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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

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

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Table of contents

1 SUMMARY 7
1.1 Scope of the submission 7
1.2 Critique of the decision problem in the company submission 7
1.3 Summary of clinical effectiveness evidence submitted by the company 8
1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted 9
1.5 Summary of cost effectiveness evidence submitted by the company 9
1.6 Summary of the ERG's critique of cost effectiveness evidence submitted 11
1.7 End of life criteria 11
1.8 ERG commentary on the robustness of evidence submitted by the company 12
1.9 Summary of exploratory and sensitivity analyses undertaken by the ERG 13
1.10 ERG conclusions 14
2 BACKGROUND 15
2.1 Critique of company's description of underlying health problems 15
2.2 Critique of company's overview of current service provision 17
2.3 Current pathway of care 18
2.4 Estimated size of the eligible population 20
2.5 Equality 20
2.6 Innovation 20
3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM 22
3.1 Population 24
3.2 Intervention 25
3.3 Comparators 26
3.4 Outcomes 28
3.5 Economic analysis 29
3.6 Subgroups to be considered 29
3.7 Other relevant factors 30
4 CLINICAL EFFECTIVENESS 31
4.1 Critique of the methods of review(s) 31
4.2 Results of the company's searches 33
4.3 Critique of the direct evidence: AMPLIFY and AMPLIFY-EXT 36
4.4 Description and critique of the statistical approach 40
4.5 Results from the direct evidence 45
4.6 Adverse events 55
4.7 Critique of the indirect evidence 63
4.8 Results of the network meta-analyses 74
4.9 Conclusions of the clinical effectiveness section 85
5 COST EFFECTIVENESS 88
5.1 Introduction 88
5.2 ERG comment on company's review of cost effectiveness evidence 88
5.3 ERG critique of the company's literature review 90
5.4 Summary and critique of the company's submitted economic evaluation by the ERG 91
5.5 Detailed critique of company's economic model 109

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG 122
7 END OF LIFE 131
8 OVERALL CONCLUSIONS 132
8.1 Direct evidence 132
8.2 Indirect evidence 134
8.3 Implications for research 137
9 References 138
10 Appendices 144

Abbreviations:

AC	Appraisal Committee
AE	Adverse event
AMPLIFY	Apixaban for the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis as First-Line Therapy
AMPLIFY-EXT	Apixaban for the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis as First-Line Therapy-Extended Treatment
CI	Confidence interval
CRNM	Clinically relevant non-major bleeding
CS	Company submission
CSR	Clinical study report
CTEPH	Chronic thromboembolic pulmonary hypertension
CV-related	Cardiovascular-related
DVT	Deep vein thrombosis
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EPAR	European Public Assessment Report
ERG	Evidence Review Group
HRQoL	Health-related quality of life
IC	Intracranial
ICER	Incremental cost effectiveness ratio
INR	International normalised ratio
ITT	Intention to treat
IVRS	Interactive voice recognition system
K-M	Kaplan-Meier
LMWH	Low molecular weight heparin
LY	Life year
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NOAC	Novel oral anticoagulant
ORR	Objective response rate
OS	Overall survival
PE	Pulmonary embolism
PH	Proportional hazards
PSA	Probabilistic sensitivity analysis
PTS	Post-thrombotic syndrome
RR	Relative risk
QALY	Quality adjusted life year
SA	Sensitivity analysis
SAE	Serious adverse event
SAP	Statistical analysis plan
STA	Single technology appraisal
ToT	Time on treatment
TSAP	Trial statistical analysis plan
UFH	Unfractionated heparin
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence were submitted to NICE from Bristol-Myers Squibb Pharmaceuticals Ltd together with Pfizer Ltd (hereafter referred to as 'the company') in support of the use of apixaban (Eliquis®) for the treatment and secondary prevention of deep vein thrombosis (DVT) and/or pulmonary embolism (PE).

On 28 July 2014, the European Medicines Agency (EMA) issued an extension to the existing marketing authorisation for apixaban. The EMA approved apixaban for the treatment of DVT and PE and prevention of recurrent DVT and PE in adults.

Apixaban is also licensed for: i) the prevention of venous thromboembolism (VTE) in patients who have undergone elective hip or knee surgery and ii) the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors.

1.2 Critique of the decision problem in the company submission

The company has submitted evidence for the clinical effectiveness of apixaban for the short-term treatment of patients with a VTE and for extended treatment of up to 1 year for a cohort of patients who are considered to be at clinical equipoise (i.e. those for whom the risks and benefits of extended anticoagulation treatment are uncertain). The company does not provide evidence to support the clinical effectiveness of apixaban for: i) patients for whom extended treatment is definitely required; ii) patients with active cancer; iii) patients for whom treatment with a vitamin K antagonist (VKA) is unsuitable; iv) patients with distal DVT or v) patients with provoked DVT with no other risk factors for VTE recurrence.

The ERG asked the company (via the clarification process) to carry out a series of 12 Kaplan-Meier (K-M) analyses. These were required to allow the ERG to validate the parameters used in the company's economic model. In response to the ERG's clarification request only two K-M analyses were provided. One of these revealed a significant error in the company's calculation of the risk of treatment discontinuation, and the other showed a significant difference between survival gain estimated by the model and that shown by the AMPLIFY trial results. The ERG believes that it is likely that other discrepancies and errors

may remain undetected in the submitted economic model but this cannot be confirmed without access to the other ten requested analyses of trial data (from both the AMPLIFY and AMPLIFY-EXT studies). Without the requested K-M analyses, the ERG is unable to check the company's estimates and can only conclude that the company economic model may not be reliable and that any cost effectiveness results generated by it cannot be confirmed to be robust.

1.3 Summary of clinical effectiveness evidence submitted by the company

The company has presented direct evidence to support the use of apixaban for the treatment and secondary prevention of VTE. Direct evidence from the AMPLIFY trial suggests that for the initial treatment of VTE (up to 6 months), apixaban is non-inferior to enoxaparin/warfarin for the primary outcome of VTE/VTE-related death (Relative risk [redacted]; apixaban was not shown to be superior to enoxaparin/warfarin. In addition, a statistically significant reduction in major bleeding events was associated with the comparison of apixaban with enoxaparin/warfarin (RR 0.31; 95% CI 0.17 to 0.55; p<0.001).

Direct evidence from the AMPLIFY-EXT trial supports the use of apixaban rather than placebo for the secondary prevention of VTEs in a population of patients at clinical equipoise. Treatment with apixaban for 12 months statistically significantly reduced the risk of recurrent VTE or all-cause death (RR: 0.33; 95% CI 0.22 to 0.48; [redacted]). Apixaban was not statistically significantly different to placebo for major bleeding events. There is currently no direct evidence comparing apixaban with rivaroxaban and dabigatran. Hence, the company carried out two network meta-analyses (NMAs).

Results of the company's NMA that was undertaken for the initial treatment period suggest that there is no statistically significant difference between apixaban and any of the comparators in terms of recurrent VTE or VTE-related death. Treatment with apixaban statistically significantly reduced the risk of all bleeding outcomes in comparison to treatment with the combination of low molecular weight heparin (LMWH) and VKA. Apixaban also reduced the risk of major or clinically relevant non-major bleeding (CRNM) bleeding in comparison to rivaroxaban and dabigatran, and reduced the likelihood of major bleeding in comparison to dabigatran and CRNM bleeding in comparison to rivaroxaban.

Results of the company's secondary prevention period NMA suggest that there is no statistically significant difference between apixaban and either dabigatran, rivaroxaban or LMWH/VKA in terms of risk of recurrent VTE or VTE-related death. Apixaban statistically

significantly reduced the likelihood of recurrent VTE or VTE-related death when compared to treatment with either aspirin or placebo. For safety outcomes, apixaban was shown to statistically significantly reduce the likelihood of major or CRNM bleeding (composite outcome) in comparison to dabigatran, rivaroxaban or LMWH/VKA. There were no statistically significant differences between treatment with apixaban and aspirin or treatment with apixaban and placebo for any of the safety outcomes.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG considers both the AMPLIFY and AMPLIFY-EXT trials to be robust and of good quality. The ERG notes that patients in the trials were younger than those seen in clinical practice in England and Wales and that none of the participating treatment centres in AMPLIFY were based in the UK. The ERG considers that the lack of health-related quality of life (HRQoL) data from the trials is a significant omission. The ERG notes that the AMPLIFY study populations do not include patients with provoked VTE (with no risk factors for recurrence) or distal DVT and that the study population of AMPLIFY-EXT comprises patients in whom the risks and benefits of extended long-term anticoagulation treatment are uncertain. The use of apixaban by patients at a lower risk of VTE recurrence (i.e. those with provoked VTE) or by patients at a higher risk of VTE recurrence in whom long-term anticoagulation is definitely indicated, has not been evaluated by the company.

The ERG identified significant flaws in the methodology used by the company to carry out the secondary prevention period NMA and advises caution when considering the results of this analysis. Specifically, data from the included studies should not have been combined as there was considerable variation in the time on treatment and follow-up times reported for the included studies.

The ERG also had concerns about the company's use of continuity corrections to take account of the fact that some of the included studies reported no events for some of the outcomes of interest. In both the initial treatment and secondary prevention period NMAs this approach led to high estimates of relative risks (RR) for some of the relevant comparisons. The ERG asked the company to re-run their NMAs using a vague prior. The revised RRs were less extreme and were used alongside the ERG's own estimates of incremental cost effectiveness ratios (ICERs).

1.5 Summary of cost effectiveness evidence submitted by the company

The company developed a de novo Markov state transition model which comprised 13 health states. The 11 main health states are: index PE, index DVT, recurrent PE, recurrent

DVT, chronic thromboembolic pulmonary hypertension (CTEPH), intracranial (IC) bleed, non-IC major bleed, CRNM bleed, PE off treatment, DVT off treatment and death; whilst two further health states, PE second-line and DVT second-line, are only used in the sensitivity analyses. Patients enter the model having experienced either an index PE ([redacted]) or an index DVT ([redacted]). The base-case evaluation compares treatment with apixaban with three alternatives: LMWH/VKA, rivaroxaban or LMWH/dabigatran; and results are presented for two scenarios: 6-month treatment duration and lifelong treatment duration.

The model has been developed in Microsoft Excel using a 3-month cycle length. It includes a half-cycle correction and the time horizon is set to patient lifetime (i.e. a maximum follow-up of 65 years and a maximum age of 100 years). As recommended by NICE, a discount rate of 3.5% has been used for both costs and outcomes; outcomes are measured in quality adjusted life years (QALYs). The model perspective is that of the UK NHS. Resource use, costs and utilities were estimated based on information from AMPLIFY, AMPLIFY-EXT, published sources and clinical experts. The company reports that their modelling approach is consistent with the approach adopted in published NICE rivaroxaban submissions (TA287 and TA261).

For the 6-month treatment duration scenario, the ICER for the comparison of apixaban versus LMWH/VKA is estimated to be £2,406 per QALY gained. When compared with either rivaroxaban or LMWH/dabigatran, apixaban is dominant. For the lifelong treatment scenario, the ICER for apixaban versus LMWH/VKA is estimated by the company to be £16,676 per QALY gained, whilst the company's ICERs per QALY gained for apixaban compared with rivaroxaban and LMWH/dabigatran are £809 and £5,058 respectively. In addition, the company undertook an analysis in which lifelong apixaban treatment was compared with LMWH/VKA for 6 months followed by no treatment for the remaining lifetime. The company's model generated an ICER per QALY gained of £17,917 for this analysis.

The company carried out a wide range of deterministic sensitivity analyses. For the 6-month treatment time period, the ICER for the comparison of apixaban versus LMWH/VKA varied from £1,628 to £5,330 per QALY gained, whilst for the lifelong time period, it varied from £2,157 to £41,394 per QALY gained.

The results of the company's probabilistic sensitivity analysis (PSA) suggest that, for the 6-month treatment period, the comparison of apixaban versus LMWH/VKA results in an ICER of less than £20,000 per QALY gained in 100% of runs. However, when considering the lifelong treatment period, this comparison was shown to be 54% cost effective at a threshold

of £20,000 per QALY gained and 77% cost effective at a threshold of £30,000 per QALY gained.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG is satisfied with the search strategy employed by the company to identify cost effectiveness studies, and is reasonably confident that no other relevant published articles exist.

A single economic model, constructed in MS Excel, has been submitted by the company. However, the decision problem encompasses two distinct assessments based on the results from two clinical trials in two quite different populations over two different time periods. The ERG considers that two separate models should have been developed to avoid compromising either assessment.

