14th September 2012

NHS
National Institute for Health and Clinical Excellence

NICE
Midcity Place
71 High Holborn
London
WC1V 6NA

[redacted]

Re: Single Technology Appraisal – Apixaban for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation

The Evidence Review Group BMJ Technology Assessment Group and the technical team at NICE have now had an opportunity to take a look at the submission received on the 17th August 2012 by Bristol-Myers Squibb and Pfizer. 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 **14:00, 28th September 2012**. 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]
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1. **Priority Request:** Please provide the clinical study reports for ARISTOTLE and AVERROES (references 67 and 68 in the manufacturer's submission).

Inclusion and exclusion criteria for the AVERROES and ARISTOTLE trials

A2. Please clarify the rationale for including *a prior* systemic embolism in the inclusion criteria for ARISTOTLE and not in AVERROES.

A3. Please clarify whether people with AF due to reversible causes were excluded from AVERROES.

A4. Please clarify whether people with mitral stenosis were excluded from AVERROES.

A5. Please clarify why an exclusion criteria based upon liver function was included in AVERROES.

Baseline characteristics of the AVERROES and ARISTOTLE trial populations

A6. Please provide details of the number of patients, mean dose (and SD), and median dose (and the range) in each trial arm of AVERROES who at baseline were on:

i) non-study concomitant aspirin;
ii) clopidogrel;
iii) NSAIDs;
iv) other anti-platelet drugs e.g. dipyridamole.

A7. Please provide details of the number of patients in each trial arm of ARISTOTLE who had atrial flutter at baseline.

A8. Please provide the number of people in each trial arm at baseline in AVERROES who had a history of prior MI.

Trial populations and populations included in analysis

A9. **Priority question:** Please complete the table below for the ITT populations in (two tables in total):

i) ARISTOTLE;

ii) AVERROES

Event	Apixaban		Comparator		HR and 95% CI	p value
	n	N	n	N		
Haemorrhagic stroke						
Mild						
Moderate						
Severe						
Fatal						
Other fatal intracranial haemorrhage						
Ischaemic stroke						
Mild						
Moderate						
Severe						
Fatal						
Fatal systemic embolism						
Other CV hospitalisation (as defined in the economic model)						
Other major bleeds (as defined in the economic model)						
Non- ICH and non- GI related bleeds						
Fatal major bleeds						
Other cause mortality (as defined in the economic model)						
Other treatment discontinuations (as defined in the economic model)						

A10. Please provide the per protocol results for the primary efficacy outcome (stroke or SE) in ARISTOTLE.

A11. Please clarify the numbers reported in Figure 4, page 51 of the manufacturer's submission (the Participant Flow for AVERROES) for patients discontinuing from both the apixaban and aspirin trial arms of AVERROES as the total numbers do not appear to equal the sum of the numbers reported for the individual reasons (subject request, AE, death and other reasons).

A12. Please provide details of the number of patients in each study arm in ARISTOTLE who experienced ≥1 study-drug interruption and the duration of the study drug interruptions.

Subgroups

Stroke risk $CHAD_2$ scores

A13. **Priority Question:** Please complete the table below to provide the safety and efficacy results of ARISTOTLE and AVERROES by the following baseline $CHADS_2$ scores (six tables in total, three for each trial)

i) ≤1;

ii) 2;

iii) ≥3

Event	Apixaban		Comparator		HR and 95% CI	p value
	n	N	n	N		
Stroke or systemic embolism						
Stroke (any)						
Fatal stroke						
Disabling stroke						
Non-disabling stroke						
Ischaemic stroke						
Mild						
Moderate						
Severe						
Fatal						
Intracranial haemorrhage (ICH)						
Haemorrhagic stroke						
Mild						
Moderate						
Severe						
Fatal						
Other ICH						
Fatal						
Systemic embolism						
Fatal						
Myocardial Infarction (MI)						
Other CV hospitalisation (as defined in the economic model)						
Any bleeding						
Major bleeding						
Other major bleeds (as defined in the economic model)						
Gastrointestinal (GI) bleeds						
Non- ICH and non- GI related bleeds						
Fatal major bleeds						
CRNM bleed						
All-cause mortality						
Other cause mortality (as defined in the economic model)						
Discontinuations						
Other treatment discontinuations (as defined in the economic model)						

A14. Please complete the table below to provide further details of the baseline $CHADS_2$ scores in both ARISTOTLE and AVERROES:

	ARISTOTLE		AVERROES	
$CHADS_2$ score	**Apixaban**	**Warfarin**	**Apixaban**	**Aspirin**
	n	**n**	**n**	**n**
0				
1				
2				
3				
4				
5				
6				

A15. Please complete the table below to provide the results for the primary efficacy and safety outcomes for each $CHADS_2$ subgroup in:

i) ARISTOTLE;
ii) AVERROES.

