Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism [ID726]

BMS/Pfizer Response to Evidence Review Group (ERG) Clarification questions
20th November 2014

Executive Summary

BMS/Pfizer welcomes the opportunity to respond to the ERG's clarification questions from the Liverpool Reviews and Implementation Group (LRiG) for the review of apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism [ID726].

BMS/Pfizer note that we received no clarification questions on the economic modelling section of the submission. Despite this, additional Kaplan-Meier (KM) data were requested by the ERG for the purpose of verifying economic modelling assumptions, as confirmed by NICE on the 12th of November. Given that the economic modelling is an important stage of the appraisal process; BMS/Pfizer would like to reiterate our willingness to provide clarification regarding the clinical assumptions underlying the apixaban model, so as to avoid misinterpretation, which could lead to avoidable uncertainty for the NICE appraisal committee. We are happy to engage in any further dialog with the ERG to ensure that they receive any clarification required and any concerns are addressed.

We understand and we are willing to facilitate the testing of the modelling assumptions to ensure a transparent evaluation of apixaban. Therefore, we have undertaken extensive analyses to respond to questions A1 to A26. Due to the limited time available, the number of new analyses requested and the need to include new variables into the data sets (including extensive validation and quality assurance) we have not be able to provide answers to questions A27-38 before the deadline date of the 20th November. We are still in the process of dealing with the request and we will be in touch shortly.

With respect to interpretation of the data provided in this response we would like to provide guidance and highlight three concerns with the clarification questions received. These are:

1. **ERG request to re-run network meta-analysis 2 (prevention period) with a fixed study effect variable**
2. **ERG request to provide KM data for a number of outcomes from the AMPLIFY study**
3. **ERG request to provide KM data that is likely to be highly uncertain especially for DVT and PE subgroups for AMPLIFY and AMPLIFY-EXT study**

BMS/Pfizer believes that findings from these analyses should be interpreted with caution for the reasons outlined below:

1. **Request to re-run NMA 2 with a fixed study effect variable**

BMS/Pfizer consider that the request to re-run the NMA 2 (prevention period) with a fixed study effect variable (informative prior) is likely to lead to a biased estimate of the relative treatment effectiveness between interventions given the conceptual heterogeneity observed in NMA 2. BMS/Pfizer suggests that the study effect should not be fixed for NMA 2 given these issues.

2. **Request to provide KM data for AMPLIFY**

BMS/Pfizer realise that the ERG may be testing assumptions within the model regarding the temporal distribution of events within the trial period of AMPLIFY. However, the extrapolation of data beyond the end of AMPLIFY is likely to have limited applicability for the interpretation of apixaban effectiveness and safety, as the 2.5 mg twice daily dose should be initiated, according to label, following completion of 6 months of treatment with Eliquis 5 mg twice daily (the dose in AMPLIFY). The extrapolation of Eliquis 5mg twice daily beyond the six months treatment would not be appropriate and is outside our licensed indication.

3. **Request to provide KM data that is likely to be underpowered to detect differences especially for DVT and PE subgroups for AMPLIFY and AMPLIFY-EXT studies**

A number of the requests for KM data received from the ERG for outcomes from both AMPLIFY and AMPLIFY-EXT are likely to provide a highly uncertain estimation of the relative effectiveness of apixaban compared to comparators. For some of these requests there are only few events and this can cause the KM curves to fluctuate with large steps, which implies a large degree of uncertainty. Tests between groups based on KM are sensitive to event counts and it is likely they will lack power to show any differences. This is especially relevant for the analyses conducted on the DVT and PE subgroups.

BMS/Pfizer is confident that the clinical evidence of apixaban demonstrates efficacy and safety in both the treatment and the prevention of DVT and/or PE. Throughout the economic modelling we have selected conservative inputs and assumptions when data is limited or missing. Therefore we are confident that we have presented a conservative estimate of apixaban's cost effectiveness relative to the comparators in the appraisal. Apixaban is a cost-effective use of NHS resources.

The following sections provide responses to each of the clarification questions and further details on these key points for consideration.

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.

As detailed in Table 4 (page 37 of the main submission), potentially eligible citations were screened to establish whether they met the pre-specified inclusion/exclusion criteria including efficacy and safety outcomes of interest. The pre-specified efficacy and safety outcomes are in line with the Apixaban for VTE final NICE scope. From the 4,966 titles ± abstracts excluded (Figure 1, page 39), 197 citations were due to various reasons including 'not outcomes of interest', as presented below:

- Cost-effectiveness
- Cost-of-illness studies
- Pharmacokinetics
- Optimal time in therapeutic range
- In vitro outcomes

We appreciate that although we cannot be certain that the 197 excluded publications did not report an outcome of interest within the abstract, it is clear that the principal focus of these publications was not the efficacy or safety of anticoagulation for the treatment or prevention of VTE. Additionally, the majority of these publications were excluded for multiple reasons (e.g. study design, patient population). As duplicated screening (i.e. two reviewers working independently) was employed at both titles ± abstracts and full-paper screening stages, with any disagreements resolved through team consensus or the involvement of a third reviewer, we are confident that all relevant citations were identified.

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

The authors of the eight publications were not contacted to assess whether an outcome of interest had indeed been measured in the publication. However, we were confident that the full text information presented in the primary publications of these studies is sufficient to establish if the relevant outcome of interest for inclusion was measured or otherwise. For example, the publication by Bamber et al. (2013) reported on, "patient-reported treatment satisfaction", an outcome assessed in the EINSTEIN DVT study which had previously been published (reference (50) of the main submission), as no other outcomes relevant to this

submission were reported in either publication, we are certain that all the studies reporting on the outcomes of interest have been identified.

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.

The 27 (12 apixaban + 15 enoxaparin/warfarin) subjects classified as "qualifying diagnosis could not be evaluated" in Table 9 actually represented subjects in whom the index event was "adjudicated as not event" (N=[redacted]), "not evaluable" (N=[redacted]), or "not reported" (N=[redacted]), as summarized in Table 1 below.

[redacted]

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].

Table 10.1.1 in Appendix 1 presents a cross tabulation showing the distribution of patients by 5 year age band and gender in AMPLIFY study.

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]

Table 10.1.2 in Appendix 2 presents a cross tabulation table showing the distribution of patients by 5 year age band and gender in AMPLIFY-EXT study.

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

The demographic and clinical characteristics of AMPLIFY-EXT subjects who participated in AMPLIFY and subjects newly recruited in AMPLIFY-EXT are provided in Tables 10.2.1 and 10.2.2 in Appendices 3 and 4 respectively.

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" ?

The footnote included in Appendices 6a and 6b of the main submission was taken from the footnote to Table 2 of the primary RE-COVER study publication (72), i.e. "*The efficacy analysis was based on the number of randomly assigned patients who received at least one dose of study drug and who had events during the 6-month treatment period, regardless of early discontinuation of study drug.*" The efficacy analysis of data from the RECOVER trial, based on the ITT population included patients who received ≥1 dose of study drug. Also, all events occurring within 6 months post randomisation were counted as events in the analysis regardless of early discontinuation of study drug. Therefore, this statement should read as

"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.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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.

In the AMPLIFY study, patient from the enoxaparin/warfarin arm (n=) and patients from the apixaban arm (n=) experienced more than one major bleeding episode. Similarly, patient from the placebo arm (n=) and zero patients from the apixaban arms (either 2.5 mg or 5 mg), experienced more than one major bleeding episode in AMPLIFY-EXT.

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.

The number of patients who experienced at least one major bleeding episode during the treatment period and a recurrent VTE event during the intended treatment period was for Apixaban and for Enoxaparin/Warfarin in the AMPLIFY trial. . Reference tables are Table 10.3.1 and Table 10.3.2 in Appendices 5 and 6 respectively.

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

A summary of the main study characteristics for the studies included in NMA1 and NMA2 are presented in Tables 2 and 3, respectively. Full details of the study characteristics can be found in the primary publications, protocols, or on-line supplementary evidence of the respective studies.