The company failed to provide sufficient information to allow the ERG to validate many of the company model parameters. First, the company's approach to deriving key model parameter values is not transparent (often referenced as 'AMPLIFY secondary analysis') and the ERG considers that substantiating evidence for important assumptions concerning the long-term level of key risk variables has not been provided. Second, as previously described, the company only provided two of the 12 K-M analyses that were requested as part of the clarification process. Analyses of these two data sets identified parameter estimation errors and a mis-match between the model and an important trial result. There are, therefore, concerns that parameter values derived from the outstanding ten K-M analyses that were not carried out by the company may be similarly flawed.

The ERG is concerned about the use, within the model, of a number of the RR values generated by the company's secondary prevention period NMA. These RR values are unrealistic and lead to the generation of ICERs per QALY gained that appear to unduly favour treatment with apixaban.

In addition, the company model does not incorporate the impact of an accumulating history of recurrent VTE events on future risks; an omission that is likely to lead to exaggerated estimates of long-term health gains for apixaban. Furthermore, the ERG considers that background age is inadequately represented, treatment costs have been underestimated, incorrect UK utility values have been employed, and an excessive mean body weight estimate for a UK population has been applied.

1.7 End of life criteria

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The company has not put forward a case for apixaban to be considered under NICE's end of life criteria. The ERG considers this to be appropriate.

1.8 ERG commentary on the robustness of evidence submitted by the company

1.8.1 Strengths

Clinical effectiveness

- The company provided a detailed submission. The ERG's requests for further clinical information were fulfilled promptly and to a good standard
- The key clinical evidence is derived from two good quality randomised controlled trials (RCTs), AMPLIFY and AMPLIFY-EXT
- Data are provided from the AMPLIFY trial for the initial treatment of patients and for a treatment period of 6 months
- Data are provided from the AMPLIFY-EXT trial for the treatment of patients for whom the risks and benefits of extended anticoagulation treatment are uncertain
- The company included dabigatran as a comparator in the decision problem even though it was not included in the NICE scope
- In the absence of direct evidence comparing apixaban with rivaroxaban and dabigatran, the company carried out two NMAs, one relevant to the initial treatment period, the other to the secondary prevention period

Cost effectiveness

The model used cost assumptions that had been accepted by the Appraisal Committee during earlier appraisals of rivaroxaban (TA287 and TA296).

1.8.2 Weaknesses and areas of uncertainty

Clinical effectiveness

- There are no data for patients with distal DVT or for those with provoked DVT who are at lower risk of VTE recurrence. This means that the applicability of the AMPLIFY trial results to these patients is uncertain. The use of apixaban in patients with active cancer has not been evaluated
- The secondary prevention period NMA only included patients for whom the risks and benefits of extended long-term anticoagulation were unclear. This means that the clinical effectiveness of apixaban in patients at a higher risk of recurrence – due to persisting risk factors or who suffered a recurrence in the first 6 months of treatment – has not been demonstrated
- There are no new HRQoL data provided in the submission. This means that the patient experience of treatment with apixaban compared with enoxaparin/warfarin (initial treatment period) and compared with placebo/no treatment (secondary prevention period) is unknown
- There are no trials that directly compare apixaban with rivaroxaban or with dabigatran for either initial treatment or secondary prevention. The ERG considers that the company's NMA comparing apixaban with rivaroxaban and dabigatran in the

secondary prevention setting is flawed due to differences in the time on treatment and follow-up times reported for each of the included trials

- In the NMAs, to allow the use of data from treatment arms of the included studies in which no events had occurred for some outcomes, the company used continuity correction factors. This approach resulted in unrealistically high estimates of RR for some relevant comparisons; the company then used these values in the economic model. The ERG did not agree with the company's approach and asked the company to re-run the NMAs using a vague prior to allow the ERG to calculate revised ICERs
- There were small numbers of events for many trial outcomes and this resulted in wide confidence intervals for many of the RR estimates in the company's NMAs

Cost effectiveness

- The decision problem encompasses two distinct assessments based on results from two clinical trials in two quite different populations. The company submitted a single model which risks compromising both assessments
- The company failed, both within the CS and during the clarification process, to provide sufficient information to allow the ERG to validate many of the parameters in the company's submitted model
- The use of unrealistic RR values (generated by the company's secondary prevention period NMA) leads to the generation of ICERs per QALY gained which appear to unduly favour treatment with apixaban
- The company model does not incorporate the impact of an accumulating history of recurrent VTE events on future risks; an omission that is likely to lead to exaggerated estimates of long-term health gains for apixaban
- The ERG considers that, within the company model, background age is inadequately represented, treatment costs have been underestimated, incorrect UK utility values have been employed and an excessive mean body weight estimate for a UK population has been applied

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1.9 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG applied six specific model changes using the ERG's preferred alternative parameter values or formulae. These changes were in relation to age/sex mortality rates, treatment costs, age-varying utility, annual discounting, use of a body weight value based on an English population (rather than trial data) and rebasing of the model for assessment of treatment in the prevention period. The impact of each of these changes on the company's long-term base-case results for the comparisons between apixaban and either LMWH/VKA, rivaroxaban or LMWH/dabigatran were small, with changes to the ICERs per QALY gained of ±£2,700 in the most extreme cases. The impact of the ERG's changes on the company's short-term base-case results for the comparisons between apixaban and all three of the comparators was, again, modest with changes in the ICERs per QALY gained being less than ±£300. The ERG also generated model results using parameter values that had been generated by three different alternative methods of calculating RRs from the secondary prevention period NMA. In addition, the ERG carried out a single stand-alone scenario

analysis. The results from all of the ERG's analyses should be viewed with caution due to the underlying uncertainty with regard to the magnitude of the various model parameter values that the ERG has been unable to verify.

1.10 ERG conclusions

The ERG has identified a number of concerns with regard to the company's submitted economic model. Resultant model modifications implemented by the ERG have only resulted in small changes to the company's base-case cost effectiveness results. However, the ERG's review of the model has been severely hampered by the lack of information provided by the company. This has resulted in the ERG being unable to verify the magnitude of a number of model parameters. The ERG is, therefore, forced to conclude that cost effectiveness results generated by the company's model (even with the amendments/corrections proposed by the ERG) cannot currently be considered to be a reliable basis for estimating the relative cost effectiveness of apixaban, compared with LMWH/VKA, rivaroxaban or LMWH/dabigatran, for the initial treatment of either DVT and/or PE or when used for the secondary prevention of DVT and/or PE in adults.

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

The context section (Section 2) of the company submission CS[1] presents the key issues relating to the underlying health problem including clinical features, prognosis and incidence. This information is summarised in Box 1.

Box 1 Pathophysiology, prognosis and incidence of venous thromboembolism (VTE) in the UK

Venous thromboembolism (VTE) is a condition in which a blood clot (thrombus) forms in a vein. Deep vein thrombosis (DVT) and pulmonary embolism (PE) are manifestations of VTE with serious and potentially fatal outcomes.[2] A DVT most commonly occurs in the deep veins of the legs, and can cause a spectrum of symptoms such as cramping pain, redness and/or swelling of the leg, or have no symptoms at all.[3] A PE is caused when a thrombus detaches and travels to block the main pulmonary artery or one of its branches, which delivers de-oxygenated blood to the lungs. A PE can cause breathlessness, chest pain, and sudden death.

DVT may also result in poor venous circulation causing venous ulceration and/or development of post-thrombotic syndrome (PTS) which is characterised by chronic pain, swelling and skin changes; the prevalence of severe PTS has been reported as 8.1% amongst patients with DVT.[4]

Following an episode of PE, the embolus may also increase blood flow resistance leading to chronic thromboembolic pulmonary hypertension (CTEPH) which can eventually lead to heart failure.[5] The rate of CTEPH amongst patients with PE is reported to be 1.25% over a period of 2.1 years.[6]

Approximately two-thirds of patients with a VTE present with a DVT and one third present with a PE.[7] Up to 50% of patients with symptomatic DVT may have an asymptomatic PE and less than a third of patients with PE exhibit signs or symptoms of DVT.[8] When VTE is associated with an identifiable (and often reversible or transient) risk factor(s), such as surgery, trauma, or prolonged immobilisation, it is referred to as a provoked VTE.[3,9] A VTE is considered unprovoked (idiopathic) if it occurs without a clearly identifiable provoking factor.

Mortality from VTE can be as high as 22% in the year following the first event.[10] Of those who sustain an acute event, a proportion will die immediately. Overall, approximately 6% of patients die within 30 days after their first DVT event, while 12% die within 30 days of a PE.[7]

Patients who experience a first episode of VTE have an increased risk of recurrence. The risk of recurrence decreases over time following the first event (being highest during the first 6 to 12 months), however the risk never falls to zero.[11,12] The reported cumulative incidence of recurrent VTE in patients not receiving any treatment [following an initial course of anticoagulation] is reported to be 11.0% after 1 year, 19.6% after 3 years, 29.1% after 5 years, and 39.9% after 10 years.[13] Recurrent DVT is associated with a substantially higher likelihood of PTS,[14] whilst PE predisposes patients to CTEPH,[15] and recurrent PE is fatal in up to 9% of cases.[12]

In the UK, the incidence of people presenting with clinical symptoms of VTE each year is 2 in 1000.[16] The incidence of VTE varies with age; for people under 40 years the annual incidence of VTE is 1 in 10,000, rising to 1 in 100 for those over 80 years.[16] It is estimated that there will be 58,392 incident patients in England and Wales who will begin treatment for VTE in 2015, rising to 60,045 in 2019.[1]

The ERG notes that a 2014 study by Martinez et al[17] reported the rates of DVT compared with PE as 54% to 46% (rather than 66% to 33% cited in the CS[1]). The Martinez et al[17] study is based on data collected in primary care and on hospital data collected in the UK.

The ERG also notes that the incidence rate (as cited in the CS[1]) for people presenting with symptoms of VTE each year is widely reported as 2 in 1000; however data from the Martinez et al[17] study suggest that the incidence rate is closer to 1 in 1000.

The ERG considers the company's description of the underlying health problem to be relevant and appropriate.

The ERG notes that in NICE Clinical Guideline CG92,[3] a number of risk factors for the development of a VTE are identified. For information, the ERG lists these in Box 2.

Box 2 Underlying risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (body mass index over 30 kg/m2)
- One or more significant medical comorbidities (for example: heart disease; metabolic endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis

There are two types of DVT that occur in the legs, proximal DVT or isolated distal DVT. Proximal DVTs are located in the popliteal, femoral, or iliac veins. Isolated distal DVTs have no proximal component and are confined to the calf veins below the knee.[18] Clinical advice to the ERG suggests that the duration of treatment for proximal and distal DVTs might differ. Patients with isolated distal calf DVT are likely to be given 6 weeks of anticoagulation treatment; this is in contrast to patients with proximal DVT or PE who are likely to be treated for at least 3 months.[19,20]

In clinical practice in England and Wales a number of tests are available to aid in the diagnosis of DVT. These include a D-dimer test, ultrasound scan or venogram.[21] A PE may be diagnosed using a blood test, a D-dimer test, computerised tomography pulmonary angiography or ventilation-perfusion scan.[22]

2.2 Critique of company's overview of current service provision

The company's overview of current service provision is presented in Section 2.4 and 2.5 of the CS.[1] The CS[1] includes an overview of current NICE guidelines (CG144[20]) and a summary of NICE guidance (TA261,[23] TA287[24]) relevant to this appraisal. These are summarised in Box 3 and Box 4.

Box 3 Overview of CG144 (CS)

NICE Clinical Guideline 144[20] (CG144, June 2012): Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing.

This guideline gives best practice advice on the treatment and care of adults with VTE. It also gives recommendations for DVT and PE diagnostic investigations. The guideline was produced prior to the first NICE Technology Appraisal for the first factor Xa inhibitor, rivaroxaban (Xarelto®), and therefore considers only the older treatment options, i.e. low molecular weight heparin (LMWH), fondaparinux (Arixtra®) and vitamin K antagonists (VKAs). CG144[19,20] recommends:

- patients presenting with confirmed proximal DVT or PE are offered a choice of LMWH, unfractionated heparin (UFH) or fondaparinux for at least 5 days or until the international normalised ratio (INR) is ≥2 for at least 24 hours. A VKA should be started concomitantly and continued for 3 months.
- reassessing the need for continued VKA treatment at 3 months, taking into account the risk of bleeding versus. the risk of recurrent VTE.
- where patients have idiopathic VTE, extend treatment beyond 3 months. The exact treatment duration is not specified.

Recommendations in NICE CG144[20] for patient subgroups

- The recommendation for treatment in patients with PE and haemodynamic instability includes unfractionated heparin (UFH) and other thrombolytic therapies.
- The recommendation for the treatment and prevention of recurrent DVT and PE in patients with active cancer is LMWH. This should be used for duration of 6 months, at which point the risk/benefit ratio of continued anticoagulation is assessed
- The recommendations for patients with severe renal impairment or established renal failure (estimated glomerular filtration rate <30 ml/min/1.73 m^2) includes UFH or LMWH.
- The treatment recommendation for patients with an increased risk of bleeding is UFH.