Subgroup	**Event**	**Apixaban**		**Comparator**		**HR and 95% CI**	**p value**
		n	**N**	**n**	**N**		
	Primary efficacy outcome						
CHADS score 0							
CHADS score 1							
CHADS score 2							
CHADS score 3							
CHADS score 4							
CHADS score 5							
CHADS score 6							
	Primary safety outcome						
CHADS score 0							
CHADS score 1							
CHADS score 2							
CHADS score 3							
CHADS score 4							
CHADS score 5							
CHADS score 6							

% TTR

A16. Please provide the % TTR for each of the following region subgroups in ARISTOTLE:

i) North America;
ii) Latin America;
iii) Europe;
iv) Asia/Pacific;
v) US;
vi) Eastern EU;
vii) Western EU.

A17. Please provide the % TTR for the following age subgroups in ARISTOTLE:

i) <65 years;
ii) 65 to <75years;
iii) ≥75 years.

A18. Please provide the total number of people included in each analysis for each cTTR subgroup reported in tables 19 and 28 for each trial arm (i.e. apixaban and warfarin groups).

Region subgroups

A19. **Priority Question:** Please complete the table below to provide the safety and efficacy results of ARISTOTLE for the Western Europe subgroup (as defined in table 15, page 49 of the manufacturer's submission)

Event	Apixaban		Comparator		HR and 95% CI	p value
	n	N	n	N		
Stroke or systemic embolism						
Stroke (any)						
Fatal stroke						
Disabling stroke						
Non-disabling stroke						
Ischaemic stroke						
Mild						
Moderate						
Severe						
Fatal						
Intracranial haemorrhage (ICH)						
Haemorrhagic stroke						
Mild						
Moderate						
Severe						
Fatal						
Other ICH						
Fatal						
Systemic embolism						
Fatal						
Myocardial Infarction (MI)						
Other CV hospitalisation (as defined in the economic model)						
Any bleeding						
Major bleeding						
Other major bleeds (as defined in the economic model)						
Gastrointestinal (GI) bleeds						
Non- ICH and non- GI related bleeds						
Fatal major bleeds						
CRNM bleed						
All-cause mortality						
Other cause mortality (as defined in the economic model)						
Discontinuations						
Other treatment discontinuations (as defined in the economic model)						

Other subgroups

A20. Please provide a breakdown of the reasons why people were taking 2.5 mg apixaban in both ARISTOTLE and AVERROES and the number of people for which each reason applies.

A21. Please complete the table below to provide the safety and efficacy outcome data for the following subgroups (five tables in total):

a. people on 2.5mg apixaban in ARISTOTLE;
b. people on 5mg apixaban in ARISTOTLE;
c. people on 2.5mg apixaban and aged over 80years in ARISTOTLE;
d. people <65years age in ARISTOTLE;
e. people contraindicated to warfarin in AVERROES.

Event	Apixaban		Comparator		HR and 95% CI	p value
	n	N	n	N		
Stroke or systemic embolism						
Stroke (any)						
Fatal Stroke						
Disabling stroke						
Non-disabling stroke						
Ischaemic stroke						
Mild						
Moderate						
Severe						
Fatal						
Intracranial haemorrhage (ICH)						
Haemorrhagic stroke						
Mild						
Moderate						
Severe						
Fatal						
Other ICH						
Fatal						
Systemic embolism						
Fatal						
Myocardial Infarction (MI)						
Other CV hospitalisation (as defined in the economic model)						
Any bleeding						
Major bleeding						
Other major bleeds (as defined in the economic model)						
Gastrointestinal (GI) bleeds						
Non- ICH and non- GI related bleeds						
Fatal major bleeds						
CRNM bleed						
All-cause mortality						
Other cause mortality (as defined in the economic model)						
Discontinuations						
Other treatment discontinuations (as defined in the economic model)						

A22. Please provide the results for all subgroups in AVERROES specified in table 15 for the primary efficacy outcome (stroke or SE).