Table 2: Study characteristics for the studies included in NMA 1

Study	Study location	Inclusion criteria	Exclusion criteria	Primary outcomes (methods and timing of assessments)	Secondary efficacy outcomes	Study design
AMPLIFY(14)	International, multicenter (358 clinical centres in 28 countries)	Patients 18 years of age or older and had objectively confirmed, symptomatic proximal DVT or PE (with or without DVT) *Full details are presented in Table 8 (pages 45-47) of the main submission*	Patients were excluded if they had active bleeding or other contraindications to treatment with enoxaparin and warfarin; if they had cancer and long term treatment with LMWH was planned; if their DVT or PE was provoked; if less than 6 months of anticoagulant was planned; or if they had another indication for long tern anticoagulant therapy, dual antiplatelet therapy, treatment with aspirin at a dose of more than 165mg daily or treatment with potent inhibitors of cytochrome P- 450 3A4. *Full details are presented in Table 8 (pages 45-47) of the main submission*	**Efficacy** 6 month Incidence of the adjudicated composite of symptomatic, recurrent VTE (non-fatal DVT or non-fatal PE) or VTE-related death occurring at any time from randomisation until the end of the originally intended treatment period of 6 months (PE was judged to occur where symptoms of PE were present along with one of the following including Intraluminal filling defect, sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram and perfusion defect of at least 75%. DVT was judged to occur where symptoms of DVT were present along with one of the following findings including abnormal CUS or intraluminal filling defect) **Safety** Incidence during treatment period of adjudicated major	**Efficacy** Symptomatic non-fatal PE, symptomatic non-fatal DVT, VTE related death, all-cause death **Safety** Minor bleeding, composite of major or CRNM, total adjudicated bleeding, CRNM bleeding *Full details presented in Table 11 (page 51 -53) of the main submission*	Randomised, double blind, non-inferiority study

Study	Study location	Inclusion criteria	Exclusion criteria	Primary outcomes (methods and timing of assessments)	Secondary efficacy outcomes	Study design
				bleeding. (Bleeding defined according to according to ISTH guidelines (66)) described as fatal bleeding, symptomatic bleeding in a critical area or organ and bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells) *Full details presented in Table 11 (page 51 -53) of the main submission*		
RECOVER(72)	International, multicenter (228 clinical centres in 29 countries)	Patients 18 years of age or older who had acute, symptomatic, objectively verified proximal deep-vein thrombosis of the legs or pulmonary embolism and for whom 6 months of anticoagulant therapy was considered to be an appropriate treatment were potentially eligible	Exclusion criteria were duration of symptoms longer than 14 days, pulmonary embolism with hemodynamic instability or requiring thrombolytic therapy, another indication for warfarin therapy, recent unstable cardiovascular disease, a high risk of bleeding, liver disease with an aminotransferase level that was two times the local upper limit of the normal range, an estimated creatinine clearance of less than 30 ml per minute, a life expectancy of less than 6 months, a	**Efficacy** 6-month incidence of recurrent symptomatic VTE and deaths related to VTE (assessed with the use of compression Ultrasonography or venography of leg veins and ventilation-perfusion lung scanning, angiography or spiral computed tomography of pulmonary arteries) **Safety** Major bleeding	**Efficacy** Symptomatic DVT, symptomatic non-fatal PE, VTE-related death **Safety** Major or CRNM bleeding, any bleeding event	Randomised, double blind, non-inferiority study

Study	Study location	Inclusion criteria	Exclusion criteria	Primary outcomes (methods and timing of assessments)	Secondary efficacy outcomes	Study design
			contraindication to heparin or to radiographic contrast material, pregnancy or risk of becoming pregnant, or a requirement for long-term antiplatelet therapy (≤100 mg of acetylsalicylic acid daily was acceptable). There were no weight restrictions	(Bleeding was defined as major if it was clinically overt and associated with a fall in haemoglobin level of 20 g per litre or more resulted in the need for transfusion of 2 or more units of red cells, involved a critical site, or was fatal)		
RE-COVER II(73)	International, multicenter (220 clinical centres in 31 countries)	Patients 18 years or older who has acute symptomatic, objectively verified proximal DVT of the legs, or PE for whom 6 months of anticoagulant therapy was considered to be an appropriate treatment were potentially eligible	Exclusion criteria were persistent symptoms of VTE, PE requiring urgent intervention, use of vena cava filter, contraindications to anticoagulant therapy, allergy to study medications and elevated Aspartate-aminotransferase (AST) or ALT >3x ULN or known liver disease expected to have an impact on survival, severe renal impairment.	**Efficacy** 6-month incidence of recurrent symptomatic VTE and deaths related to VTE (assessed with the use of compression Ultrasonography or venography of leg veins and ventilation-perfusion lung scanning, angiography or spiral computed tomography of pulmonary arteries) **Safety** Major bleeding (Bleeding was defined as major if it was clinically overt and associated with a fall in haemoglobin level of 20 g per litre or more resulted in the need for transfusion of 2 or more	**Efficacy** Symptomatic DVT, symptomatic non-fatal PE, VTE-related death **Safety** Major or CRNM bleeding, any bleeding event	Randomised, double blind, non-inferiority study

Study	Study location	Inclusion criteria	Exclusion criteria	Primary outcomes (methods and timing of assessments)	Secondary efficacy outcomes	Study design
				units of red cells, involved a critical site, or was fatal)		
EINSTEIN PE(50)	International, multicenter (300 clinical centers in over 30 countries)	Patients were eligible if they were of legal age and had an acute, symptomatic pulmonary embolism with objective confirmation, with or without symptomatic deep-vein thrombosis	Patients were ineligible if they had received a therapeutic dose of low-molecular-weight heparin, fondaparinux, or unfractionated heparin for more than 48 hours or if they had received more than a single dose of a vitamin K antagonist before randomization; if thrombectomy had been performed, a vena cava filter placed, or a fibrinolytic agent administered for treatment of the current episode; or if they had any contraindication listed in the local labelling of enoxaparin, warfarin, or acenocoumarol. Other criteria for ineligibility were another indication for a vitamin K antagonist; a creatinine clearance below 30 ml per minute.	**Efficacy** 3,6,12 month incidence of symptomatic recurrent venous thromboembolism (DVT assessed using new non-compressible venous segment a substantial increase (4mm or more) in the diameter of a thrombus. Criteria for PE were a new intraluminal filling defect on a spiral CT or pulmonary angiography)) **Safety** First major or CRNM (Bleeding was defined as major if it was clinically overt and associated with a fall in haemoglobin level of 2.0g per decilitre or more, etc. CRNM defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention)	**Efficacy and safety** Major bleeding, death from any cause, vascular events (ACS, IS, TIA or SE) and Net clinical benefit (composite of primary efficacy outcome or major bleeding)	Randomised, open-label non-inferiority study
EINSTEIN DVT(50)	International, multicenter (300 clinical centers in over 30 countries)	Patients were eligible if they were of legal age for consent and had acute, symptomatic, objectively confirmed proximal DVT, without symptomatic	Patients were ineligible if they had received therapeutic doses of low-molecular-weight heparin, fondaparinux, or unfractionated heparin for more than 48 hours	**Efficacy** 3,6,12 -month incidence of symptomatic recurrent venous thromboembolism (DVT assessed using a new non-compressible venous	**Efficacy and safety** All cause mortality, vascular events (ACS, IS, TIA or SE) and Net clinical benefit (composite of primary efficacy	Randomised, open-label non-inferiority study

Study	Study location	Inclusion criteria	Exclusion criteria	Primary outcomes (methods and timing of assessments)	Secondary efficacy outcomes	Study design
		pulmonary embolism	or if they had received more than a single dose of a vitamin K antagonist before randomization; if they had been treated with thrombectomy, a vena cava filter, or a fibrinolytic agent for the current episode of thrombosis; or if they had any contraindication listed in the labelling of enoxaparin, warfarin, or acenocoumarol	segment a substantial increase (4mm or more) in the diameter of a thrombus. Criteria for PE were a new intraluminal filling defect on a spiral CT or pulmonary angiography, etc.) **Safety** First major or CRNM (Bleeding was defined as major if it was clinically overt and associated with a fall in haemoglobin level of 2.0g per decilitre or more. CRNM defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention)	outcome or major bleeding)	

CRNM – clinically relevant non-major; DVT – deep vein thrombosis; PE- pulmonary embolism; VTE – venous thromboembolism