Box 4 Current NICE Guidance (CS)

NICE recommended rivaroxaban in the following two appraisals:

- NICE TA287.[24] Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism. June 2013
- NICE TA261.[23] Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. July 2012

Dabigatran etexilate (Pradaxa®)

Dabigatran etexilate is currently being appraised by NICE for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism

During the course of this appraisal (31 October 2014) NICE issued a final appraisal determination[25] recommending the use of dabigatran etexilate as an option for the treatment and secondary prevention of DVT and/or PE. For brevity, this ERG report refers to dabigatran etexilate as dabigatran.

In addition to the guidance and guidelines described, the ERG is aware that NICE has published quality standards (QS29[26]) for the diagnosis and treatment of VTE disease. Of relevance to the current appraisal, QS29[26] advises that:

- people with active cancer and confirmed proximal DVT or PE are offered anticoagulation therapy
- people with active cancer who receive anticoagulation therapy have a clinical review within 6 months of confirmed diagnosis of proximal DVT or PE to discuss the risks and benefits of continuing anticoagulation therapy
- people without cancer who receive anticoagulation therapy have a clinical review within 3 months of diagnosis of confirmed proximal DVT or PE to discuss the risks and benefits of continuing anticoagulation therapy

The CS[1] also discusses related international guidance documents. These are summarised in Box 5.

Box 5 International guidelines

- SIGN 122[27] Scottish Intercollegiate Guidelines Network 122, Prevention and management of venous thromboembolism (2010).
- European Society of Cardiology (ESC) Guidelines on the diagnosis and management of acute pulmonary embolism, 2014[28]
- American College of Chest Physicians (ACCP) Antithrombotic therapy for VTE disease (9th Edition, 2012).[9]

The ESC[28] guidelines cover only PE, whereas the SIGN[27] and ACCP[9] guidelines cover both DVT and PE. As the published evidence base has rapidly developed over the time period covering the publication of these guidelines, there are some differences in the interventions that are recommended. The 2010 SIGN[27] guidelines do not discuss novel oral anticoagulant (NOAC) use, the 2012 ACCP[9] guidelines mention the paucity of data available for NOACs at the time of guideline preparation, whilst the 2014 ESC[28] guidelines recommend NOACs as alternatives to treatment with LMWH/VKA. Aspirin is not recommended as a sole prophylactic agent in the SIGN[27] guidelines and is not mentioned in the ACCP[9] guidelines; however, the ESC[28] guidelines recommend the use of aspirin for patients who refuse or are unable to take anticoagulants.

2.3 Current pathway of care

The CS[1] presents the current pathway of care for patients with VTE in the NHS in England and Wales and the proposed place in the pathway for apixaban. This is summarised in Box 6 and

Box 7. The ERG notes that the recommendations made in CG144[20] are pertinent only to patients with confirmed proximal DVT and PE. Patients with a distal DVT do not appear to be included in the guideline.

The ERG is satisfied with the description provided in the CS,[1] but notes that the pathway described is not relevant to patients with active cancer, who should be treated with low molecular weight heparin (LMWH) for 6 months instead of a vitamin K antagonist (VKA), rivaroxaban or unfractionated heparin.[20]

Box 6 Current pathway of care (CG144)

The current pathway of care is described in NICE CG144.[20] Between suspicion and diagnosis of VTE parenteral anticoagulants are administered. Patients with a confirmed diagnosis of proximal DVT or PE may undergo a combination of pharmacological therapy, thrombolytic therapy and/or mechanical interventions. Pharmacological treatment is currently initiated in secondary care and may involve a hospital admission; however, with the NICE approval of the oral treatment, rivaroxaban, treatment is being increasingly managed in a primary care setting.[29]

Currently, treatment with VKA (warfarin) is the recommended pharmacological therapy for treatment of VTE.[20] As a result of the delayed onset of action of VKA, which takes at least 5 days to achieve therapeutic levels, there is a sub-therapeutic gap bridged with a parenteral anticoagulant, such as LMWH (most commonly enoxaparin in England), fondaparinux or UFH. Once therapeutic oral anticoagulation is achieved, parenteral therapy is discontinued and oral therapy with VKA continued for the remaining treatment period, the duration of which is dependent upon individual assessment of patient risk factors for VTE recurrence versus their risk of bleeding from the anticoagulant. Patients receiving a VKA initially require more frequent blood tests for INR monitoring and dose adjustments until their INR is within therapeutic range (INR of 2–3).

CG144[20] recommends 3 months of treatment in those with a provoked VTE and assessment of the risk/benefit of continuing treatment and or prevention at 3 months. Clinical experts at a recent advisory board meeting indicated that in routine practice, patients may receive between 3–6 months of initial treatment because of the delay in stabilising patients on VKA, or there may be a delay in patients being seen by their GP or anticoagulation service.[30] Recent analysis using the Clinical Practice Research Datalink (CPRD)[31] database indicates that the time to discontinuation of anticoagulation after an acute VTE in UK routine practice is between 3 and 6 months (see Appendix 13g, Section 10.32). VKAs should be offered "beyond 3 months to patients with unprovoked PE or unprovoked proximal DVT, if their risk of VTE recurrence is high and there is no increased risk of bleeding or major bleeding".[20] The guideline does not specify the duration of treatment for preventing recurrent events. In clinical practice it is up to the clinician to evaluate the individual risk/benefit ratio of continuing anticoagulation or stopping treatment.

Box 7 NICE recommended treatment options for VTE

For initial treatment and prevention of VTE

- Treatment with LMWH plus initiation of oral VKA within 24 hours. LMWH continued for at least 5 days or until INR ≥2 for at least 24 hours, whichever is longer. INR monitoring to ensure warfarin is within therapeutic range
- Rivaroxaban monotherapy (15mg twice daily for 21 days, 20mg once daily thereafter).28,29
- Dabigatran (150mg twice daily) following treatment with LMWH for at least 5 days
- Apixaban monotherapy (10mg twice daily for 7 days, 5mg twice daily thereafter)

Treatment should be for at least 3 months, according to risk/benefit.

For long term prevention of VTE

Treatment is continued according to risks and benefits.

- Dosing schedule as above
- Apixaban 2.5mg twice daily
- Aspirin and no preventative therapy are also treatment options

The ERG agrees with the company that warfarin is the vitamin K antagonist (VKA) therapy that is most commonly used in clinical practice in England and Wales. The ERG is aware that patients who are treated with warfarin are required to undergo frequent blood tests. Blood tests are used to assess the efficacy of warfarin to prevent blood clots as measured against the international normalised ratio (INR) level. If the INR level is too high, the patient

is at risk of bleeding; if the INR level is too low, the patient is at risk of further blood clots. Warfarin doses are adjusted in order to ensure that the INR level lies between 2 and 3.[32]

2.4 Estimated size of the eligible population

The CS[1] (Section 2.2) provides an estimate of the number of people in England and Wales who are eligible for treatment with apixaban for the treatment and secondary prevention of VTE. The CS[1] also provides an estimate of the number of people who are eligible for treatment with apixaban within its other licensed indications (i.e. for the prevention of VTE in patients who have undergone elective hip or knee surgery and for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors). The company calculations are presented in

Box 8.

Box 8 Eligible population in England and Wales

It is estimated that there will be 58,392 incident patients in England and Wales who will begin treatment for VTE in 2015, rising to 60,045 in 2019.[1] The number of patients covered by the other indications not under consideration in this submission were estimated in the relevant NICE technology appraisals, TA245[33] [for use in the prevention of VTE after hip and knee surgery] and TA275[34] [for use in the prevention of VTE in patients with atrial fibrillation]. The submission for TA245[33] estimated that in 2014 to 15 the number of eligible patients would be 98,459 while the submission for TA275[34] estimated that in 2014 the number of eligible patients would be 456,000.

The ERG considers that the company's estimate of the number of people in England and Wales likely to be eligible for treatment with apixaban for the treatment of VTE is reasonable but notes that the company's calculations do not appear to allow for changes in the age-structure of the population in England and Wales over time. However, the number of patients estimated to be eligible for treatment with apixaban are within 10% of the number of patients who were estimated to be eligible for treatment in the in the evidence submission for the appraisal of dabigatran.[25]

2.5 Equality

No issues relating to equality were noted in the CS.[1]

2.6 Innovation

The company (CS[1] Section 4) asserts that apixaban offers a number of advantages compared with current care. These are summarised in

Box 9.

Box 9 Comparison of apixaban with current treatment options

Compared with LMWH/VKA

- Apixaban is a single oral treatment without the need for parenteral therapy
- Apixaban does not require laboratory INR monitoring or subsequent dose adjustments
- Apixaban significantly reduces the risk of the composite of major or clinically relevant non-major (CRNM) bleeding and major bleeding compared with LMWH/VKA

Compared with other NOACs

- Apixaban requires only 1 week of higher initial dose therapy versus rivaroxaban which requires 3 weeks
- Apixaban does not require parenteral therapy compared to dabigatran
- Apixaban provides comparable effectiveness in terms of recurrent VTE or VTE-related death compared to dabigatran and rivaroxaban, but has significantly lower rates of major or CRNM bleeding

Compared with no treatment

- Some patients who may benefit from long-term anticoagulation to prevent VTE recurrence currently receive no treatment, due to high risk of bleeding. Apixaban offers a step-change in treatment options by providing considerable benefit by reducing the risk of recurrent VTE and VTE-related death with a bleeding risk comparable to placebo/no treatment

It is emphasised in the CS[1] (p31), that compared to LMWH and VKA treatment, the use of apixaban offers simple treatment administration, negates the need for regular injection/INR monitoring/dose adjustments and has minimal food and drug interactions. In addition, compared with patients treated with a VKA, patients treated with apixaban need not be concerned about the consequences of not remaining within the set INR range. The ERG notes that rivaroxaban and dabigatran are also oral treatments that do not require INR monitoring and have few drug or food interactions. Patients treated with dabigatran are required to have concomitant treatment with LMWH for 7 days and patients treated with rivaroxaban are required to take a higher initial dose of rivaroxaban for 3 weeks.

The ERG notes that patients treated with apixaban do not require regular blood monitoring to ensure that anticoagulation treatment is optimal. This means that there is no measure of treatment compliance with apixaban. For patients who are treated with apixaban, failure to take the prescribed doses of apixaban result in sub-therapeutic levels of anticoagulation. Authors of a recently published paper[35] suggest that missing doses of novel oral anticoagulants (NOACs) may be more serious than missing doses of warfarin as NOACs have a shorter half-life than warfarin. Therefore, only patients likely to be fully compliant with the apixaban treatment regimen will be recommended for treatment with apixaban.

The ERG is also aware that at present there is no antidote to apixaban or other NOACs; however clinical advice to the ERG is that most bleeds experienced by patients treated with NOACs are manageable. The CS[1] (p28) states that research in this area is in progress.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The decision problem described in the final scope[16] issued by NICE and the company rationale for any deviation from the scope are presented in Section 5 of the CS[1] and this information is reproduced in Table 1.

