NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Single Technology Appraisal (STA)

Edoxaban tosylate for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation [ID624]

Dear [redacted]

The Evidence Review Group, Liverpool Review and Implementation Group, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 20 January 2014 by Daiichi Sankyo. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by 5pm on 26 February 2015. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact [redacted] Any procedural questions should be addressed to [redacted] in the first instance.

Yours sincerely

Janet Robertson
Associate Director – Appraisals
Encl. checklist for in confidence information

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Section A: Clarification on effectiveness data

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

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 $CHADS_2$ 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.

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.

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.

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.

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

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

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

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

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

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

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

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.

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.

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

Example of output (SAS) required from specified Kaplan-Meier analyses

- The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP...		0.8548	0.1452	0.0447	9	53
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

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.

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.

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.

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.

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.

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".

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

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.

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.

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.

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.

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.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

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.

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).

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.

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).

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.

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:

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

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.

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

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?

Table 1 List of references requested in question A3.

The references in Table 1 are listed in the order in which they appear in the Reference section of the CS.

(1) Bunch TJ, Gersh BJ. Rhythm Control Strategies and the Role of Antiarrhythmic Drugs in the Management of Atrial Fibrillation: Focus on Clinical Outcomes. J Gen Intern Med 26[5], 531-537. 2011.
(2) Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. American College of Cardiology; American Heart Association Task Force; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm SocietyEuropace. Circulation 114, e257-e354. 2006.
(3) Kannel W, Benjamin E. Status of the epidemiology of atrial fibrillation. Med Clin North Am 92[1], 17-40. 2008.
(4) Lloyd-Jones D, Adams RJ, Brown TM, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation* 2010; 121:e46-e215.
(8) Royal College of Physicians Clinical Effectiveness and Evaluation Unit on behalf of the Intercollegiate Stroke Working Party. Sentinel Stroke National Audit Programme.Clinical audit first pilot public report. 2013.
(10) Stambler BS. A new era of stroke prevention in atrial fibrillation: comparing a new generation of oral anticoagulants with warfarin. *International archives of medicine* 2013;

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

2013/11/01:46.
(11) Turpie AG. Oral, direct factor Xa inhibitors in development for the prevention and treatment of thromboembolic diseases. 2007; 2007/03/24:1238-1247.
(12) Weitz JI, Bates SM. New anticoagulants. *J Thromb Haemost* 2005; 2005/08/17:1843-1853.
(13) Ogata KM-H. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. *J Clin Pharmacol* 2010; 50(7):743-753.
(15) Mendell J, Zahir H, Matsushima N, Noveck R, Lee F, Chen S et al. Drug-drug interaction studies of cardiovascular drugs involving P-glycoprotein, an efflux transporter, on the pharmacokinetics of edoxaban, an oral factor Xa inhibitor. *Am J Cardiovasc Drugs* 2013; 13(5):331-342.
(17) Gonzalez-Quesada CJ, Giugliano RP. Comparison of the phase III clinical trial designs of novel oral anticoagulants versus warfarin for the treatment of nonvalvular atrial fibrillation: implications for clinical practice. *Am J Cardiovasc Drugs* 2014; 14(2):111-127.
(18) Bathala MS, Masumoto H, Oguma T, He L, Lowrie C, Mendell J. Pharmacokinetics, biotransformation, and mass balance of edoxaban, a selective, direct factor Xa inhibitor, in humans. *Drug Metab Dispos* 2012; 40(12):2250-2255.
(19) De CR, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F et al. New oral anticoagulants in atrial fibrillation and acute coronary syndromes: ESC Working Group on Thrombosis-Task Force on Anticoagulants in Heart Disease position paper. *J Am Coll Cardiol* 2012; 59(16):1413-1425.
(21) National Institute for Health and Care Excellence. NICE Commissioning guides [CMG49] - Support for commissioning: anticoagulation therapy. 2013.
(22) Desai N, Giugliano R. Can we predict outcomes in atrial fibrillation? Clin Cardiol 35[Suppl 1], 10-14. 2012.
(23) Fuster V, Rydén LE, Asinger RW, et al. ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation) Developed in Collaboration With the North American Society of Pacing and Electrophysiology. Circulation 104, 2118. 2001.
(26) Calum A. Symptoms in atrial fibrillation: Why keep score? Circulation 2, 215-217. 2009.
(29) Odum LE, Cochran KA, Aistrope DS, Snella KA. The CHADS(2)versus the new CHA2DS2-VASc scoring systems for guiding antithrombotic treatment of patients with atrial fibrillation: review of the literature and recommendations for use. *Pharmacotherapy* 2012; 32(3):285-296.
(30) Lin HJ, Wolf PA, Kelly-Hayes M, et al. Stroke severity in atrial fibrillation. The