Note: Study references correspond to those presented in the main submission

Table 3: Study characteristics for the studies included in NMA 2

Study	Study location	Inclusion criteria	Exclusion criteria	Primary outcomes (methods and timing of assessments)	Secondary efficacy outcomes	Study design
AMPLIFY-EXT (16)	International, multicenter (328 in 28 countries)	Patients 18 years of age or older and had objectively confirmed, symptomatic proximal DVT or PE (with or without DVT); if they had been treated for 6 to 12 months with standard anticoagulant therapy or had completed treatment with apixaban or enoxaparin and warfarin as participants in the AMPLIFY trial; if they had not had a symptomatic recurrence during prior anticoagulant therapy; and if there was clinical equipoise about the continuation or cessation of anticoagulant therapy *Full details are presented in Table 8 (pages 45-47) of the main submission*	Patients were ineligible if they had a contraindication to continued anticoagulant therapy or if they required ongoing anticoagulant therapy, dual antiplatelet therapy, or aspirin at a dose higher than 165 mg daily; hemoglobin level of less than 9 mg per deciliter, a platelet count of less than 100,000 per cubic millimeter, a serum creatinine level of more than 2.5 mg per deciliter (221 µmol per liter) or a calculated creatinine clearance of less than 25 ml per minute *Full details are presented in Table 8 (pages 45-47) of the main submission*	**Efficacy** Incidence of an adjudicated composite of symptomatic, recurrent VTE or all-cause death occurring at any time from randomisation until the end of the intended treatment period of 6 months (PE was judged to occur where symptoms of PE were present along with one of the following; Intraluminal filling defect, sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram and perfusion defect of at least 75%. DVT was judged to occur where symptoms of DVT were present along with one of the following findings including abnormal CUS or intraluminal filling defect) **Safety** Incidence during treatment period of adjudicated major bleeding. (Bleeding defined according to according to ISTH guidelines (66)) described	**Efficacy** Symptomatic non-fatal PE, symptomatic non-fatal DVT, VTE related death, all-cause death **Safety** Minor bleeding, composite of major or CRNM, total adjudicated bleeding, CRNM bleeding *Full details presented in Table 11 (page 51 -53) of the main submission*	Randomised, double blind, placebo controlled study

Study	Study location	Inclusion criteria	Exclusion criteria	Primary outcomes (methods and timing of assessments)	Secondary efficacy outcomes	Study design
				as fatal bleeding, symptomatic bleeding in a critical area or organ and bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells) *Full details presented in Table 11 (page 51 -53) of the main submission*		
ASPIRE (55)	International, multicenter (Australia, India, Singapore, New Zealand and Argentina)	Male and female patients were eligible for inclusion If, they were at least 18 years of age and had had a first unprovoked episode of objectively diagnosed symptomatic deep-vein thrombosis involving the popliteal vein or more proximal leg veins or an acute pulmonary embolism. All patients were required to have completed initial anticoagulation therapy with heparin followed by warfarin (or an effective alternative anticoagulant). The duration of the initial anticoagulation therapy had to be between 6 weeks and 24 months; however, it was	Patients were not eligible for inclusion if, the first unprovoked episode of venous thromboembolism had occurred more than 2 years before enrollment; if they had an indication or contraindication for the use of aspirin, other antiplatelet therapy, or a non-steroidal anti-inflammatory drug; if they had an indication for continuing oral anticoagulation therapy; or if they had other medical problems that would interfere with participation in the trial or limit life expectancy	**Efficacy** Recurrence of venous thromboembolism (The diagnosis of a recurrence of venous thromboembolism required the presence of new symptoms and objective evidence on appropriate imaging of new thrombosis that was not identified on previous imaging (as detailed in the study protocol) **Safety** Major or clinically relevant non-major bleeding (Major bleeding was defined as overt bleeding that was associated with a	**Efficacy and safety** Major vascular events (a composite of venous thromboembolism, myocardial infarction, stroke, or cardiovascular death) and a measure of the net clinical benefit (a reduction in the rate of the composite of venous thromboembolism, myocardial infarction, stroke, major bleeding, or death from any cause)	Randomised, double blind, placebo controlled study

Study	Study location	Inclusion criteria	Exclusion criteria	Primary outcomes (methods and timing of assessments)	Secondary efficacy outcomes	Study design
		recommended that a target international normalized ratio of 2 to 3 be maintained with warfarin therapy for 6 to 12 months		decrease in hemoglobin of at least 2 g per deciliter or that necessitated transfusion of 2 or more units of blood, involved a critical site (e.g., retroperitoneal or intracranial bleeding), was disabling, required surgical intervention, or contributed to death)		
EINSTEIN- EXT (78)	International, multicenter (322 clinical centres in 34 countries)	Patients 18 years or older with confirmed symptomatic PE or DVT who have been treated for 6 or 12 months with VKA or rivaroxaban	Patients with another indication for a VKA, with severe renal insufficiency or clinically significant liver disease, bacterial endocarditis, active bleeding or high risk of bleeding, uncontrolled arterial hypertension, concomitant pregnancy or breast feeding, and coexistent use of strong cytochrome P450 3A4 inhibitors or inducers were not included in the study	**Efficacy** Incidence of symptomatic recurrent VTE (Events were assessed based on either compression ultrasound (for DVT), venography (for DVT), spiral computed tomography (CT) scanning (for PE), pulmonary angiography (for PE), ventilation/perfusion lung scan (for PE), lung scintigraphy (for PE), autopsy (for fatal PE) or unexplained death for which DVT/PE could not be ruled out (for fatal PE), and/or case summaries) **Safety** Major bleeding (Defined as overt bleeding associated with a fall in	**Efficacy and safety** All-cause mortality and cardiovascular events (i.e., acute coronary syndrome, ischemic stroke, transient ischemic attack or systemic embolism) and Net clinical benefit (derived from the composite of the primary efficacy outcome and major bleeding)	Randomised, double-blind, placebo-controlled superiority study

Study	Study location	Inclusion criteria	Exclusion criteria	Primary outcomes (methods and timing of assessments)	Secondary efficacy outcomes	Study design
				the hemoglobin level at least of 20 g per litre or if it led to transfusion of two or more units of red cells or if it occurred in a critical site or contributed to death)		
LAFIT (80)	Multicenter (Canada and USA)	First episode of symptomatically, objectively confirmed venous thromboembolism were eligible if they had completed three uninterrupted months of oral anticoagulant therapy after an initial course of treatment with unfractionated or low molecular-weight heparin. Patients with previous venous thromboembolism were eligible, provided such episodes were secondary to a transient risk factor	Patients were ineligible if they had other indications for or a contraindication to long-term anticoagulant therapy; required long-term treatment with non-steroidal anti inflammatory drugs, ticlopidine, sulfinpyrazone, dipyridamole, or more than 160 mg of aspirin per day; had a familial bleeding diathesis; had a major psychiatric disorder, were pregnant or could become pregnant; were allergic to contrast medium; had a life expectancy of less than two years; were initially treated with a non-licensed preparation of low-molecular-weight heparin; were considered likely to be noncompliant; or were unable to complete follow-up visits because of the distance from	**Efficacy** Symptomatic, objectively confirmed recurrence of VTE during 24 months after randomisation (DVT assessed using compression ultrasonography and PE was diagnosed using ventilation perfusion lung scanning **Safety** Major bleeding (Bleeding was defined as major if it was clinically overt and associated with either a fall in the hemoglobin level of at least 2.0 g per deciliter or a need for the transfusion of two or more units of red cells; if it was retroperitoneal or intracranial; or if it warranted the permanent discontinuation of the study drug. Deaths were classified as due to pulmonary embolism	**Efficacy and safety** Minor bleeding, all-cause death, biochemical abnormalities	Randomised, double-blind study

Study	Study location	Inclusion criteria	Exclusion criteria	Primary outcomes (methods and timing of assessments)	Secondary efficacy outcomes	Study design
			their residence to the medical center	(when there was substantive evidence), hemorrhage, or another cause, or as sudden death)		
PREVENT (75)	Multicenter (Canada, USA and Switzerland)	Men and women 30 years of age or older with documented idiopathic venous thromboembolism were eligible if they had completed at least three uninterrupted months of oral anticoagulation therapy with full-dose warfarin	Patients were ineligible for the trial if they had a history of metastatic cancer, major gastrointestinal bleeding, hemorrhagic stroke, or a life expectancy of less than three years. Patients who were being treated with dipyridamole, ticlopidine, clopidogrel, heparin, more than 325 mg of aspirin, or drugs that affect the prothrombin time and patients who had known lupus anticoagulant antibodies or antiphospholipid antibodies were excluded	**Efficacy** clinically relevant recurrent thromboembolic events (All events were confirmed by objective criteria at the central clinical coordinating center on the basis of venography or reports from compression ultrasonography or magnetic resonance imaging (MRI) in the case of deep venous thrombosis and on the basis of ventilation–perfusion scanning, angiography, or computed tomography (CT) of the chest in the case of pulmonary embolism)	**Efficacy** Net clinical benefit (composite of recurrent VTE, major bleeding, and all-cause mortality) **Safety** Major hemorrhage, minor bleed or deaths	Randomised, double blind study
RE –SONATE (79)	International, multinational (147 sites in 21 countries)	Patients ≥18 years of age with objectively confirmed, symptomatic, proximal DVT or PE and treated with an approved anticoagulant or with dabigatran in one of two previously conducted short-term clinical trials (RE-COVER or RE-COVER	Indication for VKA other than DVT and/or PE, actual bacterial endocarditis, uncontrolled hypertension, life expectancy <6 months, active liver disease or liver disease decreasing survival, active bleeding	**Efficacy** Recurrent symptomatic and objectively verified VTE or death associated with VTE or unexplained death (assessed using pre-specified imaging studies) **Safety**	**Efficacy** Symptomatic DVT, symptomatic non-fatal PE, unexplained death **Safety** Major or CRN bleeding event, any bleeding event, adverse events, acute coronary events	Randomised, double blind, placebo controlled study