Table 1 Decision problem issued by NICE (reproduced from CS)

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Population	People with DVT and/or PE	No difference	Not applicable
Intervention	Apixaban	No difference	Not applicable
Comparator(s)	• Initial treatment with a LMWH or fondaparinux and continued VKA • Rivaroxaban For people for whom a vitamin K antagonist is unsuitable: • LWMH or fondaparinux alone • Rivaroxaban	As stated with the following exceptions: • Fondaparinux/VKA, and fondaparinux alone were not included as comparators in this submission • LMWH monotherapy is a relevant comparator for the submission. However, no relevant evidence was identified in people for whom VKA is unsuitable (not including cancer patients). • LMWH/dabigatran etexilate was however considered a relevant comparator and is therefore included in this submission.	• We believe that fondaparinux is not a relevant comparator for this appraisal, as in Section 4.2 of the NICE technology appraisals of rivaroxaban (TA287[24]), the NICE Appraisal Committee stated that fondaparinux is rarely used and it was accepted that it was not a relevant comparator. • There is no evidence identified in the systematic review on the use of LMWH monotherapy and rivaroxaban relative to apixaban for treatment and prevention of DVT and/or PE in unsuitable for warfarin population (not including cancer patients). The efficacy and safety of apixaban is not established in patients with active cancer. • LMWH/dabigatran etexilate is now licensed for the treatment and prevention of recurrent DVT and /or PE, and is currently being appraised by NICE for this indication.[25] LMWH/dabigatran was acknowledged at the scoping meeting for the apixaban appraisal by the NICE Chair and VTE clinical experts as being a relevant comparator; however it was not included in the final scope. Based on the discussion with stakeholders at the scoping meeting, we have included LMWH/dabigatran as a comparator for this submission.
Outcomes	The outcome measures to be considered include: Mortality • Venous thromboembolism recurrence • Complications following deep vein thrombosis or	No difference with the exception of post thrombotic syndrome, chronic thromboembolic pulmonary hypertension and health-related quality of life which were not addressed in the submission.	• There were insufficient data on post thrombotic syndrome and chronic thromboembolic pulmonary hypertension from the included trials to allow for any analysis to be carried out. However these have been included in the economic model from the published literature.

	pulmonary embolism, including post thrombotic syndrome and chronic thromboembolic pulmonary hypertension • Adverse effects of treatment (particularly bleeding, including intracranial and gastrointestinal bleeding) • Health-related quality of life.		• Health-related quality of life was not measured in the AMPLIFY[36] and AMPLFY-EXT[37] trials nor in any of the other NOAC trials identified in the systematic review.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	No difference	Not applicable as no difference between scope and evidence submission
Subgroups to be considered	If evidence allows, subgroups will be considered by type of venous thromboembolism (pulmonary embolism or deep vein thrombosis). The analysis should consider both those who require a limited period of anticoagulation (3 to 6 months) and those who require long-term anticoagulation (usually lifelong). If evidence allows the analysis should also consider people for whom the need for long-term anticoagulation is uncertain and aspirin or no preventative treatment might be considered. If the evidence allows, the analysis should consider separately people with active cancer and include any effect on the person's	No difference with the exception that a subgroup of patients with active cancer was not considered	There were no trials in this specific population and the safety and efficacy of apixaban is not established in patients with active cancer.[12]

	cancer or cancer treatment.		
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations guidance will be issued in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	No difference	Not applicable

3.1 Population

The clinical evidence submitted by the company consists of two published randomised controlled trials (RCTs), AMPLIFY[36] and AMPLIFY-EXT.[37]

The AMPLIFY[36] trial recruited patients who required initial treatment for a VTE event. The trial compared apixaban versus enoxaparin/warfarin in adult patients with symptomatic proximal DVT or PE (with or without DVT) over a 6-month period.

The AMPLIFY-EXT[37] trial recruited patients with symptomatic, proximal DVT or PE (with or without DVT), who were treated with standard anticoagulation therapy for between 6 and 12 months without VTE event recurrence. A number of patients had completed the AMPLIFY[36] trial. The patients recruited to the trial were people considered to be at clinical equipoise wherein the risks and benefits of extended anticoagulation treatment were unclear. Patients who definitely required extended anticoagulant treatment were not included. The ERG considers that the results of the AMPLIFY-EXT[37] trial are relevant only to one of the subgroups of patients identified in the NICE scope,[16] i.e., to patients for whom the risks and benefits of extended anticoagulation are uncertain. The extent to which the results of the AMPLIFY-EXT[37] trial are directly applicable to patients who definitely require extended anticoagulation treatment is not discussed in the CS.[1]

No definition of clinical equipoise is described in the published paper for AMPLIFY-EXT[37] or in the CS.[1] The ERG is concerned that the patient population in the AMPLIFY-EXT[37] trial may not be easily identifiable in clinical practice in England and Wales. The European Public Assessment Report (EPAR)[38] for apixaban published by the European Medicines Agency (EMA) states that the population in the AMPLIFY-EXT[37] trial was poorly defined and open to subjectivity. The ERG notes that similar concerns were raised in the ERG reports submitted during the NICE appraisals of rivaroxaban[23] and dabigatran[25] regarding the pivotal trials for treatment extension in cohorts of patients described as being at clinical equipoise.[25]

The ERG agrees that the trial populations in AMPLIFY[36] and AMPLIFY-EXT[37] include patients with DVT and/or PE as identified in the NICE scope.[16] However, the ERG notes that the main inclusion criteria for the AMPLIFY[36,37] trials have led to the exclusion of two subgroups of patients who are treated in clinical practice in England and Wales, patients with distal DVT and patients who have a provoked index event without risk of VTE recurrence.

In the AMPLIFY[36,37] trials, the inclusion criteria explicitly state that for patients with DVT, only those with a proximal DVT were eligible for inclusion in the trial. This means that patients with distal DVT were excluded from the AMPLIFY[36] trial. The ERG considers that the exclusion of patients with distal DVT may be appropriate as clinical advice to the ERG is that the duration of treatment for patients with distal DVT is likely to be for 6 weeks, whereas the duration of treatment for proximal DVT and/or PE is likely to be at least 3 months.[19]

The AMPLIFY[36,37] trials inclusion criteria explicitly limited entry to patients who had experienced an unprovoked index event or a provoked index event with a risk factor for VTE recurrence. Patients who had a provoked event without risk of VTE recurrence were therefore excluded from the trial. This is in line with the aims of the trial which were to assess the effectiveness of treatment in patients who required at least 6 months of treatment for VTE. The ERG is aware that patients with a provoked VTE with no other risk factors are likely to receive treatment for less than 6 months. The ERG also notes that in the EPAR[38] for apixaban, the EMA concluded that patients who are treated for only 3 months are at lower risk of VTE recurrence than the patients included in the AMPLIFY[36] trial. The EMA also concluded that since apixaban is effective in patients with a high risk of recurrence, it can be assumed to be effective in patients at lower risk. The ERG has some concerns about this assumption as no clinical data are available from the AMPLIFY[36] trial to support the use of apixaban in patients with a provoked index event without risk of recurrence or in patients with distal DVT.

3.2 Intervention

The intervention described in the CS[1] is apixaban and this matches the intervention defined in the scope.[16] Apixaban is an orally active selective inhibitor of Factor Xa. It inhibits free Factor Xa, thrombus associated Factor Xa and Factor Xa within the prothrombinase complex. The inhibition of Factor Xa decreases thrombin generation and reduces fibrin formation, coagulation and platelet activation.

On 28 July 2014, the EMA approved an extension to the existing marketing authorisation for the use of apixaban for the treatment of DVT and PE and prevention of recurrent DVT and PE in adults.[38]

Apixaban is formulated as film-coated tablets of either 2.5mg or 5mg. The recommended dose of apixaban for the treatment of initial VTE is 10mg taken orally twice daily for the first 7 days followed by 5mg taken orally twice daily.[39]

The recommended dose of apixaban for the secondary prevention of recurrent VTE is 2.5mg taken orally twice daily. When prevention of recurrent VTE is indicated, the 2.5mg twice daily dose should be initiated following completion of 6 months of treatment with either apixaban 5mg twice daily or with another anticoagulant.[39]

The Summary of Product Characteristics[39] (SPC) states that whether a short duration of treatment (at least 3 months) is required the decision should be based on the presence of transient risk factors (e.g., recent surgery, trauma, immobilisation). The SPC[39] further states that the duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk of bleeding.

Apixaban should be used with caution in patients with severe renal impairment (creatinine clearance 15-29 mL/min). It is not recommended in patients with creatinine clearance <15ml/min or in patients undergoing dialysis. Patients with serum creatinine ≥ 1.5mg/dL (133micromole/L) associated with age ≥ 80 years or body weight ≤ 60 kg should receive the lower dose of apixaban 2.5mg twice daily.[39]

Page superseded by erratum

3.3 Comparators

The final scope[16] issued by NICE states that the comparators to apixaban are:

- initial treatment with a LMWH or
- fondaparinux and continued VKA or
- rivaroxaban

3.3.1 Initial treatment with a LMWH

In the CS,[1] the evidence for the clinical effectiveness of treatment with apixaban versus LMWH and continued VKA is derived from the AMPLIFY[36] trial. Patients in the AMPLIFY[36] trial were treated for 6 months. The LMWH used in the AMPLIFY[36] trial is enoxaparin and the VKA used is warfarin. The CS[1] states that enoxaparin and warfarin are the standard treatments used in clinical practice in the NHS in England and Wales. Clinical advice to the ERG agrees with the company's statement.

3.3.2 Fondaparinux

The CS[1] does not provide a comparison of apixaban versus fondaparinux and continued VKA or apixaban versus fondaparinux monotherapy. The company states that fondaparinux is not a relevant comparator and supports this claim by referring to the appraisal of rivaroxaban described in TA287[24] (rivaroxaban for the treatment of PE). The CS[1] states that in TA287[24] the appraisal committee (AC): i) noted that fondaparinux is rarely used in clinical practice in England and Wales and ii) accepted that fondaparinux is not a relevant comparator. The ERG agrees with the company's exclusion of fondaparinux as a comparator for this appraisal. Clinical advice to the ERG is that fondaparinux is rarely used in clinical practice in England and Wales as a treatment for VTE.

3.3.3 Rivaroxaban

In the absence of any direct trials that compare apixaban versus rivaroxaban, the company conducted two NMAs.

The NICE scope[16] also states that for patients who are unsuitable for treatment with a VKA, the comparators are:

- continued treatment with LMWH
- fondaparinux or
- rivaroxaban

The CS[1] does not provide a comparison of apixaban versus LMWH monotherapy or apixaban versus rivaroxaban in patients for whom VKA is unsuitable. The ERG understands that this patient group consists of people with an allergy to or intolerance of VKA, people with cancer, pregnant women, people with highly unstable INRs, intravenous drug users, people with human immunodeficiency virus, people with chronic alcoholism and patients at high risk of non-compliance with VKA therapy. The company sought clinical effectiveness evidence to support the use of apixaban in all of these patient populations (with the exception of patients with cancer). No evidence was identified. The ERG considers that the company has endeavoured to find evidence relevant to these subgroups and that none is available.

The company states that it did not seek evidence of the effectiveness of apixaban in patients with active cancer as apixaban is not licensed for use in patients with cancer. The CS[1] advises that the apixaban SPC[40] is referred to when considering the use of apixaban in patients unsuitable for warfarin.

The ERG notes that a small percentage of the patient population in the AMPLIFY[36] and AMPLIFY-EXT[37] trials (2.5% and 2% respectively) were reported to have active cancer. The ERG considers that the characteristics of patients with active cancer who were recruited to

the trials are not clearly defined. The ERG notes that patients with active cancer for whom treatment with LWMH was planned were excluded from the AMPLIFY[36] trial. The ERG agrees that this is reasonable given that the recommended treatment for patients with active cancer is LMWH. As LMWH is the standard of care for this patient group, it is unclear to the ERG why some patients with active cancer were recruited to the AMPLIFY[36] trial.

Similarly, the AMPLIFY-EXT[37] trial excluded patients with cancer who were to be treated indefinitely with anticoagulation therapy. The ERG is aware that in clinical practice in England and Wales, the majority of patients with active cancer are routinely treated with indefinite periods of anticoagulation and therefore they are not at clinical equipoise as there is no doubt about the course of treatment.

The ERG is aware of the EMA's[38] criticism of the inclusion of patients with active cancer in the AMPLIFY[36] and AMPLIFY-EXT[37] trials. The EPAR[38] highlights that LMWH is the recommended treatment for patients with cancer rather than a VKA (the comparator in AMPLIFY[36]) and therefore patients with cancer in the AMPLIFY[36] trial may have received sub-optimal treatment. With reference to extended treatment (as received in the AMPLIFY-EXT[37] trial), the EPAR[38] points out that in clinical practice, patients with active cancer are treated with LMWH for extended periods and therefore would not meet the clinical equipoise criteria for inclusion in the AMPLIFY-EXT[37] trial.

3.3.4 Dabigatran

The company has included dabigatran as a relevant comparator to apixaban; however, the CS[1] acknowledges that dabigatran is not specified as a comparator in the NICE scope.[16] The company justifies the inclusion of dabigatran as a comparator on the grounds that it is licensed for the initial treatment and secondary prevention of recurrent DVT and/or PE and (at the time of preparing the CS[1]) dabigatran was being appraised by NICE. In addition, the CS[1] states that LMWH/dabigatran was acknowledged at the scoping meeting as being a relevant comparator to apixaban.

NICE has recently (31 October 2014) recommended dabigatran[25] for use in the NHS and the ERG agrees that dabigatran is a relevant comparator to apixaban. The ERG highlights that in the absence of any direct evidence comparing apixaban to dabigatran, the company has included dabigatran in two NMAs.

3.4 Outcomes

The outcomes specified in the NICE final scope[16] include mortality, VTE recurrence, complications following DVT or PE including post-thrombotic syndrome (PTS), CTEPH,

adverse events (AEs), particularly bleeding including intracranial (IC) and gastrointestinal bleeding and HRQoL.