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Framingham Study. *Stroke* 1996; 27(10):1760-1764.
(31) Rivero-Ayerza M, Scholte op Reimer W, Lenzen M, et al. New-onset atrial fibrillation is an independent predictor of in-hospital mortality in hospitalized heart failure patients: results of the EuroHeart Failure Survey. Eur Heart J 29, 1618-1624. 2008.
(32) Marini C, De Santis F, Sacco S, et al. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. *Stroke* 2005; 36(6):1115-1119.
(33) Heeringa J, van der Kuip DA, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006; 27(8):949-953.
(35) Caldwell JC, Contractor H, Petkar S, et al. Atrial fibrillation is under-recognized in chronic heart failure: insights from a heart failure cohort treated with cardiac resynchronization therapy. *Europace* 2009; 11(10):1295-1300.
(36) Barrios V, De la Figuera M, Coca A. Prevención de la fibrilación auricular en el paciente hipertenso. . 2007;128:148-54. Med Clin (Barc) 128, 148-154. 2007.
(37) Barrios V, Calderon A, Escobar C, et al. Patients with atrial fibrillation attended in primary care setting. The Val-FAAP study. Rev Esp Cardiol 65[1], 47-53. 2012.
(39) Fernandez MM, von Schéele B, Hogue S, et al. Review of challenges in optimizing oral anticoagulation therapy for stroke prevention in atrial fibrillation. Am J Cardiovasc Drugs 13[2], 87-102. 2013.
(40) McBride D, Mattenklotz AM, Willich SN, Bruggenjurgen B. The costs of care in atrial fibrillation and the effect of treatment modalities in Germany. *Value Health* 2009; 12(2):293 301.
(42) Jonsson L, Eliasson A, Kindblom J, Almgren O, Edvardsson N. Cost of illness and drivers of cost in atrial fibrillation in Sweden and Germany. *Applied health economics and health policy* 2010; 8(5):317-325.
(43) Saka O, McGuire A, Wolfe C. Cost of stroke in the United Kingdom. *Age and ageing* 2009; 38(1):27-32.
(45) The RealiseAF registry, Initial results. 2015
(48) Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 98[10], 946-952. 1998.
(52) Ansell J, Hirsh J, Poller L, et al. The pharmacology and management of the vitamin K antagonists the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. CHEST Journal 2004;126(3_suppl):204S-33S. CHEST journal 126[3 Suppl], 204S-233S. 2004.
(53) You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141[2 Suppl], e531S-75S. 2012.

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

(56) Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. Archives of internal medicine 165[10], 1095-1106. 2005.
(57) Diener H-C, Verheugt F. Introduction. *Eur Heart J Suppl* 2005; 7(Supple E):E3.
(59) Zahir H, Brown KS, Vandell A, Desai M, Maa JF, Dishy V et al. Edoxaban Effects on Bleeding Following Punch Biopsy and Reversal by a 4-Factor Prothrombin Complex Concentrate. *Circulation* 2014.
(60) Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition 1. *Chest* 2008; 133(6 Suppl):160S-198S.
(63) Laliberté F, Nelson WW, Lefebvre P, Schein JR, Rondeau-Leclaire J, Duh MS. Impact of daily dosing frequency on adherence to chronic medications among nonvalvular atrial fibrillation patients. *Advances in therapy* 2012; 29(8):675-690.
(92) EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990; 16(3):199-208.