Study	Study location	Inclusion criteria	Exclusion criteria	Primary outcomes (methods and timing of assessments)	Secondary efficacy outcomes	Study design
		II). The required duration of initial treatment before enrolment was 6-18 months	or high risk of bleeding. Also, shortly after starting the placebo-control study, patients with active cancer were excluded	Major bleeding (Defined as overt bleeding associated with a fall in the hemoglobin level at least of 20 g per litre or if it led to transfusion of two or more units of red cells or if it occurred in a critical site or contributed to death)	(including cerebrovascular events)	
RE-MEDY (79)	International, multinational (265 sites in 33 countries)	Patients ≥18 years of age with objectively confirmed, symptomatic, proximal DVT or PE and treated with an approved anticoagulant or with dabigatran in one of two previously conducted short-term clinical trials (RE-COVER or RE-COVER II). The required duration of initial treatment before enrolment was 3-12 months	Actual/anticipated use of vena cava filter, need for anticoagulant treatment disorders other than VTE, interruption of anticoagulant therapy for 2 or more weeks during the 3-6 months of treatment for the prior VTE, patients who in the investigator's judgement are perceived as having an excessive risk of bleeding	**Efficacy** Recurrent or fatal thromboembolism (assessed using pre-specified imaging studies) **Safety** Major bleeding (Defined as overt bleeding associated with a fall in the hemoglobin level at least of 20 g per litre or if it led to transfusion of two or more units of red cells or if it occurred in a critical site or contributed to death)	**Efficacy** Symptomatic DVT, symptomatic non-fatal PE, death related to venous thromboembolism **Safety** Major or CRN bleeding event, any bleeding event, adverse events, acute coronary events	Randomised, double blind, active controlled study
WARFASA (54)	Multicenter (Italy, Austria)	Patients ≥18 years of age with a first-ever, objectively confirmed, symptomatic, unprovoked proximal DVT, PE, or both and had been treated for 6-18 months with VKA (target INR of 2.0-3.0)	Patients with, known cancer, known major thrombophilia (antiphospholipid antibodies or lupus anticoagulant or homozygous factor V Leiden or prothrombin G21210A or double	**Efficacy** Symptomatic, objectively confirmed recurrence of VTE (Diagnosis of recurrence of PE was intraluminal defect on computed tomography angiography	**Efficacy** Non-fatal MI Unstable angina Stroke TIA Acute ischaemia of the lower limbs **Safety**	Randomised, double blind study

Study	Study location	Inclusion criteria	Exclusion criteria	Primary outcomes (methods and timing of assessments)	Secondary efficacy outcomes	Study design
			heterozygosity for factor V Leiden and prothrombin G21210A or deficiency of antithrombin, protein C or S), active or high risk of bleeding, and indication for long-term anticoagulant therapy other than VTE (as atrial fibrillation or prosthetic heart valve), anticipated non-adherence to study medications	or pulmonary angiography or a new high probability perfusion defect on lung scan. The criteria for recurrence of DVT were a newly non-compressible venous segment or a substantial increase in the diameter of the thrombus during full compression on ultrasonography or a new intraluminal filling defect on venography **Safety** Major bleeding	CRNM bleeding All-cause mortality	
WODIT DVT (81)	Multicenter (Italy)	Patients 15-85 years of age With a first episode of symptomatic idiopathic proximal DVT and had completed 3 months of uninterrupted oral anticoagulation without a recurrence of thromboembolism or bleeding	Patients who required prolonged anticoagulant therapy for reasons other than venous thromboembolism were excluded from the study, as were patients with major psychiatric disorders, patients with a life expectancy shorter than two years, those who could not return for the follow-up visits, and those who declined to participate	**Efficacy** Recurrence of symptomatic, objectively confirmed recurrence of VTE during a follow-up period of ≥2 years after randomization (DVT was verified using a compression ultrasonography or venography. PE were a diagnostic pulmonary angiogram, a ventilation–perfusion lung scan indicating a high probability of pulmonary embolism, or an indeterminate lung scan with a high degree of clinical suspicion of pulmonary embolism in a	**Efficacy and safety** Mortality, adverse events	Randomised, open-label study

Study	Study location	Inclusion criteria	Exclusion criteria	Primary outcomes (methods and timing of assessments)	Secondary efficacy outcomes	Study design
				patient with an objectively diagnosed asymptomatic recurrence of deep venous thrombosis) **Safety** Major bleeding (Bleeding was defined as major if it was clinically overt and associated with either a decrease in the hemoglobin level of at least 2 g per deciliter or the need for the transfusion of 2 or more units of red cells, etc)		
WODIT PE (82)	Multicenter (Italy)	Patients 15-85 years of age with a first episode of symptomatic idiopathic proximal DVT and had completed 3 months of uninterrupted oral anticoagulation without a recurrence of thromboembolism or bleeding	Patients with, PE associated with permanent risk factors (known cancer or known thrombophilia), requirement for prolonged anticoagulation for reasons other than VTE, major psychiatric disorder, life expectancy <2 years, or unable to return for follow-up visits	**Efficacy** Recurrence of symptomatic, objectively confirmed recurrence of VTE after the initial 3 months of anticoagulation **Safety** Major bleeding	**Efficacy** Cumulative incidence of adverse outcome events (i.e. VTE recurrence, death, major bleeding) **Safety** Mortality, adverse events	Randomised, open-label study
ELATE (76)	Multicenter (Canada and USA)	Patients with ≥1 episodes of unprovoked VTE and had completed ≥3 months of oral anticoagulation at conventional intensity	Other indications for warfarin therapy, contraindication to long-term warfarin therapy, including a high risk of bleeding, antiphospholipid antibodies, allergy to	**Efficacy** Recurrent VTE (Verified by means of objective diagnostic testing) **Safety**	**Efficacy and safety** Major bleeding, any bleeding episode, all-cause mortality	Randomised, double blind study

Study	Study location	Inclusion criteria	Exclusion criteria	Primary outcomes (methods and timing of assessments)	Secondary efficacy outcomes	Study design
			contrast medium, life expectancy of <2 years	Major bleeding (Bleeding was defined as major if it was clinically overt and associated with a decrease in the hemoglobin level of at least 2.0 g per deciliter or a need for transfusion of two or more units of red cells or if it involved a critical site (e.g., retroperitoneal or intracranial bleeding)		

ACS, acute coronary syndrome; AE, adverse event; ALT, alanine aminotransferase; ASA, acetylsalicylic acid; AST, aspartate aminotransferase; CRNM, clinically relevant, non-major; CV, cardiovascular; DVT, deep vein thrombosis; GI, gastrointestinal; ICH, intra-cranial haemorrhage; LMWH, low molecular weight heparin; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; PE, pulmonary embolism; UFH, unfractionated heparin; ULN, upper limit of normal; SE, systemic embolism; TIA, transient ischaemic attack; VKA, vitamin K antagonist; VTE, venous thromboembolism

Note: Study references correspond to those presented in the main submission

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.

NMA1

The NMA was conducted under a Bayesian framework. The parameters of the models were estimated using a Markov Chain Monte Carlo (MCMC) method as implemented in the WinBUGS 1.4.3 software package. A first series of 50,000 iterations from the WinBUGS sampler were discarded as 'burn in' and the inferences were based on an additional 50,000 iterations using three chains. Convergence of the chains was confirmed by examining the Gelman-Rubin statistic.

NMA2

The NMA was conducted under a Bayesian framework. The parameters of the models were estimated using a Markov Chain Monte Carlo (MCMC) method as implemented in the WinBUGS 1.4.3 software package. A first series of 100,000 iterations from the WinBUGS sampler were discarded as 'burn in' and the inferences were based on an additional 50,000 iterations using three chains. Convergence of the chains was confirmed by examining the Gelman-Rubin statistic.