The majority of the specified outcomes are described in the CS;[1] however, the company reports that the exceptions are PTS and CTEPH and HRQoL. The CS[1] states that there were insufficient data available from the included trials to allow for any analyses of PTS or CTEPH events to be undertaken. The company states that HRQoL data were not collected during the AMPLIFY[36] and AMPLIFY-EXT[37] trials and that this is the same for all other trials of NOACs identified by the company's systematic review. The ERG is of the opinion that the lack of any HRQoL data is a disappointing omission from the CS.[1]

3.5 Economic analysis

As specified in the NICE scope,[16] the cost effectiveness of treatments is expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. The time horizon is up to 65 years (maximum) which is sufficiently long to capture any differences in costs or outcomes between the technologies. Costs are considered from an NHS and Social Services perspective.

3.6 Subgroups to be considered

The final NICE scope[16] states that, subject to available evidence, a number of patient subgroups should be considered including:

- outcomes by type of VTE event
- outcomes for patients requiring treatment for a limited period (3 to 6 months)
- long-term treatment (usually lifelong)
- people for whom the long-term need for treatment with anticoagulation is uncertain and for whom aspirin and no preventative treatment might be considered
- patients with active cancer and any effect on the person's cancer or treatment

The ERG notes that subgroup data relevant to the type of VTE event for the clinical effectiveness of apixaban versus enoxaparin/warfarin are available from the AMPLIFY[36] trial. Data are also available from the AMPLIFY[36] trial regarding the effectiveness of apixaban versus enoxaparin/warfarin for a limited initial treatment period up to 6 months.

There are no data available to support the clinical effectiveness of long-term or lifelong treatment with apixaban.

Data describing the clinical effectiveness of apixaban versus no treatment in people for whom the long-term risks and benefits of extended anticoagulation are uncertain are

available from the AMPLIFY-EXT[37] trial. The ERG notes that the AMPLIFY-EXT[37] trial only compares apixaban with no preventative therapy in a subgroup of patients who were considered to be at clinical equipoise. The AMPLIFY-EXT[37] trial does not include patients for whom anticoagulation for longer than 12 months was planned. This issue was discussed in Section 3.1 of this ERG report. The ERG also notes that the AMPLIFY-EXT[37] trial does not compare apixaban with active treatment. The company states that the results of the secondary prevention treatment NMA allow a comparison of apixaban versus aspirin in patients for whom the risks and benefits of extended anticoagulation are uncertain.

The lack of clinical effectiveness evidence to support the use of apixaban in the treatment of patients with active cancer is discussed in Section 3.3 of this ERG report.

3.7 Other relevant factors

No equality issues were identified by the company. The ERG is unaware of any Patient Access Scheme application submitted by the company.

4 CLINICAL EFFECTIVENESS

This section provides a structured critique of the clinical evidence submitted by the company in support of apixaban for the treatment and secondary prevention of DVT and/or PE.

4.1 Critique of the methods of review(s)

The company conducted two main systematic reviews. One systematic review was designed to identify RCT evidence relevant to the efficacy and safety of NOACs and relevant comparators in the treatment and secondary prevention of VTE. The second systematic review was designed to identify non-RCT evidence relevant to the efficacy and safety of apixaban in the treatment and secondary prevention of VTE.

The CS[1] reports that additional systematic reviews were carried out to identify evidence relevant to patients who are unsuitable for treatment with a VKA. The company states that this search was not intended to identify evidence relevant to patients with active cancer as the clinical effectiveness of apixaban is not established in patients with active cancer.

The methods used by the company to identify relevant articles for inclusion in the systematic are reported in Section 6 of the CS[1] and in the Appendices of the CS[1] (10.2 and 10.22).

4.1.1 Searches

Searches for evidence from randomised controlled trials

The searches for RCT evidence aimed to identify clinical data on the efficacy and safety of NOACs were conducted on 14 July 2014 and the following databases were searched:

- Medline (OVID)
- Medline In-Process Citations and Daily Update (OVID)
- Embase (OVID)
- The Cochrane Library, incorporating;
    - Cochrane Database of Systematic Reviews (CDSR)
    - Database of Abstracts of Reviews of Effects (DARE)
    - Cochrane Central Register of Controlled Trials (CENTRAL)
    - Health Technology Assessment Database (HTA)
    - NHS Economic Evaluation Database (NHS EED)

The search strategy included comprehensive terms covering DVT, VTE and PE and 'secondary' and 'treatment' to isolate the second-line treatment for DVT. This may have excluded relevant results if papers did not specifically use the terms secondary or treatment (i.e., 2nd line or treat). The search included the drug terms and all the comparator drugs. An RCT filter was user and case reports, letters, historical articles and case reviews were removed from the results using 'NOT'.

The company also ran searches for grey literature on the following websites:

- American Society of Hematology (ASH)
- International Society on Thrombosis and Haemostasis (ISTH)
- European Hematology Society (EHS)
- European Society of Cardiology (ESC)
- American College of Cardiology(ACC)
- American Heart Association (AHA)

Searches for non-randomised evidence

The search strategy for non-RCTs aimed to identify clinical data on the efficacy and safety of apixaban in the treatment and secondary prevention of recurrent DVT and/or PE. The strategy included comprehensive terms covering DVT, VTE and PE and 'secondary' and 'treatment' to isolate the second-line treatment for DVT. The search only included the drug terms for apixaban and no comparator drugs. A non-RCT filter was used for this search strategy. This search was conducted on 14 July 2014 using the major databases listed previously and was also run within the grey literature websites as listed above.

Searches for evidence of effectiveness in VKA-unsuitable patients

These searches were run on 6 October 2014 and the searches were run in the databases listed previously. No grey literature searches were completed.

Overall, the searches for RCTs, non-RCTs and VKA-unsuitable patients are of reasonable quality and appear to include all of the terms required to identify relevant papers. The ERG is confident that the search strategies employed by the company are appropriate and sufficiently comprehensive to be able to identify all relevant studies.

4.1.2 Eligibility criteria

The study selection process used by the company is presented in Section 6.2 of the CS[1] (see Table 2 and

Table 3). The ERG is satisfied that the eligibility criteria are relevant to the aims of the company's systematic reviews.

Table 2 Eligibility criteria for systematic review of RCTs

Inclusion criteria	Description	
Population	Adult patients (≥18) with symptomatic objectively confirmed VTE (DVT and/or PE)	
Interventions	Treatment	Secondary prevention
	Apixaban	Apixaban
	Dabigatran	Dabigatran
	Rivaroxaban	Rivaroxaban
	LMWH/VKA (any allowed)	LMWH/VKA (any allowed)
		Aspirin
		Placebo
Outcomes	Recurrent VTE (DVT and/or PE) VTE-related death Major bleeding CRNM bleeding Intracranial bleeding Other major bleeding Other deaths Overall treatment discontinuation All-cause mortality	
Study design	Prospective, RCTs, with open-label or double-blind designs Trials on both VTE treatment and/or secondary prevention of recurrence were included	

CRNM=clinically relevant non-major bleeding; DVT=deep vein thrombosis; LMWH/VKA=low molecular weight heparin/vitamin K antagonist; PE=pulmonary embolism; VTE=venous thromboembolism
Source: Table 4 of CS[1]

Table 3 Eligibility criteria for systematic review of non-RCTs

Inclusion criteria	Description
Population	Adult patients (≥18) with symptomatic objectively confirmed VTE (DVT and/or PE)
Interventions	Apixaban
Outcomes	Recurrent VTE (PE/DVT) VTE-related death Major bleeding CRNM bleeding Intracranial bleeding Other major bleeding Other deaths Overall treatment discontinuation All-cause mortality
Study design	Observational non-RCTs

CRNM=clinically relevant non-major bleeding; DVT=deep vein thrombosis; LMWH/VKA=low molecular weight heparin/vitamin K antagonist; PE=pulmonary embolism; VTE=venous thromboembolism
Source: Table 5 of CS[1]

4.2 Results of the company's searches

The company's search for RCT evidence identified 5021 non-duplicate records and 55 were selected for full-text screening. A total of 16 publications met the full inclusion criteria, six of these were relevant for initial treatment for VTE and a further ten were relevant for the

secondary prevention of VTE. The company's PRISMA diagram outlining the inclusion process is presented in Figure 1 of the CS.[1]

The ERG notes that in Figure 1 of the CS,[1] 197 studies were reported to be excluded on the basis of study outcome. The ERG asked the company (via the clarification process) how these 197 studies were judged to not have reported the outcome of interest when only the title and abstract were available. In its response, the company stated that they could not be certain that the 197 publications did not report an outcome of interest; however, it was clear from the abstracts that the principal focus of the reported investigations was not the efficacy or safety of anticoagulation for the initial treatment or secondary prevention of VTE. The company also pointed out that the majority of the publications were excluded for multiple reasons. The company further stated that as two independent reviewers conducted the screening process (with disagreements resolved by a third or through team consensus), they are confident that all relevant citations were identified.

The company's search for non-RCT evidence for the clinical effectiveness of apixaban identified 40 non-duplicate records all of which were excluded from the review on the basis of title and abstract. The company's PRISMA diagram outlining the inclusion process is presented in Figure 1 of the CS.[1]

The company's search for evidence (RCT and non-RCT) for the clinical effectiveness of apixaban in patients for whom treatment with a VKA is unsuitable did not identify any relevant articles for inclusion in a systematic review.

4.2.1 Identified studies

Two RCTs were identified that are relevant to the treatment of VTE with apixaban. The AMPLIFY[36] trial compares apixaban with enoxaparin/warfarin in a population of untreated patients with VTE. The AMPLIFY-EXT[37] trial compares apixaban with placebo/no treatment in a population of patients with VTE who had completed 6 to 12 months of anticoagulation therapy and for whom there was clinical equipoise regarding further anticoagulation treatment.

The CS[1] reports that the report of a phase II dose-ranging trial of apixaban versus LMWH/VKA (the BOTTICELLI[41] trial) was excluded from the review as the doses of apixaban administered in the trial are not the licensed doses. The ERG agrees with the exclusion of the BOTTICELLI et al[41] publication from the review.

The CS[1] also reports that there is an on-going RCT of apixaban versus unfractionated heparin followed by warfarin. The CS[1] states that the results of the trial are due to be

published in a conference abstract in April 2015. The CS[1] states that the results of the trial are not relevant to the present appraisal as the INR therapeutic range used was 1.5 to 2.5 and the trial was conducted in a Japanese population. The INR used in clinical practice in England and Wales is 2 to 3. The ERG agrees with the company's assessment.

The ERG is not aware of any other studies of apixaban relevant to the present appraisal.

4.2.2 Critique of data extraction

The CS[1] reports that two reviewers independently assessed titles and abstracts of the studies identified from the searches and two reviewers applied inclusion criteria to the publications selected for full text review. Throughout the process, any disagreements were discussed with a third reviewer or were resolved through team discussion. The ERG considers this to be good standard practice.

The ERG notes that the CS[1] does not report the methods used by the company to extract the data from the included studies.

4.2.3 Quality assessment

The company conducted a quality assessment of all included studies using the checklist recommended for RCTs published in NICE's guide to the methods of technology appraisal.[42]

4.2.4 Evidence synthesis

No data synthesis was conducted using the results of the AMPLIFY[36] and AMPLIFY-EXT[37] trials as the trials included different patient populations. The results of each trial are reported narratively.

In the absence of any direct evidence, the company conducted two NMAs. The initial treatment period NMA was conducted to allow a comparison of treatment with apixaban versus rivaroxaban and apixaban versus dabigatran for the initial treatment period of VTE; fondaparinux was not included in the analysis for reasons discussed in Section 3 of this ERG report. The secondary prevention period NMA was conducted to compare apixaban to rivaroxaban, dabigatran, aspirin, warfarin and no treatment in a secondary prevention setting. The ERG's critique of the company's NMAs is presented in Section 4.7 of this ERG report.

4.3 Critique of the direct evidence: AMPLIFY and AMPLIFY-EXT

The AMPLIFY[36] and AMPLIFY-EXT[37] trials are published in a peer reviewed journal and the company also provided the clinical study report for each trial.

The AMPLIFY[36] trial compared apixaban versus enoxaparin/warfarin for the treatment of VTE over a 6-month period. Treatment with apixaban was 5mg twice daily for 7 days, then 5mg twice daily. Treatment with enoxaparin was 1mg/kg twice daily and warfarin was administered at a dose required to achieve an INR of 2.0 to 3.0.

The AMPLIFY-EXT[37] trial compares apixaban 2.5mg (twice daily) and 5mg (twice daily) to placebo/no treatment in patients who had been treated for 6 to 12 months with standard anticoagulant therapy, for the secondary prevention of recurrent VTE over a 12-month period. The company states that only the 2.5mg apixaban arm and placebo/no treatment arm from the AMPLIFY-EXT[37] trial were considered in the submission, as 2.5mg is the EMA licensed dose.[38]

4.3.1 Trial characteristics

The key characteristics of AMPLIFY[36] and AMPLIFY-EXT[37] are summarised in Table 4.

