associated PDF.

e) ENGAGE AF-TIMI 48 trial data. Time to myocardial infarction Kaplan-Meier analysis, stratified by treatment arm and by index event type.

Please see Analyses 1-5.1 (ITT) & 1-5.2 (mITT) in the associated PDF.

f) ENGAGE AF-TIMI 48 trial data. Time to Other-intracerebral haemorrhage Kaplan-Meier analysis, stratified by treatment arm and by index event type.

Please see Analyses 1-8.1 (ITT) & 1-8.2 (mITT) in the associated PDF.

g) ENGAGE AF-TIMI 48 trial data. Time to transient ischaemic attack Kaplan-Meier analysis, stratified by treatment arm and by index event type.

Please see Analyses 1-6.1 (ITT) & 1-6.2 (mITT) in the associated PDF.

h) ENGAGE AF-TIMI 48 trial data. Time to Non-intracerebral haemorrhage major bleed Kaplan-Meier analysis, stratified by treatment arm and by index event type.

Please see Analyses 1-9.1 (ITT) & 1-9.2 (mITT) in the associated PDF.

i) ENGAGE AF-TIMI 48 trial data. Time to clinically relevant non-major bleeds Kaplan-Meier analysis, stratified by treatment arm and by index event type.

Please see Analyses 1-7.1 & 1-7.2 in the associated PDF.

j) ENGAGE AF-TIMI 48 trial data. Time to permanent treatment discontinuation, stratified by treatment arm and by index event type.

Please see Analyses 1-10.1 & 1-10.2 in the associated PDF.

A4. **Priority question:** Please provide a cross-tabulation table showing the distribution of randomised ENGAGE AF-TIMI 48 trial patients by 5 year age bands (e.g. 20-24, 25-29, etc) and gender (male/female) split, for each treatment arm.

All analyses are provided in a PDF which accompanies this response (titled to correspond with the question number). Please note these data are confidential.

Tables 2-1.1.1 (ITT) & 2-1.1.2 (mITT) present the distribution by 5-year age bands; tables 2-1.2.1 (ITT) & 2-1.2.2 (mITT) present the distribution by gender and 5-year age bands.

A5. The company submission cites a number of references for which full text versions were not included within the submission documents. These are listed in Table 1 below. Please provide copies of the full text article for each of the listed references.

Please accept our apologies for the omission of these references. They are provided as attachments accompanying this response.

A6. Several of the reported outcomes of the ENGAGE AF-TIMI 48 trial are derived from the appendices of the clinical study report. To enable the ERG to verify these outcomes, please provide the appendices to the clinical study report.

A full version of the clinical study report (main body + appendices) accompanies this response. Please note this document is provided in confidence.

A7. Please provide justification for the use of the modified intention-to-treat (mITT) population and the "On-Treatment Period" for the primary efficacy analysis of the ENGAGE AF-TIMI 48 trial, rather than the intention-to-treat (ITT) population.

For the primary efficacy outcome, the non-inferiority analysis was done in the mITT on-treatment population. It is a regulatory requirement to do a non-inferiority analysis in an on-treatment population. Analyses of studies with long follow ups have concluded that, as patients discontinue treatment over time, any true differences between arms are reduced. In that respect, an on-treatment analysis gives a clearer indication of whether a comparator is truly non-inferior to the reference therapy.

Please note, the superiority analysis for the primary efficacy endpoint was done on the ITT analysis set, overall study period, as set out in the Overall Multiplicity Adjustment Testing Procedure for Efficacy Analyses (see pages 20-23 in the SAP).

A8. In the statistical analysis plan (page 30) for the ENGAGE AF-TIMI 48 trial, it is stated that all efficacy endpoints were to be analysed using the ITT, mITT and Per Protocol populations. The statistical analysis plan does not state that both "On-Treatment Period" and "Overall Study Period" would be used in the analyses. Please clarify whether it was pre-specified that the following ENGAGE AF-TIMI 48 trial secondary endpoints would be analysed using data from both "On-Treatment Period" and "Overall Study Period" for ITT, mITT and Per Protocol populations:

- Composite of stroke, systemic embolic event (SEE), and CV mortality
- MACE (the composite of non-fatal myocardial infarction, non-fatal stroke, non-fatal SEE, and death due to cardiovascular cause or bleeding)
- Composite of stroke, SEE, and all-cause mortality.

We confirm that these endpoints were pre-specified for both "On-Treatment Period" and "Overall Study Period" for ITT, mITT and Per Protocol populations – see section 7.7.3 of the SAP (page 34). In this section it states that "Analyses as described in Section 7.7 will be performed for the three secondary efficacy endpoints as follows…."

On page 25 of the SAP, it states: "The majority of statistical analyses will be performed on each analysis set (ITT, mITT, Per Protocol, and Safety) for both the "On Treatment" Period and the Overall Study Period as shown in Table 7.1.1."