*Note: A longer burn-in of 100,000 iterations was used in the prevention period network (compared with 50,000 in the initial/long-term network) because numerous studies reported on outcomes with zero events (i.e. patients did not have an event) and therefore, a longer 'burn-in' was required for convergence of the chains***.**

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)*

The ERG proposed two additional analyses that would consider the sensitivity of the model parameters to different approaches to carrying out meta-analysis estimation. In brief, the two different approaches were:

1. To include a more informative prior for the study effect;

The standard approach to NMA is to use non-informative priors unless there is substantial evidence otherwise. Informative priors recognise that an analysis is based on more than the available data set and therefore require considerable judgement prior to their use in any analysis. That is, one would expect information for an informative prior outside of the dataset as opposed to using the dataset itself as proposed by the ERG. We have not identified external data outside of the available dataset to inform the prior and therefore, we do not support the use of an informative prior. This argument is further supported by the results presented for the 'second analysis' which demonstrate that the alternative vague prior had a minimal impact on the majority of analyses.

2. To use an alternative vague prior for the study effect.

The NICE TSD2 outlines that a "last resort" approach to the issue of zero events in the NMA of binary outcomes, is to put a random effect model on the treatment baselines as well as the relative treatment effects. In sparse networks in particular, where a single treatment is included in one trial and that trial includes a zero cell, it may not be possible to estimate a treatment effect. Solutions outlined in the NICE TSD2 include the use of a continuity correction or placing a distribution on the baseline model.

In summary, both of the above methods proposed by the ERG require strong justification.

First analysis proposed fixing the study effect variable, mu, at a single value representing the log-odds of an event in 1 year for the baseline treatment. For NMA1, the baseline treatment was LMWH/VKA, and for NMA2, it was placebo. The standard model used in the original analysis, and as taken from TSD2, uses the following equation*; logit(p[i,k]) = mu[i] + d[t[i,k]] - d[t[i,1]] as the model for the linear predictor where mu[i] ~ dnorm(0,.0001).*Therefore, using the proposed analysis, this equation becomes; *logit(p[i,k]) = mu + d[t[i,k]] - d[t[i,1]]* where mu is a fixed value.

The fixed value for mu needed to be calculated in the code. Furthermore, there was some variation in the length of study follow-up i.e. trials assessing VKA, aspirin had longer follow-up times than those evaluating the NOACs (apixaban, dabigatran, rivaroxaban).Therefore, using the same approach as that of Castelucci et al.(2013) which considers only the analysis of events that occurred during the time period that patients received study drugs, placebo, or observation, this assumes comparable follow-up times across studies i.e. the majority of events occurring during the treatment period rather than the follow-up period. However, due to the time constraints in responding to the ERG questions, this assumption was not investigated further.

Therefore, the new value for mu was fixed as*; mu=log (BR)*

where BR was already defined in the original code as

BR= total number of events for patients in any study reference arm / total number of patients in the study reference arms

Note: The reference arm refers to the control arm of any study and was selected based on the ERG suggestion (i.e. 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").

Second analysis ensures that the study effect, mu, be treated as a random effect in the model. This involves a change to the same line of code as the first analysis. So, in the original code

logit(p[i,k]) = mu[i] + d[t[i,k]] - d[t[i,1]] where mu ~ dnorm(0,.0001)

and the new code contains extra lines and becomes

logit(p[i,k]) = mu[i] + d[t[i,k]] - d[t[i,1]]

where

mu[i] ~ dnorm(m,tau.m)
m ~ dnorm(0,.0001) # vague prior for mean
var.m ~ dgamma(0.01,0.01) # between-trial variance
tau.m <- 1/var.m #between trial precision

Note: the var.m ~ dgamma(0.001,0.001) proposed by the ERG was too disseminated for the analysis to run and WinBUGS returned a "cannot bracket slice for node var.m" error. Therefore, this term was adjusted to var.m ~ dgamma(0.01,0.01).

By considering an alternative vague prior for the study effect, the sensitivity of the analysis results to the initial assumption can be determined. This approach is comparable with the method reported in both TSD2 and TSD5, where an alternative way to set vague priors is suggested using an inverse gamma prior on the between trial variance, that is a gamma prior on the precision, where the precision, tau = 1/variance, then tau ~ Gamma (.001,.001). Many other authors have also used the gamma distribution as an alternative distribution for the precision (Lunn et at. 2012) suggestive of gamma distributions being suitable as sampling distributions for positive and skewed data. (Lunn et at. 2012 and Ntzougras, 2009). Additionally, the TSD2 document states that

> *"This approach gives a low prior weight to unfeasibly large σ on the logit scale. The disadvantage is that this puts more weight on values of σ near zero. On the other hand, there are occasions where it may be an advantage that this prior rules out values of σ at zero, because it is not uncommon, particularly when data is sparse, that MCMC sampling can "get stuck" at σ = 0, leading to spikes in the posterior distribution of both σ and the treatment effect parameters. In these cases, a Gamma prior may improve numerical stability and speed convergence"*.

Consequently, the code was altered to reflect the TSD2 approach and two outcomes; VTE and VTE-related death, and major bleeding for NMA2 were analysed. All the results were identical to those where the expression *var.m ~ dgamma (0.01,0.01) to within 2 dps* was used. It was therefore considered that the results using the two approaches are likely to be equivalent for the remaining outcomes.

A summary of the results using both the first analysis and second analysis in comparison to the base case is presented in A16 to A26

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).

	First analysis NMA2 Major bleeds			Second analysis NMA2 Major bleeds		
	Mean	*95% CI Lower*	*95% CI Upper*	*Mean*	*95% CI Lower*	*95% CI Upper*
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabigatran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LMWH/VKA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LMWH monotherapy	1	0.9	1.1	1	0.9	1.1
Aspirin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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).

	First analysis NMA2 CRNM bleeds			Second analysis NMA2 CRNM bleeds		
	Mean	*95% CI Lower*	*95% CI Upper*	*Mean*	*95% CI Lower*	*95% CI Upper*
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabigatran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LMWH/VKA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LMWH monotherapy	1	0.9	1.1	1	0.9	1.1
Aspirin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 4: Base case analysis for treatment period network (NMA 1) results – 6 month time point – fixed-effect model (statistically significant results are shown in bold) [Updated Table 34 of the submission]

Outcome	Apixaban vs. LMWH/VKA, RR (95% CrI)	Apixaban vs. LMWH/dabigatran, RR (95% CrI) (89)	Apixaban vs. rivaroxaban, RR (95% CrI) (89)
Recurrent VTE or VTE-related death*			
Basecase	[redacted]	[redacted]	[redacted]
First analysis (fixed value for mu)	[redacted]	[redacted]	[redacted]
Second analysis (RE on mu)	[redacted]	[redacted]	[redacted]

Outcome	Apixaban vs. LMWH/VKA, RR (95% CrI)	Apixaban vs. LMWH/dabigatran, RR (95% CrI) (89)	Apixaban vs. rivaroxaban, RR (95% CrI) (89)
Major or CRNM bleeding			
Basecase	[redacted]	[redacted]	[redacted]
First analysis (fixed value for mu)	[redacted]	[redacted]	[redacted]
Second analysis (RE on mu)	[redacted]	[redacted]	[redacted]
Major bleeding			
Basecase	[redacted]	[redacted]	[redacted]
First analysis (fixed value for mu)	[redacted]	[redacted]	[redacted]
Second analysis (RE on mu)	[redacted]	[redacted]	[redacted]
CRNM bleeding			
Basecase	[redacted]	[redacted]	[redacted]
First analysis (fixed value for mu)	[redacted]	[redacted]	[redacted]
Second analysis (RE on mu)	[redacted]	[redacted]	[redacted]
Overall treatment discontinuation			
Basecase	[redacted]	[redacted]	[redacted]
First analysis (fixed value for mu)	[redacted]	[redacted]	[redacted]
Second analysis (RE on mu)	[redacted]	[redacted]	[redacted]
All-cause mortality			
Basecase	[redacted]	[redacted]	[redacted]
First analysis (fixed value for mu)	[redacted]	[redacted]	[redacted]
Second analysis (RE on mu)	[redacted]	[redacted]	[redacted]

*VTE or VTE-related death outcome is composed of the sum of the incidences of non-fatal PE, DVT and VTE-related deaths

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

The mITT (SA1) and base case results for the three outcomes of major bleeding; CRNM bleeding; and major or CRNM bleeding are similar. Any new analyses based on the new code for SA1 will be similar to the new results reported for the base case in response to A16 (table 4 above). Therefore, these were not re-assessed.

Table 5: Analysis for Modified ITT population and RE-COVER/RE-COVER II pooled analysis. Sensitivity for treatment period network (NMA 1) results– 6 month time point – fixed-effect model (statistically significant results are shown in bold) [Updated Table 35 of the submission]

Outcome	Apixaban vs. LMWH/VKA, RR (95% CrI)	Apixaban vs. LMWH/dabigatran, RR (95% CrI)	Apixaban vs. rivaroxaban, RR (95% CrI)
Recurrent VTE or VTE-related death - modified ITT population			
mITT	[redacted]	[redacted]	[redacted]
First analysis (fixed value for mu)	[redacted]	[redacted]	[redacted]
Second analysis	[redacted]	[redacted]	[redacted]

(RE on mu)			

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

The mITT (SA1) and base case results for the three outcomes major bleeding; CRNM bleeding and major or CRNM bleeding are similar. Any new analyses based on new code and excluding dabigatran studies for SA1 will be similar to the new results reported for the base case in response to A20 (Table 9 below). Therefore, these were not re-assessed.

