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)

Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism (ID 726)

Dear [redacted]

The Evidence Review Group, the Liverpool Reviews and Implementation Group, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 13th October 2014 by BMS / Pfizer. In general terms they felt that it is well presented and clear. The ERG would like to express their appreciation for having received the clinical study reports for the key apixaban trials alongside the company submission. 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 20th November 2014. 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

[redacted]

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Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: Clarification on effectiveness data

Systematic review

A1. Figure 1 on page 39 of the company submission shows that 197 studies were excluded from the systematic review of RCT evidence on the basis of study outcome. Please clarify how these studies were judged to not have reported the outcome of interest when only the title and abstract were available.

A2. The 'reasons for exclusions' table (section 10.3, appendix 2a Appendices of the company submission) reports that 8 of the studies (Bamber et. al, 2013; Barrett et. al, 2011; Campbell et. al, 2007; Kovacs et. al, 2003; Farahmand et. al, 2011; Quiroz et. al, 2006; Raskob et. al, 2011; Vitovec et. al, 2009) were excluded as they had 'no outcome of interest'. Guidance (Kirkham et. al, 2010) recommends that studies should not be excluded because they do not report an outcome of interest as that outcome may have been have measured as part of the study but not reported (outcome reporting bias). Please clarify whether any of the authors of the 8 studies were contacted in order to verify that the outcome of interest was not measured rather than simply not reported.

Characteristics of participants in the AMPLIFY and AMPLIFY-EXT trials

A3. In the company submission, the baseline demographics for the participants in the AMPLIFY trial are listed in Table 9. In this table under the 'qualifying diagnosis' criteria, 12 people in the apixaban arm and 15 people in the enoxaparin/warfarin arm could not be evaluated as having had a DVT, PE or DVT with PE. Please clarify why a qualifying diagnosis could not be evaluated in these people.

A4. Please provide a cross-tabulation table showing the distribution of patients randomised in AMPLIFY by 5 year age band (e.g. 20-24, 25-29, etc) and gender (male/female), for each treatment arm by index VTE event type (PE+/- DVT vs DVT only) [i.e. 4 tables].

A5. Please provide a cross-tabulation of the distribution of patients randomised in AMPLIFY-EXT by 5 year age band (e.g. 20-24, 25-29, etc) and gender (male/female), for each treatment arm by index VTE event (PE+/- DVT vs DVT only) [i.e. 4 tables].

A6. Please provide a comparison of the demographic and clinical patient characteristics for the AMPLIFY-EXT trial between:

- People continuing in AMPLIFY-EXT who had participated in the AMPLIFY trial,
- People newly recruited to AMPLIFY-EXT.

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Efficacy and safety outcomes from AMPLIFY and AMPLIFY-EXT

A7. In Appendices 6a and 6b of the company submission, the following statement is made with reference to the population included in the efficacy analyses:

> "ITT population (randomly assigned patients who received ≥1 dose of study drug and who had events during the 6-month treatment period, regardless of early discontinuation of study drug)".
>
> Should this statement read:
>
> "ITT population (randomly assigned patients who received ≥1 dose of study drug). Events occurring within 6 months post randomisation were counted as events in the analysis regardless of early discontinuation of study drug" ?

A8. In the company submission (page 74), it is stated that no clinically important observations were noted for the pre-specified subgroup analyses of AMPLIFY-EXT. However from inspection of the tests for interaction provided in the clinical study report, it is noted that three subgroup analyses (gender, age and geographic region) had p-values <0.10, (the company's chosen cut-off point for further investigation of the results of subgroup analyses). Please clarify why these findings were judged to be clinically unimportant.

A9. Please state the number of patients in each arm of the AMPLIFY and AMPLIFY-EXT trials who experienced more than one major bleeding episode within the study period.

A10. Please state the number of patients in each arm of the AMPLIFY and AMPLIFY-EXT trials who experienced at least one major bleeding episode in addition to a recurrent VTE event during the study period.

Studies included in the network meta-analyses

A11. Please provide information on the following study characteristics for the studies included in network meta-analysis 1 (NMA 1) for the treatment period and network meta-analysis 2 (NMA 2) for the prevention period: i) study location; ii) inclusion/exclusion criteria; iii) primary outcomes (including scoring methods and timing of assessments); iv) secondary outcomes (including scoring methods and timings of assessments) using the table below.

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	Study name	Study name	Study name (add more columns as required)
Study location			
Inclusion/exclusion criteria			
Primary outcome(s)			
Secondary outcomes			

Network meta-analysis methodology

A12. For the treatment period (NMA 1) and prevention period (NMA 2), please provide more details on the statistical approach used. For each NMA, please state the number of iterations which were discarded as part of the burn-in period, and how much further iteration the final treatment effect estimates were based on.

A13. In order to allow consideration of the sensitivity of model parameters to different approaches to carrying out meta-analysis estimation, please provide results from the following 2 alternative assumptions for the meta-analyses listed in questions **A14–A26** (for all analyses please do not include continuity adjustments for zeros):

- First analysis: Remove the term *mu[i]* (study effects) and replace it with a single *mu* which would represent the log-odds of an event in 1 year for the baseline treatment, i.e. fit a model of the form *logit(rate_{ik}) = mu + delta_{k}* where *k* indexes treatment and *delta_1 == 0*

- Second analysis: Treat the study effects *mu[i]* as random effects rather than fixed effects, i.e. fit a model of the form
  logit(rate_{ik}) = mu_i + delta_{k} where *mu_{i} ~ N(mu_0, sigma^2)*.