AMPLIFY

The AMPLIFY[36] trial was conducted internationally and randomised a substantial number of patients (N=5395) in a 1:1 ratio to receive either apixaban or enoxaparin/warfarin. The trial follow-up period was 6 months. The ERG considers that the trial is well-designed and conducted with satisfactory methods of randomisation and blinding. The ERG notes that none of the participating treatment centres were located in England and Wales, however clinical advice to the ERG is that clinical practice in the 28 countries in which the trial was conducted would be representative of clinical practice in England and Wales.

The ERG also notes that the dose of enoxaparin as administered in the AMPLIFY trial[36] (1mg/kg twice daily) is different to that administered to patients in clinical practice in England and Wales (1.5mg/kg once daily). The company (CS, p131) states the dose administered in the trial is that licensed in the US. The company cites evidence from a published paper[43] that demonstrates that once daily or twice daily doses of enoxaparin are as effective as unfractionated heparin in the treatment of VTE. The company further reports that the US dose of enoxaparin was used in the two trials[44,45] that provided the key evidence in the recent NICE appraisals of rivaroxaban.[23,24] In TA261[23,24] it was accepted that even although dosing differed between the trials and clinical practice in England and Wales, the difference did not appear to lead to clinically significant differences in efficacy or safety. Clinical advice

to the ERG suggests that the difference in the dose of enoxaparin as used in the AMPLIFY[36] trial and that used in clinical practice in England and Wales is unlikely to have any impact on the outcomes of the AMPLIFY[36] trial.

AMPLIFY–EXT

The AMPLIFY-EXT[37] trial was conducted internationally (including seven centres in the UK); 1669 patients were randomised in a 1:1:1 ratio to receive apixaban 2.5mg (twice daily), apixaban 5mg (twice daily) or placebo/no treatment. The trial follow-up period was 12 months. The ERG is of the opinion that the trial is well-designed and conducted.

Table 4 Summary of AMPLIFY and AMPLIFY-EXT trials

	AMPLIFY[36]	**AMPLIFY-EXT[37]**
Primary objective	To determine if apixaban was non-inferior to standard enoxaparin/warfarin therapy for the composite endpoint of adjudicated recurrent symptomatic VTE (non-fatal DVT or non-fatal PE) or VTE-related death over 6-months of therapy	To determine if at least one of the apixaban dose regimens was superior to placebo/no treatment for the composite endpoint of symptomatic, recurrent VTE (non-fatal DVT or non-fatal PE) or all-cause death in patients who had completed 6 to 12-months of anticoagulant therapy
Location	Multicentre (N=358) in 28 countries. There were no centres in the UK	Multicentre (N=328) in 28 countries. There were 7 centres in the UK
Design	Phase III, randomised, active controlled, parallel-group, double-blind, triple-dummy trial	Phase III, randomised, parallel-group, double-blind, placebo-controlled trial
Duration of trial	6 months (plus 30-day follow-up)	12 months (plus 30-day follow-up)
Method of randomisation	Patients were randomised 1:1 to apixaban 5mg bd or enoxaparin (1mg/kg bd) /warfarin (INR 2.0–3.0) therapy via IVRS	Patients were randomised 1:1:1 to apixaban 2.5mg bd, apixaban 5mg bd or placebo using the IVRS method
Method of blinding (care provider, patient and outcome assessor)	Trial medications were prepared using placebo that matched the active treatments The trial used blinded INR monitoring. All outcomes were adjudicated by a blinded, independent adjudication committee	Trial medications were prepared using placebo that matched the active treatments Patients, investigators, members of any of the administrative and adjudicating committees, and the sponsors' staff involved in the conduct of the trial did not have access to individual subject treatment assignments
Intervention(s) (n =) and comparator(s) (n =)	Apixaban 10mg bd x 7 days, then 5mg bd (n=2691) Enoxaparin 1mg/kg bd SC/warfarin (INR 2-3) (n=2704)	Apixaban 2.5mg (n=840) bd Apixaban 5mg (n=813) bd Placebo (n=829)

bd=twice daily; DVT=deep vein thrombosis; INR=international normalised ratio; IVRS=interactive voice-response system; PE=pulmonary embolism; SC=subcutaneous; VTE=venous thromboembolism
Source: Table 7 of the CS[1]

4.3.2 Participant characteristics

The participant characteristics of AMPLIFY[36] and AMPLIFY-EXT[37] are summarised in Table 5 and Table 6. Overall, the ERG agrees with the company's conclusion that demographic and baseline disease characteristics are well balanced between treatment arms in both

trials. The ERG notes that the participants in both trials are younger than the patients seen in clinical practice in England and Wales, with relatively few patients aged ≥75 (14.3% and 13.3% in AMPLIFY[36] and AMPLIFY-EXT[37] respectively). The authors of a recent cohort study[17] found that the mean age of UK unprovoked VTE patients was 64 years, which is older than the age of the populations in the AMPLIFY[36] and AMPLIFY-EXT[37] trials. The cohort study[17] also comprised 47.1% males, which is a substantially smaller percentage than the percentages of males in the AMPLIFY[36] and AMPLIFY-EXT[37] trials (58% and 56% respectively). This means that female VTE patients are under-represented in both RCTs.

The ERG notes that the eligibility criteria for AMPLIFY[36] (see Appendix 1 for the full eligibility criteria) mean that the patient population is likely to be somewhat different to the population treated in standard clinical practice in England and Wales, as the trial excluded patients with provoked DVT who had no other risk factors for recurrence, and those with distal DVT.

Table 5 Baseline demographic and disease characteristics (AMPLIFY trial)

AMPLIFY[36]	**Apixaban (N=2691)**	**Enoxaparin/warfarin (N=2704)**
Age, years Mean (SD)	57.2 (16.0)	56.7 (16.0)
Male, n (%)	1569 (58.3)	1598 (59.1)
Race, n (%)		
White	2218 (82.4)	2243 (83.0)
Black or African American	106 (3.9)	98 (3.6)
American Indian or Alaska Native	6 (0.2)	2 (<0.1)
Asian	227 (8.4)	226 (8.4)
Other race	89 (3.3)	85 (3.1)
Not reported	45 (1.7)	50 (1.8)
Weight, kg Mean (SD)	84.6 (19.8)	84.6 (19.8)
Weight distribution, n (%)		
≤60 kg	231 (8.6)	245 (9.1)
>60 to <100 kg	1932 (71.8)	1936 (71.6)
≥100 kg	522 (19.4)	518 (19.2)
Data missing	6 (0.2)	5 (0.2)
Creatinine clearance, n (%)		
≤30 ml/min	14 (0.5)	15 (0.6)
>30 to ≤50 ml/min	161 (6.0)	148 (5.5)
>50 to ≤80 ml/min	549 (20.4)	544 (20.1)
>80 ml/min	1721 (64.0)	1757 (65.0)
Data missing	246 (9.1)	240 (8.9)
Qualifying diagnosis, n (%)		
DVT	1749 (65.0)	1783 (65.9)
PE	678 (25.2)	681 (25.2)
PE with DVT	252 (9.4)	225 (8.3)
Could not be evaluated	12 (0.4)	15 (0.6)
VTE clinical presentation, n (%)		
Unprovoked	2416 (89.8)	2429 (89.8)
Provoked with risk factor(s)	272 (10.1)	272 (10.1)
Not reported	3 (0.1)	3 (0.1)
Location of qualifying DVT, n (%)		
Popliteal vein	426/1749 (24.4)	441/1783 (24.7)
Femoral vein	570/1749 (32.6)	585/1783 (32.8)
Common femoral or iliac vein	753/1749 (43.1)	754/1783 (42.3)
Distal vein	0/1749 (0.0)	3/1783 (0.2)
Anatomic extent of qualifying PE, n (%)		
Limited	79/930 (8.5)	89/906 (9.8)
Intermediate	392/930 (42.2)	395/906 (43.6)
Extensive	357/930 (38.4)	326/906 (36.0)
Not assessable	102/930 (11.0)	96/906 (10.6)
Risk factors for recurrent VTE, n (%)		
Previous PE or proximal DVT	463 (17.2)	409 (15.1)
Known thrombophilia	74 (2.8)	59 (2.2)
Active cancer†	66 (2.5)	77 (2.9)

† Data are from the AMPLIFY[36] clinical trial report; DVT=deep vein thrombosis; PE=pulmonary embolism; SD=standard deviation; VTE=venous thromboembolism. Source: Table 9 of the CS[1]

Table 6 Baseline demographic and disease characteristics (AMPLIFY-EXT trial)

AMPLIFY-EXT[37]	**Apixaban 2.5mg bd (N=840)**	**Placebo (N=829)**
Age, years Mean (SD)	56.6 (15.3)	57.1 (15.2)
Male, n (%)	487 (58.0)	468 (56.5)
Weight, kg Mean (SD)	85.7 (19.8)	84.7 (18.6)
Weight distribution, n (%)		
≤60 kg	58 (6.9)	48 (5.8)
>60 kg	780 (92.9)	778 (93.8)
Data missing	2 (0.2)	3 (0.4)
Creatinine clearance, n (%)		
≤30 ml/min	1 (0.1)	2 (0.2)
>30 to ≤50 ml/min	47 (5.6)	44 (5.3)
>50 to ≤80 ml/min	174 (20.7)	194 (23.4)
>80 ml/min	595 (70.8)	564 (68.0)
Data missing	23 (2.7)	25 (3.0)
Qualifying diagnosis, n (%)		
DVT	544 (64.8)	551 (66.5)
PE	296 (35.2)	278 (33.5)
VTE clinical presentation, n (%)		
Unprovoked	783 (93.2)	755 (91.1)
Associated with transient or reversible risk factor	56 (6.7)	72 (8.7)
Not reported	1 (0.1)	2 (0.2)
Risk factors for recurrent VTE, n (%)		
Active cancer	15 (1.8)	18 (2.2)
Persistent or permanent immobilisation	19 (2.3)	22 (2.7)
Previous DVT or PE	99 (11.8)	99 (11.9)
Known prothrombotic genotype	32 (3.8)	36 (4.3)
Use of antiplatelet agents	120 (14.3)	107 (13.0)

bd=twice daily; DVT=deep vein thrombosis; PE=pulmonary embolism; SD=standard deviation; VTE=venous thromboembolism
Source: Table 10 of the CS[1]

4.4 Description and critique of the statistical approach

4.4.1 AMPLIFY

Information relevant to the statistical approach taken by the company to analyse data from the AMPLIFY[36] trial is taken from the trial statistical analysis plan (TSAP) described in the trial protocol,[46] the clinical study report[47] (CSR) and the CS.[1]

Sample size calculation

Details of the sample size calculation performed by the company are reported in the CS[1] (p56). Using the Farrington and Manning method,[48] the trial was powered (at the 90% level) to test the non-inferiority of apixaban in comparison to enoxaparin/warfarin for the primary efficacy outcome (assuming an incidence rate of 3% over 6 months of therapy). The test assumed the true relative risk (RR) to be 1 (non-inferiority margin of RR <1.8 and risk

difference <3%). The test determined that the trial would require a sample of 4094 patients; this number was increased to 4816 patients to allow for 15% of patients discontinuing treatment early and continuing to complete all scheduled treatment visits up to 6 months after randomisation. Finally, after reviewing the overall incidence of the primary efficacy outcome after 80% of patients had been enrolled (as specified in the protocol), the sample size was increased to 5400. The ERG checked the sample size calculation and agrees that the chosen sample size had sufficient power to test the trial hypothesis.

Protocol amendments

A list of amendments is included in the AMPLIFY protocol[46] (pp2-3). Several minor changes were made in April 2008. All of these changes were implemented before recruitment began, and so could not have been influenced by the results of the trial. Further amendments were made in April 2011, before analyses began. Therefore, these changes were not driven by the results of the trial. The ERG is satisfied that none of the listed protocol amendments influenced the outcomes or analyses of the AMPLIFY[36] trial.

Clinical endpoints and statistical analyses

The company provides a list of outcome measures used in AMPLIFY[36] (summarised in Appendix 2 of this ERG report). The ERG is satisfied that all outcomes were pre-specified in the TSAP[46] and reported in full in the CSR.[47]

All efficacy analyses included data for patients who had an outcome measure available at 6 months. This population is referred to as the efficacy evaluable population. All safety analyses included data from the safety population, which is the group of patients who received at least one dose of the trial medication.

The TSAP[46] provides information relating to how the efficacy analyses were conducted. The composite primary outcome of symptomatic, recurrent VTE or VTE-related death was investigated using the Yanagawa, Tango and Hiejima (YTH) relative risk method[49] to detect non-inferiority. Descriptive statistics, such as RR and the corresponding 95% confidence interval (CI), were computed using Mantel-Haenszel's[50] method stratified by index event.