Table 6: Analysis for Modified ITT population and RE-COVER/RE-COVER II pooled analysis. Sensitivity for treatment period network (NMA 1) results– 6 month time point – fixed-effect model (statistically significant results are shown in bold) [Updated Table 35 of the submission]

Outcome	**Apixaban vs. LMWH/VKA, RR (95% CrI)**	**Apixaban vs. LMWH/dabigatran, RR (95% CrI)**	**Apixaban vs. rivaroxaban, RR (95% CrI)**
Recurrent VTE or VTE-related death - modified ITT population			
mITT	[redacted]	[redacted]	[redacted]
mITT new analysis results excluding dabigatran studies for comparison with updated code	[redacted]	[redacted]	[redacted]
First analysis (fixed value for mu)	[redacted]	[redacted]	[redacted]
Second analysis (RE on mu)	[redacted]	[redacted]	[redacted]

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

The analysis for VTE and VTE-related death was not re-assessed for this analysis using the new code. This is because the original analysis demonstrated that pooled study data had no impact on the analysis results. This was expected because the results from the pooled trials closely matched the sum of the reported data from the two individual trials. Consequently, the analysis results were almost identical (see [redacted]), the minor differences in the 2nd dp being due to the differing number of studies between the two models. Therefore, any new analyses based on the ERG's proposed code would be identical to that obtained from re-running the base case.

Table 7: Analysis for Modified ITT population and RE-COVER/RE-COVER II pooled analysis. Sensitivity for treatment period network (NMA 1) results– 6 month time point – fixed-effect model (statistically significant results are shown in bold) [Updated Table 35 of the submission]

Outcome	**Apixaban vs. LMWH/VKA, RR (95% CrI)**	**Apixaban vs. LMWH/dabigatran, RR (95% CrI)**	**Apixaban vs. rivaroxaban, RR (95% CrI)**
RE-COVER/RE-COVER II pooled analysis			

Major or CRNM bleeding			
Basecase	[redacted]	[redacted]	[redacted]
First analysis (fixed value for mu)	[redacted]	[redacted]	[redacted]
Second analysis (RE on mu)	[redacted]	[redacted]	[redacted]
Major bleeding			
Basecase	[redacted]	[redacted]	[redacted]
First analysis (fixed value for mu)	[redacted]	[redacted]	[redacted]
Second analysis (RE on mu)	[redacted]	[redacted]	[redacted]
CRNM bleeding			
Basecase	[redacted]	[redacted]	[redacted]
First analysis (fixed value for mu)	[redacted]	[redacted]	[redacted]
Second analysis (RE on mu)	[redacted]	[redacted]	[redacted]

Table 8: Comparison of analyses for base case and RE-COVER/RE-COVER II pooled analysis from Tables 34 and 35 of original submission

Outcome	**Apixaban vs. LMWH/VKA, RR (95% CrI)**	**Apixaban vs. LMWH/dabigatran, RR (95% CrI)**	**Apixaban vs. rivaroxaban, RR (95% CrI)**
Basecase			
Recurrent VTE or VTE-related death	[redacted]	[redacted]	[redacted]
RE-COVER/RE-COVER II pooled analysis			
Recurrent VTE or VTE-related death	[redacted]	[redacted]	[redacted]

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

Table 9: Analysis for Modified ITT population excluding RE-COVER/RE-COVER II pooled analysis. Sensitivity for treatment period network (NMA 1) results– 6 month timepoint – fixed-effect model (statistically significant results are shown in bold) [Updated Table 35 of the submission]

Outcome	**Apixaban vs. LMWH/VKA, RR (95% CrI)**	**Apixaban vs. LMWH/dabigatran, RR (95% CrI)**	**Apixaban vs. rivaroxaban, RR (95% CrI)**
Recurrent VTE or VTE-related death			

Basecase	[redacted]	[redacted]	[redacted]
First analysis (fixed value for mu)	[redacted]	[redacted]	[redacted]
Second analysis (RE on mu)	[redacted]	[redacted]	[redacted]
Major bleeding			
Basecase	[redacted]	[redacted]	[redacted]
First analysis (fixed value for mu)	[redacted]	[redacted]	[redacted]
Second analysis (RE on mu)	[redacted]	[redacted]	[redacted]
Major or CRNM bleeding			
Basecase	[redacted]	[redacted]	[redacted]
First analysis (fixed value for mu)	[redacted]	[redacted]	[redacted]
Second analysis (RE on mu)	[redacted]	[redacted]	[redacted]
CRNM bleeding			
Basecase	[redacted]	[redacted]	[redacted]
First analysis (fixed value for mu)	[redacted]	[redacted]	[redacted]
Second analysis (RE on mu)	[redacted]	[redacted]	[redacted]

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

For the comparison of Apixaban 2.5 mg bd vs. rivaroxaban 20 mg od on Major or CRNM bleeding, a reporting error was identified. The relative efficacy should be [redacted]) as opposed to [redacted] currently presented in the main submission. The former is applicable to the 2.5mg (dose under consideration for this appraisal) whereas the latter is for the 5mg (not relevant to this appraisal). Given the outcome is a composite of the major safety outcome, this does not affect the economic modelling approach presented in the main submission. Additionally, all other data sets and results have been quality checked to ensure that no other errors are present therefore, we are confident that the appropriate results have been presented.

Please note that the recurrent VTE-related death outcome would not run using the two new codes without applying a continuity correction first (this is identical to what occurred in the base case). As the ERG specifically stated that no adjustments should be made, the results of these analyses have not been included.

Table 10: Base case analysis for the prevention period NMA (NMA 2) – fixed-effect model (statistically significant results are shown in bold) [Updated Table 37 of the submission]

Outcome	Apixaban 2.5 mg bd vs. dabigatran 150 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. rivaroxaban 20 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. VKA (INR 2.0–3.0), RR (95% CrI)	Apixaban 2.5 mg bd vs. aspirin 100 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. placebo, RR (95% CrI)
Recurrent VTE or VTE-related death*					
Basecase					
First analysis (fixed value for mu)					
Second analysis (RE on mu)					
Recurrent VTE-related death					
Basecase					
First analysis (fixed value for mu)					
Second analysis (RE on mu)					
Major or CRNM bleeding					
Basecase					
First analysis (fixed value for mu)					
Second analysis (RE on mu)					
Major bleeding					
Basecase					
First analysis (fixed value for mu)					
Second analysis (RE on mu)					
CRNM bleeding					
Basecase					
First analysis (fixed value for mu)					
Second analysis (RE on mu)					
Overall treatment discontinuation					
Basecase					

Outcome	Apixaban 2.5 mg bd vs. dabigatran 150 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. rivaroxaban 20 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. VKA (INR 2.0–3.0), RR (95% CrI)	Apixaban 2.5 mg bd vs. aspirin 100 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. placebo, RR (95% CrI)
First analysis (fixed value for mu)					
Second analysis (RE on mu)					
All-cause mortality					
Basecase					
First analysis (fixed value for mu)					
Second analysis (RE on mu)					

*VTE or VTE-related death outcome is composed of the sum of the incidences of non-fatal PE, DVT and VTE-related death

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

The ITT (SA4) and base case results for the three outcomes major bleeding; CRNM bleeding and major or CRNM bleeding are identical due to the outcomes being analysed using the safety population. Therefore, any new analyses based on new code for SA4 will be identical to the new results reported for the base case in response to A21 (Table 10 above).