Table 7.1.1 Analysis Set and Study Period

Analysis Set	Overall Study Period	"On Treatment" Period
mITT	X	X
Per Protocol (PP)	X	X
ITT	X	NA
Safety	X	X

Please note: in Table 7.1.1 in the SAP, the results of the ITT on-treatment analysis are “NA”, because they are the same as those of the mITT on-treatment.

A9. In the statistical analysis plan (page 34) for the ENGAGE AF-TIMI 48 trial, it is stated that individual components of the primary and the secondary endpoints (stroke, SEE, cardiovascular mortality, all-cause mortality) will be analysed using the ITT, mITT and Per Protocol Analysis Sets for both “On-Treatment Period” and “Overall Study Period”. Please clarify whether it was also pre-specified that the subcomponents of stroke would be analysed using the ITT, mITT and Per Protocol Analysis Sets for both “On-Treatment Period” and “Overall Study Period”.

We can confirm that analyses of the subcomponents were also pre-specified.

A10. In the statistical analysis plan (page 34) for the ENGAGE AF-TIMI 48 trial, it is stated that the following outcomes were to be analysed using the ITT, mITT and Per Protocol Analysis Sets for both “On-Treatment Period” and “Overall Study Period”:

- Adjudicated composite endpoint of stroke, SEE, major bleeding, and all-cause mortality
- Adjudicated composite endpoint of disabling stroke, SEE, life-threatening bleeds/ICH, and all-cause mortality

The results for these outcomes are not provided or referred to in the company submission or clinical study report. Please provide the results for these outcomes for all pre-specified analysis sets.

The results are provided in the tables below. Please consider these data confidential.

- Adjudicated composite endpoint of stroke, SEE, major bleeding, and all-cause mortality

[redacted]

[redacted]

[redacted]

As noted in the answer to A8, the ITT on treatment analysis is the same as for the mITT on treatment analysis (identical patients and event rates).

Please be aware that we are confirming information with our global colleagues regarding the PP analyses and will provide you with a response as soon as one is available. Please accept our apologies for this delay.

- Adjudicated composite endpoint of disabling stroke, SEE, life-threatening bleeds/ICH, and all-cause mortality

As noted in the answer to A8, the ITT on treatment analysis is the same as for the mITT on treatment analysis (identical patients and event rates).

A11. In the statistical analysis plan (page 35) for the ENGAGE AF-TIMI 48 trial, it is stated that the following outcomes were to be analysed using the ITT, mITT and Per Protocol Analysis Sets for both "On-Treatment Period" and "Overall Study Period":

- Investigator reported VTE, including pulmonary embolism and deep vein thrombosis, as well as each individual component
- The incidence of hospitalisation
- Severity of strokes

The results for the outcomes listed above have not been provided for all pre-specified analysis sets. Please provide the results for these outcomes for all pre-specified analysis sets.

The results have been provided as PDFs which accompany this response (titled to correspond with the question number). Please consider these results confidential.

Please be aware that the PP analyses (for all above requested outcomes), and the ITT analyses (for the first two above requested outcomes) are not contained within the accompanying PDFs; we are confirming information with our global colleagues and will provide you with a response as soon as one is available. Please accept our apologies for this delay.

A12. For the network meta-analysis, more details are required on the statistical approach used. Please provide a more detailed description of the network meta-analysis methodology, including the

number of chains, the number of iterations which were discarded as part of the burn-in period, and the number of further iterations the final treatment effect estimates were based on.

We apologise for the confusion. The results presented in the submission were generated with SAS statistical software using a frequentist analysis to generate a mixed Poisson regression model; a Bayesian analysis was performed only to validate the frequentist results. The statement on page 85 and the code in Appendix 15 were incorrectly included. The submission template has now been corrected.

A13. Appendix 15 of the company submission suggests that a fixed effects model was used to conduct the network meta-analysis. Please provide the reasoning behind this choice of model, and clarify whether fixed effects were used for all conducted analyses.

Please see the response to A12 above.

A14. Section 6.10.1 of the company submission states that the network meta-analysis data should be interpreted with caution because of significant differences in patients' characteristics and trial design that exist between the four pivotal trials. Please state what these differences are.

There are several noteworthy differences in the study design and patient characteristics among the NOAC pivotal trials as highlighted below. These differences are also summarized in Table 1.

1) ARISTOTLE, ROCKET-AF, and ENGAGE AF-TIMI 48 were double-blind, double-dummy trials, whereas RE-LY administered warfarin as an open-label treatment. PROBE/open-label trials have been shown to be associated with enhanced treatment effect compared with double-blind trials for haemorrhagic stroke (Lega 2013).