The secondary outcomes are listed fully in Table 11 of the CS[1] (pp51-53) and in Appendix 2 of this ERG report. For time to first occurrence of recurrent VTE or VTE-related death, and recurrent VTE or all-cause death, graphical summaries were used to present Kaplan-Meier (K-M) estimates of cumulative incidence by treatment group along with a log-rank p-value for treatment differences. For all dichotomous secondary outcomes, analyses were designed to

detect superiority of apixaban in comparison to enoxaparin/warfarin. These tests were performed using the Mantel-Haenszel[50] test stratified by index event.

The trial was designed to detect non-inferiority of apixaban in relation to enoxaparin/warfarin in terms of the primary efficacy outcome, recurrent VTE or VTE-related death. All analyses of secondary outcomes were designed to detect superiority. Table 13 in the CS[1] (p56) describes the hierarchical statistical testing order used for the analyses of efficacy and safety outcomes, as follows:

- testing of non-inferiority of apixaban relative to enoxaparin/warfarin at a 1-sided α=0.025 for recurrent VTE or VTE-related death
- if non-inferiority was demonstrated for both the RR and risk difference (RD), then superiority of apixaban relative to enoxaparin/warfarin for major bleeding was tested at a 2-sided α=0.05
- if superiority of apixaban relative to enoxaparin/warfarin for major bleeding was demonstrated, then superiority of apixaban relative to control treatment for recurrent VTE or VTE-related death was tested at a 2-sided α=0.05
- if superiority of apixaban relative to enoxaparin/warfarin for recurrent VTE or VTE-related death was demonstrated, then superiority of apixaban relative to control treatment for major bleeding/CRNM bleeding was tested at a 2-sided α=0.05

Sensitivity analyses

Sensitivity analyses were pre-specified in the TSAP,[46] which would assess robustness of the results of the primary efficacy analysis to missing data. These sensitivity analyses repeated the primary analysis using a variety of imputation methods. The ERG is satisfied that all sensitivity analyses are reported in full in the CSR.[47]

4.4.2 AMPLIFY-EXT

Information relevant to the statistical approach taken by the company to analyse data from AMPLIFY-EXT[37] is taken from the TSAP described in the trial protocol,[51] the CSR[52] and the CS.[1]

Sample size calculation

Details of the sample size calculation performed by the company are reported in the CS[1] (p57). Using the Hochberg[53] multiple-testing method, the company performed a two-sided α=0.05 superiority test to ensure that the trial was powered (at the 90% level) to detect superiority of apixaban in comparison to placebo/no treatment for the primary efficacy outcome. The company assumed an incidence rate of 6.8% for the primary outcome for the placebo/no treatment group at 12 months and a decrease in the primary outcome of 41% with apixaban as compared with placebo/no treatment. This required a sample size of 810 patients. The ERG is satisfied that the company's pre-specified sample size calculation is correct.

Protocol amendments

A list of changes implemented to the protocol is included in the protocol[51] (p70). Minor changes were made in April 2008. As these changes were all implemented before recruitment began, they could not have been influenced by the results of the trial. Further amendments were made in April 2011. These changes were made before analyses began, and so were not driven by the results of the trial. The ERG is satisfied that none of the listed protocol amendments influenced the outcomes or analyses of AMPLIFY-EXT.[37]

Clinical endpoints and statistical analyses

The company provides a list of outcome measures used in AMPLIFY-EXT[37] in Table 11 (pp51-53) of the CS[1] (also summarised in Appendix 2 of this ERG report). The ERG is satisfied that all outcomes were pre-specified in the TSAP[51] and reported in full in the CSR.[47]

All efficacy endpoints were analysed using the ITT population. All safety analyses were conducted using the safety population, which consisted of patients who received at least one dose of trial medication. In the case of missing outcome data, imputation methods were employed. These methods are pre-specified in the TSAP,[51] and sensitivity analyses were performed to assess the robustness of the chosen imputation method.

Superiority of apixaban in comparison to placebo/no treatment was tested for the primary endpoint, of recurrent VTE or all-cause death, using the Mantel-Haenszel[50] statistic stratified by the index event and previous treatment. Superiority was achieved if the Hochberg[53] adjusted p-value was ≤0.05 and the RR was <1.

A full list of secondary outcomes is provided in Appendix 2 of this ERG report. For dichotomous outcomes, the estimated RR and corresponding 95% CI were provided using a stratified analysis. Continuous variables were summarised by the mean and standard

deviation; categorical variables were summarised using the proportion of patients who experienced an event. Summaries of time-to-event data were displayed in graphical format using K-M curves.

Sensitivity analyses

Sensitivity analyses were pre-specified in the TSAP,[51] which would assess robustness of the results of the primary efficacy analysis to missing data. As the primary efficacy analysis assumed that all patients with missing data had experienced the event, the sensitivity analyses repeated the primary analysis using a variety of other imputation methods. The ERG is satisfied that all sensitivity analyses are reported in full in the CSR.[47]

Subgroup analyses for AMPLIFY and AMPLIFY-EXT

Pre-specified subgroup analyses were listed in the trial protocols for both AMPLIFY[36] and AMPLIFY-EXT;[37] these analyses are presented in Table 7. There were also a number of post-hoc subgroup analyses conducted for the AMPLIFY[36] trial. The ERG notes that there are a large number of subgroup analyses but is satisfied that the results of all of the pre-specified and post-hoc subgroup analyses are provided in the CSRs[47,52] for both trials.

Table 7 Pre-specified subgroups analysed (AMPLIFY and AMPLIFY-EXT)

	AMPLIFY[36] trial subgroups	AMPLIFY-EXT[37] trial subgroups
Index event	PE (with or without DVT); DVT only	PE (with or without DVT); DVT only
Geographic region	North America; Latin America; Europe; Asia/Pacific	North America; Latin America; Europe; Asia/Pacific
Age Category I	<65 years; ≥65 to <75 years; ≥75 years	<65 years; ≥65 to <75 years; ≥75 years
Age Category II	<75 years; ≥75 years	-
Gender	Male; female	Male; female
Race	White; black or African American; Asian; other	White; black or African American; Asian; other
Ethnicity	Hispanic/Latino; not Hispanic/Latino	Hispanic/Latino; not Hispanic/Latino
Weight	≤60 kg; >60 kg to <100 kg; ≥100 kg	≤60 kg; >60 kg
BMI Category I	≤28 kg/m^2; >28 kg/m^2 to ≤33 kg/m^2; >33 kg/m^2	≤28 kg/m^2; >28 kg/m^2 to ≤33 kg/m^2; >33 kg/m^2
BMI Category II	≤25 kg/m^2; >25 to ≤30 kg/m^2; >30 to ≤35 kg/m^2; >35 kg/m^2	-
Level of renal function Category I	Normal; mild; moderate/severe	Normal; mild; moderate/severe
Level of renal function Category II	Normal; mild; moderate; severe	-
Fragile/not fragile patients	Fragile (those meeting at least two of age ≥80, creatinine clearance ≥1.5mg/dL, body weight ≤60 kg); Patients not meeting these criteria	-
Age, weight and serum creatinine criteria	Patients meeting at least one of age ≥75, creatinine clearance ≤50 ml/min, body weight ≤50 kg; Patients not meeting these criteria	-
Cancer	Active cancer at baseline; no active cancer at baseline	-
Centre TTR quartile	Q1; Q2; Q3; Q4	-

BMI=body mass index; DVT=deep vein thrombosis; PE=pulmonary embolism; Q=quartile; TTR=time in therapeutic range
Source: Table 14 of the CS[1]

4.4.3 Quality assessment

The company conducted a quality assessment exercise for both trials[36,37] following the recommended format in the NICE submission template and the results are presented in Appendix 3 of this ERG report. The ERG is satisfied with the quality assessment presented in the CS[1] and agrees that the trials are of good quality.

4.5 Results from the direct evidence

4.5.1 AMPLIFY

The CS[1] reports that median duration of enoxaparin treatment was 6.5 days (interquartile range, 5.0 to 8.0). Treatment was discontinued when a blinded INR for warfarin of 2 or more was achieved. The CS[1] also states that patients in the enoxaparin/warfarin group spent 61% of trial time in the therapeutic range (2 to 3), excluding the first 15 days of treatment and

during any interruptions of treatment. The ERG considers the time in therapeutic range in the trial to be similar to that expected in patients in clinical practice in England and Wales.

Sham INR measurements were conducted in the apixaban arm to preserve blinding. In the intervention arm, apixaban 10mg was administered for 7 days, followed by 5mg for the remainder of the trial period.

Treatment compliance with apixaban was measured via pill counts. The company reports (CS, p135) that treatment compliance in both arms of the AMPLIFY[36] trial was high (>80% of patients in the apixaban arm had a measured compliance rate of [redacted] and >80% of patients in the enoxaparin/warfarin arm had a compliance rate of [redacted]).

The CS[1] states that discontinuation rates of trial drugs were similar between apixaban and enoxaparin/warfarin (14.0% versus 15.3%, respectively).

Primary efficacy outcome

The results of the primary efficacy analysis, for the composite outcome of symptomatic, recurrent VTE or VTE-related death, are provided in Table 8. For the efficacy evaluable population, apixaban was shown to be non-inferior to enoxaparin/warfarin, demonstrated by the significant p-value (p<0.001). As all of the previous conditions of the pre-specified hierarchical statistical testing order were satisfied (Section 4.4), the company also performed a superiority test for the primary outcome, which suggested that there was no statistically significant difference between apixaban and enoxaparin/warfarin ([redacted]).

In Figure 5 of the CS[1] the company presents a K-M plot for the full ITT population and the results are presented alongside the efficacy evaluable population (Table 8). A number of patients from the ITT population (82 [3.05%] in the apixaban arm and 69 [2.55%] from the enoxaparin/warfarin arm) are not included in the efficacy evaluable population. Apixaban was also shown to be non-inferior to enoxaparin/warfarin in the ITT population.

Table 8 Summary of primary efficacy outcome (AMPLIFY trial)

	Primary outcome n (%) recurrent VTE or VTE-related death			
	Apixaban	**Enoxaparin/ warfarin**	**Relative risk (95% CI)**	**p-value**
Efficacy evaluable population	59/2609 (2.3)	71/2635 (2.7)	0.84 (0.60 to 1.18)	<0.001§ [redacted]*
ITT population	[redacted]	[redacted]	[redacted]	[redacted]

CI=confidence interval; ITT=intention-to-treat; VTE=venous thromboembolism
§The p-value tests for non-inferiority with respect to the RR of the primary efficacy outcome
*The p-value tests for superiority with respect to the RR of the primary efficacy outcome, as a secondary analysis
Source: Table 18 of the CS[1]

Primary efficacy outcome: subgroup analyses

Treatment effect estimates for the primary efficacy endpoint are provided for several pre-specified and post-hoc subgroups in the CS[1] (Figure 6, p67). The results from the subgroup analyses suggested that there were no significant differences between apixaban and enoxaparin/warfarin in terms of the primary efficacy outcome for any of the analysed subgroups. The subgroup results are consistent with the findings from the primary efficacy analysis.

[redacted]

Primary efficacy outcome by index event type

The company also investigated the primary efficacy endpoint by DVT and PE subgroups (Table 9). The results show that in the subgroups of DVT and PE patients, events were less likely to occur in the apixaban group than in the enoxaparin/warfarin group, although these differences were not found to be statistically significant. The RRs between the PE and DVT subgroups were similar.

Table 9 Summary of the primary efficacy outcome for DVT/PE subgroups indexed by type (AMPLIFY trial)

	Primary efficacy outcome: recurrent VTE or VTE-related death n/N (%)		
	Apixaban	**Enoxaparin/ warfarin**	**RR (95% CI)**
PE (with or without DVT) subgroup	21/900 (2.3)	23/886 (2.6)	[redacted]
DVT subgroup	38/1698 (2.2)	47/1736 (2.7)	[redacted]

CI=confidence interval; DVT=deep vein thrombosis; PE=pulmonary embolism; RR=relative risk; VTE=venous thromboembolism
Efficacy evaluable population included data for patients in the ITT population for whom the outcome status at 6 months was documented
Source: Table 20 of the CS[1]

Sensitivity analyses

For the primary efficacy analysis, no imputation methods were used in the case of missing data.

[redacted]

Secondary outcomes

The results for the secondary outcomes are provided in Table 10; secondary outcomes are categorised into efficacy, composite, or death outcomes. Analyses were performed in order to detect the superiority of apixaban in relation to enoxaparin/warfarin in terms of each of the secondary outcomes.