A23. Please provide the p value used to determine the presence of a significant between subgroup interaction in AVERROES. If the p value for between subgroup interaction in AVERROES was <0.10 (as it is in ARISTOTLE) then please suggest an explanation for the significant difference in treatment effect for age subgroups (p=0.08).

Network meta analysis

A24. **Priority Question:** Please provide the WinBUGS files containing the numerical trial data used for each of the outcomes assessed in the NMAs to enable validation of the results provided within the submission.

A25. **Priority Question:** Please provide the total residual deviance for the fixed and random effects models and the values of tau for the random effects model for each outcome assessed in the network meta analysis.

Other clarifications on clinical effectiveness

A26. Please explain how the estimate that 80% of AF is non-valvular (page 20 of the manufacturer's submission) was calculated from reference 25.

A27. Please provide the numerical values for the total number of people included in each analysis (including the number of people in each treatment arm), the hazard ratio and 95% confidence interval for each of the subgroup results presented in the following figures in the manufacturer's submission:

i) Figure 6;
ii) Figure 8;
iii) Figure 12.

A28. Please provide the absolute values for the number of people in each trial arm experiencing an event and the total number in the analysis for the following outcomes reported in the text on page 55 of the manufacturer's submission:

i) death from cardiovascular causes;
ii) death from non-cardiovascular causes.

<u>Section B: Clarification on cost-effectiveness data</u>

Requested updates to the model

B1. **Priority request:** Please provide an Excel file with a version of the model allowing a scenario analysis in which patients experiencing an SE are exposed to the same risks as patients who have experienced an ischaemic stroke (i.e. subsequent stroke events).

B2. **Priority request:** Within the submitted model, patients are modelled as surviving for up to 49 years (from 74 years to 123 years of age). Please provide an updated model which imposes a reasonable (e.g. 100 years) maximum survival for the AF patient population.

B3. **Priority request:** Please provide an updated model in which utility is adjusted for age as the model cohort ages.

Assumptions

B4. Please provide an alternative version of Table 77 running the model under the assumption that other cause mortality is not treatment specific (i.e. no trial based other cause mortality).

B5. It is noted that the reference used to inform the risk of incident death from MI reports risk according to gender for MI and stroke. However, the risk of incident death following stroke is not gender specific.

a) Please provide the rationale for using gender specific case fatality rates for MI and not for stroke

b) Provide a scenario in which stroke case fatality is also varied by gender

B6. For those patients that are VKA suitable and do not receive warfarin as first line therapy, please explain the rationale for assuming that aspirin rather than warfarin is the second line treatment following an “other ICH” or major bleed event in the base case model.

B7. Please clarify:

a) Whether data on other hospitalisation was collected in ARISTOTLE.

b) The rationale for assuming that the CV hospitalisation rate for warfarin does not differ from apixaban in the VKA suitable population.

c) The rationale for assuming that the CV hospitalisation rate for aspirin does differ from apixaban in the VKA unsuitable population.

References

B8. Please clarify whether the risk adjustment factors summarised in Table 43 (p114/115) were identified systematically and provide details of the identification process.

Other

B9. It is understood that data from the Friberg et al. study (identified in the “Targeted literature Review for the UK adaption of the Apixaban Atrial Fibrillation Cost- effectiveness Model”) has been used to calculate a hazard ratio of 1.34 for other cause mortality in an AF patient population. Please provide a step by step calculation of this hazard ratio moving from raw data extracted from the paper to the final hazard ratio.

B10. Please provide step by step calculations for the following utility decrements:

a) Other ICH;

b) Other major bleeds;

c) CRNM bleeds;

Moving from raw data presented in the cited reference to the utility decrement value implemented in the economic model.

B11. The base case results in the VKA unsuitable population (presented in Table 80, p146) indicate that apixaban is extendedly dominated. Please clarify the rationale for concluding that apixaban is extendedly dominated.

B12. Please provide:

a) a step by step calculation of acute SE costs moving from raw data presented in the cited reference to the cost used in the economic model.

b) Sensitivity analysis values for acute and long term SE costs similar to the values presented in Tables 63 and 64 for ischaemic and haemorrhagic stroke.

Section C: Textual clarifications and additional points

None