  In the WinBUGS code this involves using *mu[i] ~ dnorm(mu_0, 1/mu_var)* rather than *mu[i] ~ dnorm(0,.0001)* and it would also require inclusion of a prior for *mu_0* and the random effects variance such as *mu_0 ~ dnorm(0, 0.0001)* *mu_var ~ dgamma(0.001,0.001)*

A14. **Priority Question:** Major bleeding events in NMA2. Please present the results in the format of the Relative Risk tables in the 'Bleeding' worksheet of the company model (columns L:P).

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A15. **Priority Question:** CRNM events in NMA2. Please present the results in the format of the Relative Risk tables in the 'Bleeding' worksheet of the company model (columns L:P).

A16. Base case analysis in NMA1 (table 34 company submission).

A17. Sensitivity analysis 1- mITT in NMA1 (table 35 in company submission).

A18. Sensitivity analysis 1- mITT excluding dabigatran studies in NMA1 (table 35 company submission).

A19. Sensitivity analysis 2-Pooled RE-COVER/RE-COVER II in NMA1 (table 35 in company submission).

A20. Sensitivity analysis 3- excluding RE-COVER/RE-COVER II in NMA1 (table 35 in company submission).

A21. Base case analysis in NMA 2 (table 37 in company submission).

A22. Sensitivity analysis 4- ITT in NMA 2 (table 38 in company submission).

A23. Sensitivity analysis 5- excluding WODIT DVT/PE in NMA 2 (table 38 in company submission).

A24. Sensitivity analysis 6-excluding RE-SONATE/RE-MEDY in NMA 2 (table 38 company submission).

A25. Sensitivity analysis 4-ITT excluding dabigatran studies in NMA 2 (table 38 company submission).

A26. Sensitivity analysis 5- excluding dabigatran studies in NMA2 (table 38 company submission).

Additional Kaplan-Meier analyses of data from AMPLIFY and AMPLIFY EXT

Please provide the Kaplan-Meier analyses requested in questions **A27–A38**. In these analyses please:

- Do not impute events were outcomes data are missing
- Do not exclude lost to follow-up patients (instead, please censor patients at the time the patient was lost to follow-up or withdrew from the trial).
- Present the results in tabular form showing for each event time:
  - Time of event from baseline (days)
  - Product-limit estimate of survival proportion

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- Standard error of survival proportion
- Number of patients failed
- Number of patients remaining at risk

For your information an example of the output table required from the Kaplan Meier analyses from SAS is given at the end of this letter under additional information.

A27. **Priority Question:** AMPLIFY trial data. Time to death from any cause K-M analysis, stratified by treatment arm and by index event type (i.e. DVT only vs PE +/- DVT) [i.e. 2 x 2 analyses]. This analysis should include the 30 day observation period after treatment discontinuation.

A28. **Priority Question:** AMPLIFY trial data. Time to treatment discontinuation K-M analysis, stratified by treatment arm and by index event type (i.e. DVT only vs PE +/- DVT) [i.e 2 x 2 analyses], censoring patients at time to death from any cause.

A29. AMPLIFY trial data**.** Time to major bleed K-M analysis, stratified by treatment arm and by index event type (i.e. DVT only vs PE +/- DVT) [i.e 2 x 2 analyses].

A30. AMPLIFY trial data. Time to CRNM K-M analysis, stratified by treatment arm and by index event type (i.e. DVT only vs PE +/- DVT) [i.e 2 x 2 analyses].

A31. AMPLIFY-EXT trial data. Time to death from any cause K-M analysis, stratified by treatment arm, by index event type (i.e. DVT only vs PE +/- DVT) and by prior treatment history (apixaban vs other anti-coagulants) [i.e. 2 x 2 x 2 analyses].

A32. AMPLIFY-EXT trial data (time adjusted by AMPLIFY trial data). For only those AMPLIFY patients continuing to AMPLIFY-EXT, time to death from any cause K-M analysis, stratified by treatment arm in AMPLIFY, by treatment arm in AMPLIFY-EXT and by index event type (i.e. DVT only vs PE +/- DVT) [i.e. 2 x 2 x 2 analyses], counting elapsed time from initial randomisation to the AMPLIFY trial (including the AMPLIFY 30 day observation period after treatment discontinuation).

A33. AMPLIFY-EXT trial data. Time to first non-VTE death K-M analysis, stratified by treatment arm and by index event type (i.e. DVT only vs PE +/- DVT), censoring patients at time of death due to any VTE event.

A34. AMPLIFY-EXT trial data. Time to first PE event (fatal or non-fatal) K-M analysis, stratified by treatment arm and by index event type (i.e. DVT only vs PE +/- DVT), censoring patients at time of death due to either non-VTE cause or DVT event.

A35. AMPLIFY-EXT trial data. Time to first DVT event (fatal or non-fatal) K-M analysis, stratified by treatment arm and by index event type (i.e. DVT only vs PE +/- DVT), censoring patients at time of death due to either non-VTE cause or PE event.

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A36. AMPLIFY-EXT trial data. Time to treatment discontinuation K-M analysis, stratified by treatment arm and by index event type (i.e. DVT only vs PE +/- DVT), censoring patients at time of death from any cause.

A37. AMPLIFY-EXT trial data. Time to major bleed K-M analysis, stratified by treatment arm and by index event type (i.e. DVT only vs PE +/- DVT) [i.e 2 x 2 analyses].

A38. AMPLIFY-EXT trial data. Time to CRNM K-M analysis, stratified by treatment arm and by index event type (i.e. DVT only vs PE -+ DVT) [i.e 2 x 2 analyses].

Additional information

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