Table 11: Sensitivity analysis for prevention period network (NMA 2) results – fixed-effect model (statistically significant results are shown in bold) [Updated Table 38 of the submission]

Outcome	Apixaban 2.5 mg bd vs. dabigatran 150 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. rivaroxaban 20 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. VKA (INR 2.0–3.0), RR (95% CrI)	Apixaban 2.5 mg bd vs. aspirin 100 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. placebo, RR (95% CrI)
Recurrent VTE or VTE-related death					
ITT SA4					
First analysis (fixed value for mu)					
Second analysis (RE on mu)					

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

Table 12: Sensitivity analysis for prevention period network (NMA 2) results – fixed-effect model (statistically significant results are shown in bold) [Updated Table 38 of the submission]

Outcome	Apixaban 2.5 mg bd vs. dabigatran 150 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. rivaroxaban 20 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. VKA (INR 2.0–3.0), RR (95% CrI)	Apixaban 2.5 mg bd vs. aspirin 100 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. placebo, RR (95% CrI)
Recurrent VTE or VTE-related death SA5					
ITT					
First analysis (fixed value for mu)					
Second analysis (RE on mu)					
Major bleeding SA5 (as base case excluding WODIT DVT and WODIT PE) †					
Major bleeding					
First analysis (fixed value for mu)					
Second analysis (RE on mu)					

† No continuity correction has been applied to the new results whereas it was necessary in the original analysis

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

The A24 results for the three outcomes major bleeding; CRNM bleeding and major or CRNM bleeding will be identical to those for the new analyses in response to A25 below, since the data input to the model for the ITT and base case populations are identical due to the data being based on the safety population .

Table 13: Sensitivity analysis for prevention period network (NMA 2) results – fixed-effect model (statistically significant results are shown in bold) [Updated Table 38 of the submission]

Outcome	Apixaban 2.5 mg bd vs. rivaroxaban 20 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. VKA (INR 2.0–3.0), RR (95% CrI)	Apixaban 2.5 mg bd vs. aspirin 100 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. placebo, RR (95% CrI)
Recurrent VTE or VTE-related death				
Basecase	[redacted]	[redacted]	[redacted]	[redacted]
Recurrent VTE or VTE-related death (fixed value of mu)	[redacted]	[redacted]	[redacted]	[redacted]
Recurrent VTE or VTE-related death (RE on mu)	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 1: Sensitivity analysis for prevention period network (NMA 2) results – fixed-effect model (statistically significant results are shown in bold) [Updated Table 38 of the submission]

Outcome	Apixaban 2.5 mg bd vs. rivaroxaban 20 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. VKA (INR 2.0–3.0), RR (95% CrI)	Apixaban 2.5 mg bd vs. aspirin 100 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. placebo, RR (95% CrI)
ITT main analysis				
Recurrent VTE or VTE-related death SA4	[redacted]	[redacted]	[redacted]	[redacted]
Recurrent VTE or VTE-related death (exclude dabigatran studies – fixed value of mu)	[redacted]	[redacted]	[redacted]	[redacted]
Recurrent VTE or VTE-related death (exclude dabigatran studies – (RE on mu))	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding SA4*†	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding SA6 (exclude dabigatran studies)	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding (exclude	[redacted]	[redacted]	[redacted]	[redacted]

Outcome	Apixaban 2.5 mg bd vs. rivaroxaban 20 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. VKA (INR 2.0–3.0), RR (95% CrI)	Apixaban 2.5 mg bd vs. aspirin 100 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. placebo, RR (95% CrI)
dabigatran studies – fixed value of mu)				
Major bleeding (exclude dabigatran studies - (RE on mu)				
Major or CRNM bleeding SA4*				
Major or CRNM bleeding SA6 (exclude dabigatran studies)				
Major or CRNM bleeding (exclude dabigatran studies – fixed value of mu)				
Major or CRNM bleeding (exclude dabigatran studies – RE on mu)				
CRNM bleeding SA4*				
CRNM bleeding SA6 (exclude dabigatran studies)				
CRNM bleeding (exclude dabigatran studies – fixed value of mu)				
CRNM bleeding (exclude dabigatran studies – RE on mu)				

*Note these results are the same as the base case

† No continuity correction has been applied to the new results whereas it was necessary in the original analysis

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

This is similar but not the same as A24. This analysis differs from A24 because A26 is for the ITT population whereas A24 relates to the base case. Further, A24 only excludes the dabigatran studies whereas A26 excludes both WODIT trials and dabigatran studies. It is a new analysis for which we do not have an original analysis to compare against.

Table 15 Sensitivity analysis for prevention period network (NMA 2) results – fixed-effect model (statistically significant results are shown in bold) [Updated Table 38 of the submission]

Outcome	Apixaban 2.5 mg bd vs. rivaroxaban 20 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. VKA (INR 2.0–3.0), RR (95% CrI)	Apixaban 2.5 mg bd vs. aspirin 100 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. placebo, RR (95% CrI)
Recurrent VTE or VTE-related death SA5				
ITT	[redacted]	[redacted]	[redacted]	[redacted]
First analysis (fixed value for mu)	[redacted]	[redacted]	[redacted]	[redacted]
Second analysis (RE on mu)	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding SA5 †				
Basecase	[redacted]	[redacted]	[redacted]	[redacted]
First analysis (fixed value for mu)	[redacted]	[redacted]	[redacted]	[redacted]
Second analysis (RE on mu)	[redacted]	[redacted]	[redacted]	[redacted]

† No continuity correction has been applied to the new results whereas it was necessary in the original analysis

Kaplan-Meier analyses of data from AMPLIFY and AMPLIFY EXT
The Kaplan-Meier analyses requested in questions are below. 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*
  - *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 presented on page 6.

BMS/Pfizer response to additional request for KM analyses

BMS/Pfizer note that we received no clarification questions on the economic modelling section of the submission. Despite this, additional Kaplan-Meier (KM) data were requested by the ERG for the purpose of verifying economic modelling assumptions, as confirmed by NICE on the 12th of November in an email correspondence stating the following:

> *"Projection of VTE event rates and patient survival are central to the estimation of cost-effectiveness. The submitted model is designed to represent long-term outcomes based on limited data from 2 short trials (AMPLIFY and AMPLIFY-EXT). The trial data are used in the model only in the form of binomial event rates per 3-month time intervals, and generally most rates obtained for the final time segment of the observed data are assumed to be fixed for all subsequent model cycles. This is a very strong assumption, which should be tested against the temporal pattern of observed events for each outcome variable and their components. Without access to the full Kaplan-Meier analyses it is not possible to confirm the reliability of this assumption, or to compare the trial evidence with other sources of relevant information in the published literature.*

We understand the need to test the modelling assumptions to ensure a transparent evaluation of apixaban. However, it is unclear to BMS/Pfizer from the ERG questions A27-A38 the exact thinking that led to the request for data for each of these outcomes. Broadly we have two main concerns with regards to the requests for additional data, which we believe should be considered with regards to testing the temporal pattern of observed events. The first concerns the extrapolation of data beyond the end of the AMPLIFY trial and second regarding the request for outcomes where there is likely to a small number of events.

Regarding the first concern, BMS/Pfizer realise that the ERG may be testing assumptions within the model regarding the temporal distribution of events within the trial period of

AMPLIFY. However, we would like to highlight that the extrapolation of data via survival analysis beyond the end of AMPLIFY is likely to have limited applicability for the interpretation of apixaban effectiveness and safety. This is due to the differences in the licence doses of apixaban recommended for the treatment and prevention periods. Only the 2.5 mg twice daily dose should be initiated following completion of 6 months of treatment with Eliquis 5 mg twice daily (the dose in AMPLIFY). Therefore extrapolation of Eliquis 5mg twice daily from the AMPLIFY study beyond the six months treatment would not be appropriate and off label.

Our second concern relates to a number of the requests for KM data from AMPLIFY and AMPLIFY-EXT in outcomes that have a limited number of events observed. This data is likely to provide a highly uncertain estimation of the relative effectiveness of apixaban compared to comparators as a result. This underpowering of the outcomes will be made worse by the request to split further by DVT and PE subgroups. The consequence of few events is that the KM curves will fluctuate with large steps, which implies a large degree of uncertainty of where the true response line lies. Furthermore, tests between groups based on KM are sensitive to event counts and it is likely they will lack power to show any differences.

Despite the lack of understanding of specific ERG concerns with regards to clinical assumptions underlying the economic model, we have attempted to justify the assumption regarding each outcome requested by the ERG. We have re-presented our scenario analyses from our original submission that tested these outcomes and may address some of ERG concerns.

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.

It is unclear whether the ERG would like to test the time to death from any cause instead of the approach taken in apixaban model where mortality effects were modelled separately for VTE, bleeding and CTEPH and other death events. We suggest that a modelling approach based on death from any cause from trial data is inappropriate, as VTE related death is the only type of death that could reasonable expected to be powered in a non-inferiority trial. The reason why VTE and VTE related death was chosen as the primary endpoint in AMPLIFY.

This is consistent with advice from clinical expert involved in our submission and agreed at our HTA advisory board who suggested that mortality benefits observed from anticoagulant treatment would be solely a result of reducing recurrent VTE or bleeding events (i.e., no effects of treatment on “other deaths”), therefore substantiating modelling of “other deaths” based on life tables and observational data, rather than directly from the trials as was done in the apixaban model.