2) ENGAGE AF-TIMI 48 was the longest trial, with a median follow-up of 2.8 years, compared with 1.8 years in ARISTOTLE, 1.9 years in ROCKET-AF, and 2.0 years in RE-LY.

3) Median centre time in therapeutic range (TTR) for the warfarin comparator was higher in ENGAGE AF-TIMI 48 (64.9%), ARISTOTLE (62.2%), RELY (64.0%) than ROCKET-AF (55.0%).

4) ARISTOTLE and RE-LY enrolled patients who had a $CHADS_2$ score ≥ 1, whereas ROCKET-AF and ENGAGE AF-TIMI 48 enrolled a higher-risk population with $CHADS_2$ score ≥ 2. At baseline, more patients in ROCKET-AF and ENGAGE AF-TIMI 48 than in RE-LY and ARISTOTLE had previous stroke or transient ischemic attacks, and other comorbidities such as diabetes, hypertension, and heart failure, resulting in a higher mean $CHADS_2$ score in the populations of those trials.

Table 1. Summary of Randomized Controlled Trials of New Oral Anticoagulants vs Warfarin

	RELY (Dabigatran)	ROCKET-AF (Rivaroxaban)	ARISTOTLE (Apixaban)	ENGAGE AF TIMI-48 (Edoxaban)
Total patients in phase 3 trial	18,113	14,264	18,201	21,105
Trial design	Open-label	Double-blinded	Double-blinded	Double-blinded
Years of follow-up (median)	2.0	1.9	1.8	2.8

	RELY (Dabigatran)	ROCKET-AF (Rivaroxaban)	ARISTOTLE (Apixaban)	ENGAGE AF TIMI-48 (Edoxaban)
Male (%)	63.2% (D), 63.3% (W)	60.3% (R), 60.3% (W)	64.5% (A), 65.0% (W)	62.1% (E), 62.4% (W)
Mean $CHADS_2$ score	2.2 (D), 2.1 (W)	3.5 (R), 3.5 (W)	2.1 (A), 2.1 (W)	2.8 (E), 2.8 (W)
Patients with $CHADS_2$ score ≥ 2	67.8% (D), 69.1% (W)	100%	66%	100%
Patients with $CHADS_2$ score ≥ 3	32.6% (D), 32.1% (W)	87%	30.2%	53.4% (E); 52.6% (W)
Patients with previous stroke or transient ischemic attack	20.3% (D), 19.8% (W)	54.9% (R), 54.6% (W)	19.2% (A), 19.7%(W)	28.1% (E), 28% (W)
Patients with diabetes	23% (D), 23% (W)	40% (R), 40% (W)	25% (A), 25% (W)	36% (E), 36% (W)
Patients with hypertension	79% (D), 79% (W)	90% (R), 91% (W)	87% (A), 88% (W)	94% (E), 94% (W)
Patients with heart failure	31.8% (D), 31.9% (W)	62.6% (R), 62.3% (W)	35.5% (A), 35.4% (W)	58.2% (E), 58% (W)
Mean cTTR	64.0%	55.0%	62.2%	64.9%

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** Please clarify the source of the hazard ratios for warfarin versus edoxaban reported in Table 51.

The hazard ratios for warfarin vs edoxaban in Table 51 are those estimated in the network meta-analysis, and as such reflect the pooled effect of warfarin in the studies included in the NMA. For sensitivity analysis, the model offers the option to use the trial data from ENGAGE AF-TIMI 48 as a source of event rates for warfarin.

B2. **Priority question:** Please provide results of the analysis of EQ-5D data collected within the trial with the standard UK EQ-5D tariff applied (Dolan, Modelling Valuations for EuroQol Health States, Medical Care 1997, Vol. 35, No. 11, pp. 1095-1108).

Specifically, please provide number of observations, mean, median and standard deviations for EQ-5D single-index for each trial arm at each time point separately.

Please provide this analysis for:

i. all patients in the trial (using UK tariff for all patients) and
ii. the UK subgroup of patients (using the UK tariff).

These analyses (for both the ITT and mITT populations) are provided in a PDF which accompanies this response (titled to correspond with the question number). Please note these data are confidential.

B3. **Priority question:** Please provide additional sensitivity analyses using the following assumptions for discontinuation following a stroke: (i) All patients restarting on anti-coagulation therapy following an ischaemic stroke and (ii) All patients discontinuing therapy following a haemorrhagic stroke.

Results of the two sensitivity analyses are presented in Tables 1 and 2 below. In each scenario, all NOACs are dominated by dabigatran 150mg. In each sensitivity analysis, the total cost is slightly lower than those in the base case analysis.

It is worth noting that the base case discontinuation assumptions were based on clinical expert advice, and are therefore the most appropriate assumptions for the analyses.

Table 1. Sensitivity analysis – all patients restart on anti-coagulation therapy following an ischaemic stroke

Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Warfarin	£13,159	8.546	6.318	-	-	-	-	-
Dabigatran 150mg	£15,442	8.883	6.600	£2,283	0.336	0.281	£8,117	£8,117
Apixaban	£15,814	8.869	6.588	£372	-0.014	-0.012	£9,859	Strictly dominated
Edoxaban	£15,827	8.789	6.516	£13	-0.080	-0.072	£13,508	Strictly dominated
Dabigatran 110mg	£15,924	8.796	6.515	£97	0.007	-0.001	£14,092	Strictly dominated
Rivaroxaban	£16,611	8.694	6.437	£687	-0.102	-0.078	£29,195	Strictly dominated

Table 2. Sensitivity analysis – all patients discontinue therapy following a haemorrhagic stroke

Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Warfarin	£13,385	8.546	6.318	-	-	-	-	-
Dabigatran 150mg	£15,550	8.883	6.600	£2,165	0.336	0.281	£7,698	£7,698
Apixaban	£15,911	8.869	6.588	£361	-0.014	-0.012	£9,378	Strictly dominated
Edoxaban	£15,927	8.789	6.516	£16	-0.080	-0.072	£12,871	Strictly dominated
Dabigatran 110mg	£16,060	8.796	6.515	£133	0.007	-0.001	£13,634	Strictly dominated
Rivaroxaban	£16,711	8.694	6.437	£651	-0.102	-0.078	£28,131	Strictly dominated

B4. Please provide results of the cost-effectiveness analysis using the EQ-5D data from the ENGAGE AF-TIMI 48 trial with the UK tariff applied (UK patient subgroup).

Results of the analysis using EQ-5D data from the ENGAGE-AF TIMI 48 trial are presented in Table 3 below. Since the baseline utility value from the trial is the same as the estimate used in the base case analysis (0.78), these results are the same as those of the base case analysis.

Table 3. Sensitivity analysis –Stable AF health state utility estimated using EQ-5D data from the ENGAGE-AF TIMI 48 trial

Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Warfarin	£13,412.98	8.55	6.32	-	-	-	-	-
Dabigatran 150mg	£15,563	8.88	6.60	£2,150	0.34	0.28	£7,645.43	£7,645.43
Apixaban	£15,940	8.87	6.59	£377	-0.01	-0.01	£9,382.94	Strictly dominated
Edoxaban	£15,957	8.79	6.52	£17	-0.08	-0.07	£12,880.91	Strictly dominated
Dabigatran 110mg	£16,074	8.80	6.51	£117	0.01	0.00	£13,565.23	Strictly dominated
Rivaroxaban	£16,744	8.69	6.44	£670	-0.10	-0.08	£28,180.18	Strictly dominated

B5. The numbers reported in the text in the section on identification of studies (7.1.1) do not match the numbers presented in Figure 21. Please provide the correct figures. The differences are detailed below:

i. The sum estimated as e2 in the figure adds to 36 not 32 as presented in Table 41 and 31 stated in the text.
ii. A total of 165 records were included as i3 not 166 as reported in Section 7.1.1 – is that correct?
iii. 42 cost studies were included, not 43 as reported in Section 7.1.1.

Thank you for drawing the error to our attention. Both figure and text in the section 7.1.1 have been corrected in the submission document which accompanies this response.

B6. The details in the text of the company submission appear to differ from Figure 23 and Table 59 in the section on identification of health-related quality of life studies (Section 7.4.6). Please provide the correct information. In particular:

i. Figure 23 does not include the details listed in Section 7.4.6 regarding additional records identified in p168 and the data extraction table
ii. Figure 23 notes only 2 conference proceedings – Table 59 lists 4 conference proceedings
iii. From the literature review, 23 full texts were retrieved of which only 11 were included but Table 59 lists 14 full texts.

Thank you for drawing the error to our attention. Figure 23, Table 59 and the associated text have been corrected in the submission document which accompanies this response.

B7. Dabigatran 'blend' is referred to in Table 62 (and elsewhere). Please clarify what dabigatran 'blend' refers to.

Dabigatran blend refers to the dabigatran regimen where patients receive the 150mg dose until the age of 80, when they switch to the 110mg dose. This regimen has been labelled as "Dabigatran 110mg" elsewhere in the submission. Table 62, Table 78, Table 81, and Table 82 have been amended so that "dabigatran 110mg" is used to refer to this regimen instead of "dabigatran blend".

B8. In Section 7.3.7 (p163) of the company submission there is duplication. Please clarify whether the company submission means event rates and relative risks or probabilities and hazard ratios?

This paragraph should refer to probabilities of clinical outcomes (rather than event rates) and hazard ratios (rather than relative risks). The duplicated paragraph and the paragraph containing the incorrect text have been removed.