In the base-case analyses, age- and sex-dependent background general mortality rates based on UK life-tables were used to model other deaths unrelated to these events. Therefore a constant rate of mortality was not used, rather increased over time to reflect ageing.

These rates were adjusted by a HR of mortality for patients with VTE (excluding excess mortality due to the events modelled) versus the general population as obtained from a large cohort study following up patients for 8 years (Flinterman et al. 2012). This study found

that even 8 years after the index event, VTE-associated mortality persists even when no other co-morbidities were present (Flinterman et al. 2012).

Extrapolation of the trial data would be inappropriate beyond AMPLIFY and AMPLIFY-EXT as it may not take into account reduction of risk of VTE over time and increased risk of bleeding over time due to ageing. Therefore, BMS/Pfizer suggests that the approach to modelling mortality in the apixaban model is the most applicable given the data available.

The approach used in the submission was tested against the earlier VTE submissions for rivaroxaban which assumed patients with VTE who do not experience any events will follow the mortality pattern of the general population (NICE Rivaroxaban manufacturer submissions, Edwards et al. 2014, Harnan et al. 2012, Copley et al. 2012). Had we utilized the same previously accepted assumption results would be more favourable for apixaban as demonstrated in the submitted scenario analysis for both the 6 month and lifelong treatment durations.

Table 16: Scenario analysis for mortality: apixaban vs. LMWH/VKA, rivaroxaban, and LMWH/dabigatran (index VTE, 6-month treatment duration) – incremental cost per QALY (£)

	Rivaroxaban	Dabigatran	LMWH/VKA
Base case	Dominant	Dominant	£2,406
Background mortality set to equal general population	Dominant	Dominant	£1,485

The scenarios for the lifelong treatment suggest lower ICERs in comparison to LMWH/VKA, LMWH/VKA followed by aspirin and placebo when mortality is set equal to the general population. Therefore the scenario used in the base case can be considered conservative.

Table 17: Scenario analysis for mortality: apixaban vs., rivaroxaban, LMWH/dabigatran LMWH/VKA, LMWH/VKA and LMWH/VKA & Placebo (index VTE, lifelong treatment duration) – incremental cost per QALY (£)

	Rivaroxaban	Dabigatran	LMWH/VKA	LMWH/VKA & Placebo
Base case	£ 809.38	£ 5,058.10	£ 16,675.53	£ 17,917.37
Background mortality set to equal general population	£708	£4,586	£13,042	£12,324

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.

BMS/Pfizer agree with the ERG that constant treatment discontinuation rates unrelated to bleeding are subject to uncertainty in the model and we therefore tested this assumption through extreme one way scenarios in the model.

In the apixaban model, the first 6 months risks were obtained from AMPLIFY and subsequently a constant risk of discontinuation was assumed based on AMPLIFY-EXT.

Treatment discontinuation was modelled as a result of bleeding or that unrelated to bleeding. We therefore examined in the submission two extreme scenarios in the submission, setting the risks of other treatment discontinuation to 0 for all treatments and setting the risks of other treatment discontinuation to be equal between treatments.

Table 18: Scenario analysis for discontinuation apixaban vs. LMWH/VKA, rivaroxaban, and LMWH/dabigatran (index VTE, 6-month treatment duration) – incremental cost per QALY (£)

	Rivaroxaban	Dabigatran	LMWH/VKA
Base case	Dominant	Dominant	£2,406
Scenario: Equal discontinuation unrelated to bleeding	Dominant	Dominant	£2,402
Scenario: No discontinuation unrelated to bleeding	Dominant	Dominant	£2,525

We provide an additional scenario in the submission in the lifetime duration setting the risks of discontinuation to 0 beyond the first 18 months. The scenarios for the lifelong treatment suggest higher ICERs in comparison to LMWH/VKA, LMWH/VKA followed by aspirin and placebo, however apixaban remains cost-effective at thresholds below £20,000 and £30,000 per QALY respectively. It should be noted that the latter scenario is also conservative as it is unlikely that discontinuation is 0 beyond the first 18 months.

Table 19: Scenario analysis for discontinuation apixaban vs. LMWH/VKA, rivaroxaban and LMWH/dabigatran, (index VTE, lifelong treatment duration) – incremental cost per QALY (£)

	Rivaroxaban	Dabigatran	LMWH/VKA	LMWH/VKA & Placebo
Base case	£ 809.38	£ 5,058.10	£ 16,675.53	£ 17,917.37
Scenario: Equal discontinuation unrelated to bleeding	£ 55.45	Dominant	£ 15,712.60	£ 17,882.50
Scenario: No discontinuation unrelated to bleeding	£ 925.16	£ 205.54	£ 17,551.73	£ 22,213.33
Scenario: Discontinuation set to 0 beyond 18 months	£ 2,206.38	£ 11,793.42	£ 19,501.65	£ 21,720.98

A29. **Priority Question:** 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].

In the apixaban model, for the first 6 months, 3 monthly probabilities were obtained from AMPLIFY and subsequent to that a constant risk of bleeding was assumed based on AMPLIFY-EXT. This indeed is a strong assumption particularly in light of evidence that the risk of bleeding increases with increasing age (Button et al. 2011, Fang et al. 2004, Ariesen et al.

2003). However, it was felt to be conservative given apixaban's relative effectiveness for major and CRNM bleeds in AMPLIFY and AMPLIFY-EXT.

The submission therefore presents a scenario analysis where risks are adjusted by a factor of 1.97 per decade to reflect increased risk of bleeding due to ageing using data from Ariensen et al. This increase in risk over time may not be evident on evaluation of the AMPLIFY trial data, due to a short horizon. In the 6 month treatment period the impact of these assumptions is negligible compared to the base case due to the limited treatment period.

Table 20: Scenario analysis for bleeding apixaban vs. LMWH/VKA, rivaroxaban, and LMWH/dabigatran (index VTE, 6-month treatment duration) – incremental cost per QALY (£)

	Rivaroxaban	Dabigatran	LMWH/VKA
Base case	Dominant	Dominant	£2,406
Scenario: Adjustment factors for bleeding	Dominant	Dominant	£2,428

The adjustment of bleeding risks for the lifetime scenario resulted in decreased ICERs for apixaban across all comparisons, especially against LMWH/VKA. We therefore consider our base case conservative in light of this evidence of an increase in the risk of bleeding overtime.

Table 21: Scenario analysis for bleeding: apixaban vs., rivaroxaban, LMWH/dabigatran LMWH/VKA, and LMWH/VKA & Placebo (index VTE, lifelong treatment duration) – incremental cost per QALY (£)

	Rivaroxaban	Dabigatran	LMWH/VKA	LMWH/VKA & Placebo
Base case	£ 809.38	£ 5,058.10	£ 16,675.53	£ 17,917.37
Scenario: Adjustment factors for bleeding	£ 634.73	£ 3,909.15	£ 14,020.30	£ 17,517.97

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].

See A28 for details of the impact of bleeding outcomes on model results for the 6 month treatment duration and lifelong treatment periods.

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]

See question A27 why BMS/Pfizer believe modelling based on death from any cause is inappropriate.

Please note that there is limited number of events recorded in the AMPLIF-EXT for this event. There are 7, 4 and 14 events in the 2.5mg apixaban, 5mg apixaban and placebo arms respectively.

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 v. 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

Data not requested to be produced due to limited number of events in the AMPLIFY-EXT trial. There were only 5, 1, and 7 events for the 2.5mg apixaban, 5mg apixaban and placebo, respectively. It was judged that there were too few events for this analysis to be meaningful and therefore, this analysis was not evaluated

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.

Please note that there are a limited number of events recorded in the AMPLIF-EXT for this event. There are 8, 4 and 15 events in the 2.5mg apixaban, 5mg apixaban and placebo arms respectively.

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.

Please note that there are a limited number of events recorded in the AMPLIF-EXT for this event. There are 6, 8 and 53 events in the 2.5mg apixaban, 5mg apixaban and placebo arms respectively.

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.

Please note that there are a limited number of events recorded in the AMPLIF-EXT for this event. There are 6, 8 and 53 events in the 2.5mg apixaban, 5mg apixaban and placebo arms, respectively. Therefore, analyses using these data sets are not likely to be meaningful.

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].

Data not requested to be produced due to limited number of events in the AMPLIFY-EXT trial. There are only 5, 1, and 7 events for the 2.5mg apixaban, 5mg apixaban and placebo respectively. It was judged that there were too few events for this analysis to be meaningful.

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].

Please note that there is limited number of events recorded in the AMPLIF-EXT for this event. There are 25, 34 and 19 events in the 2.5mg apixaban, 5mg apixaban and placebo arms respectively. Therefore, analyses using these data sets are not likely to be meaningful.

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