The company states that the results describing the secondary outcomes are consistent with the findings of the primary efficacy analysis; apixaban was not shown to be superior in comparison to enoxaparin/warfarin for the primary efficacy outcome ([redacted]) and similarly, apixaban was not shown to be superior for the secondary outcomes, recurrent VTE or all-cause death and recurrent VTE or cardiovascular (CV) related death. Superiority of apixaban was demonstrated for the composite outcomes of recurrent VTE, VTE-related death or major bleeding (p=0.001), and recurrent VTE, CV-related death, MI, stroke, major bleeding or CRNM bleeding ([redacted]).

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Table 10 Summary of secondary outcomes (AMPLIFY efficacy evaluable population)

	Apixaban N=2609	Enoxaparin/ warfarin N=2635	RR (95% CI)	Risk difference	p-value[§]
Efficacy outcomes: type of first recurrent VTE n/N (%)					
Non-fatal PE	27/2609 (1.0)	23/2635 (0.9)	-	-	-
Non-fatal DVT	20/2609 (0.8)	33/2635 (1.3)	-	-	-
Composite outcomes n/N (%)					
Recurrent VTE or all-cause death	84/2609 (3.2)	104/2635 (3.9)	0.82 (0.61 to 1.08)	[redacted]	0.16
Recurrent VTE or CV-related death	61/2609 (2.3)	77/2635 (2.9)	0.80 (0.57 to 1.11)	[redacted]	0.18
Recurrent VTE, VTE-related death or major bleeding	73/2609 (2.8)	118/2635 (4.5)	0.62 (0.47 to 0.83)	[redacted]	0.001
Recurrent VTE, CV-related death, MI, stroke, major bleeding or CRNM bleeding[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death outcomes n/N (%)					
VTE-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CV-related death (including VTE-related death)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All-cause death	41[redacted]	52[redacted]	0.79 (0.53 to 1.19)	[redacted]	[redacted]

CI=confidence interval; CRNM=clinically relevant non-major; CV=cardiovascular; DVT=deep vein thrombosis; PE=pulmonary embolism; RR=relative risk; VTE=venous thromboembolism

The secondary efficacy outcomes included events that occurred at any time from randomisation until the end of the intended treatment period regardless of whether patients were receiving study medication (using the intention-to-treat principle). All efficacy analyses included data for patients in the intention-to-treat population for whom the outcome status (for each particular outcome) at 6 months was documented (efficacy evaluable population). Subjects with missing endpoint data were excluded from the analysis. As some patients had missing data for some outcomes but not others, the N numbers differ between the outcomes

[a]Patients not in the efficacy evaluable population with a bleeding event that occurred during the initial treatment period were included in the analysis

[§]The p-value tests for superiority with respect to the relative risk of the composite secondary efficacy outcomes

Source: Table 19 of the CS[1]

Secondary outcomes by index event type

The company performed analyses in order to assess the superiority of apixaban in relation to enoxaparin/warfarin in terms of each of the secondary outcomes, stratified by index event type (Table 11). Secondary outcomes are split into efficacy and composite outcomes. The company observes that results were similar between the two groups of patients and the ERG agrees with this conclusion.

Table 11 Summary of secondary efficacy outcomes for DVT/PE subgroups indexed by type (AMPLIFY trial efficacy evaluable population)

	Apixaban	Enoxaparin/ warfarin	RR (95% CI)
DVT			
Efficacy outcomes: type of first recurrent VTE n/N (%)			
Non-fatal DVT	[redacted]	[redacted]	[redacted]
Non-fatal PE	[redacted]	[redacted]	[redacted]
Composite outcomes, n/N (%)			
Recurrent VTE or all-cause death	[redacted]	[redacted]	[redacted]
Recurrent VTE or CV-related death	[redacted]	[redacted]	[redacted]
Recurrent VTE, VTE-related death or major bleeding	[redacted]	[redacted]	[redacted]
PE			
Efficacy outcomes: type of first recurrent VTE, n/N (%)			
Non-fatal DVT	[redacted]	[redacted]	[redacted]
Non-fatal PE	[redacted]	[redacted]	[redacted]
Composite outcomes, n/N (%)			
Recurrent VTE or all-cause death	[redacted]	[redacted]	[redacted]
Recurrent VTE or CV-related death	[redacted]	[redacted]	[redacted]
Recurrent VTE, VTE-related death or major bleeding	[redacted]	[redacted]	[redacted]

CI=confidence interval; CV=cardiovascular; DVT=deep vein thrombosis; PE=pulmonary embolism; RR=relative risk; VTE=venous thromboembolism
N, total number of evaluated patients in the respective groups
Source: Table 21 of the CS[1]

Primary efficacy outcome in cancer patients

The company provided primary efficacy results for the subset of patients with active cancer at baseline; these results are provided in Table 12. The results were consistent with those observed in the primary analysis. However, the ERG observes that the number of patients in this subgroup is very small, and so it is difficult to draw any conclusions about the effectiveness of apixaban in comparison to enoxaparin/warfarin within this patient group. As noted in Section 2 of this ERG report, the AMPLIFY[36] trial excluded all patients with active cancer for whom treatment with LMWH was planned. As LMWH is the standard of care for

patients with active cancer, the ERG is unclear as to why patients with active cancer were recruited into the AMPLIFY[36] trial.

Table 12 Subgroup results in the pre-specified group of patients with active cancer at baseline (AMPLIFY trial)

	Primary efficacy outcome: recurrent VTE or VTE-related death n/N (%)			
	Apixaban	**Enoxaparin/ warfarin**	**RR (95% CI)**	**Treatment interaction p value**
Active cancer at baseline	[redacted]	[redacted]	[redacted]	[redacted]
No active cancer at baseline	[redacted]	[redacted]	[redacted]	

CI=confidence interval; RR=relative risk; VTE=venous thromboembolism
Source: Table 22 of the CS[1]

Post-hoc analysis of recurrent VTE or VTE-related death to prior 6 months

The company provided the results of an analysis investigating the comparison of event rates at a range of time-points up to the time of the primary efficacy analysis at 6 months. These results are provided in the CS[1] (Table 23, p69) and in Appendix 4 of this ERG report. The results from the early time-points (7 days, 21 days and 3 months) were similar to those from the analysis at 6 months.

Hospitalisation

The company conducted an analysis investigating the effect of apixaban versus enoxaparin/warfarin on all-cause hospitalisation. The results are presented in the CS[1] (Table 24, p70) and in Appendix 4 of this ERG report. The findings suggest that apixaban statistically significantly reduces the likelihood of hospitalisation and increases the median time to first hospitalisation in comparison to enoxaparin/warfarin.

Health-related quality of life

No HRQoL data were collected during the AMPLIFY[36] trial. The ERG considers this to be a disappointing omission from the CS.[1]

4.5.2 AMPLIFY-EXT

For the primary efficacy analyses of AMPLIFY-EXT,[37] patients who were lost to follow-up were assumed to have experienced a primary efficacy event. The company has clarified that these patients were not included in the time-to-event analysis. There were 19 patients in the placebo/no treatment group (2.3%) and 13 patients in the 2.5mg apixaban group (1.5%) who were lost to follow-up.

Treatment compliance with apixaban was measured via pill counts. The company reports (CS, p135) that treatment compliance in both arms of the AMPLIFY-EXT[37] trial was high (>80% of patients in the apixaban arm had a measured compliance rate of [redacted] and >80% of patients in the placebo/no treatment arm had a compliance rate of [redacted]).

Fewer patients in the apixaban arm discontinued treatment than in the placebo/no treatment arm (13.6% versus 22.7%, respectively).

Primary efficacy outcome

The results from the primary efficacy analysis are provided in the CS.[1] Apixaban was found to statistically significantly reduce the risk of experiencing recurrent VTE or all-cause death (RR 0.33; 95% CI 0.22 to 0.48; [redacted]) compared with placebo/no treatment. The company presents the K-M plot in Figure 7 of the [1].

Subgroup analyses

Treatment effect estimates for the primary efficacy endpoint, recurrent VTE or all-cause death, are provided for several of the pre-specified subgroups in the CS[1] (Figure 9, p75). The company states that no clinically important subgroup differences were observed, however, on inspection of the tests for interaction, the ERG notes that p-values <0.10 (the company chose this value to indicate an important result for the AMPLIFY[36] subgroup analyses) were observed for the subgroup analyses of gender, age and geographic region.

The company explains in their response to the ERG's clarification letter that the reason these subgroup analyses were not considered to be clinically relevant was due to the fact that imputation for missing observations may have distorted results, and so the company preferred to consider the results of parallel subgroup analyses, considering VTE or VTE-related death, without imputation. These subgroup analyses were also pre-specified and the results are tabulated in the CS[1] (CS, Appendix 10.5).

Furthermore, the company explains that all subgroup RRs were <1.0, most subgroup RRs had a 95% CI upper limit <1.0, and no adjustments were made for multiple testing, so significant tests for interaction may have been spurious. The ERG is satisfied with this response, and does not consider there to be any important subgroup differences.

Primary efficacy outcome by index event type

The company also stratified the primary efficacy outcome by the index event type, i.e. DVT or PE event. The results are presented in the CS.[1] The RRs for the two subgroups were fairly similar (PE subgroup: [redacted] and DVT subgroup: [redacted]). The beneficial effect of apixaban in comparison to enoxaparin/warfarin remained statistically significant in both subgroups.

Sensitivity analyses

For the primary efficacy analysis, it was assumed that all patients with missing outcome data had experienced a primary outcome event. However, sensitivity analyses were conducted using a range of other imputation methods. The results of these sensitivity analyses (provided in the CSR[52]) supported the findings of the primary efficacy analysis, demonstrating superiority of apixaban in comparison to placebo/no treatment.

Secondary outcomes

Results for each of the secondary outcomes are provided in Table 13. Secondary outcomes are split into efficacy, composite, or death outcomes. Patients in the apixaban 2.5mg group were shown to be significantly less likely to experience recurrent VTE or VTE-related death in comparison to patients in the placebo/no treatment group. Apixaban was also shown to be superior in terms of the composite outcome of VTE/CV-related death. The company presented event rates and time-to-event analyses in the CS[1] (Figure 8, p74).

Table 13 Summary of secondary efficacy outcomes (AMPLIFY-EXT, ITT)

	Apixaban 2.5mg N=840	Placebo N=829	RR (95% CI)	Risk difference	p-value
Type of first recurrent VTE, n (%)					
Non-fatal PE	[redacted]	[redacted]	-	-	-
Non-fatal DVT	[redacted]	[redacted]	-	-	-
Composite outcomes, n (%)					
Recurrent VTE or VTE-related death	14 (1.7)	73 (8.8)	0.19 (0.11 to 0.33)	[redacted]	[redacted]
VTE or CV-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non–VTE-related CV death, myocardial infarction, or stroke	4 (0.5)	11 (1.3)	0.36 (0.11 to 1.12)	-	-
VTE, VTE-related death, myocardial infarction, stroke, or cardiovascular disease–related death	18 (2.1)	83 (10.0)	0.21 (0.13 to 0.35)	-	-
VTE, VTE-related death, myocardial infarction, stroke, cardiovascular disease–related death, or major bleeding as outcome	20 (2.4)	86 (10.4)	0.23 (0.14 to 0.37)	-	-
Death outcomes, n (%)					
VTE-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CV-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All-cause death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI=confidence interval; CV= cardiovascular; DVT=deep vein thrombosis; ITT= intention-to-treat; PE= pulmonary embolism; RR=relative risk; VTE=venous thromboembolism
For the analyses of the secondary outcomes patients who were lost to follow-up were classified as not having had an outcome event
Source: Table 28 in the CS[1]

Secondary efficacy outcome by index event type

The company also stratified by whether patients experienced a DVT or PE event, the results of which are presented in Table 14. The company observes that outcomes were consistent across DVT and PE subgroups, and the ERG agrees with this conclusion.

Table 14 Summary of secondary efficacy outcomes for DVT/ PE subgroups indexed by type (AMPLIFY-EXT)

	Apixaban 2.5mg (N=840)	Placebo (N=829)
DVT	**N_1=544**	**N_1=551**
Type of first recurrent VTE, n (%)		
Non-fatal PE	[redacted]	[redacted]
Non-fatal DVT	[redacted]	[redacted]
Composite outcomes, n (%)		
Recurrent VTE or VTE-related death	[redacted]	[redacted]
VTE or CV-related death	[redacted]	[redacted]
PE	**N_2=296**	**N_2=278**
Type of first recurrent VTE, n (%)		
Non-fatal PE	[redacted]	[redacted]
Non-fatal DVT	[redacted]	[redacted]
Composite outcomes, n (%)		
Recurrent VTE or VTE-related death	[redacted]	[redacted]
VTE or CV-related death	[redacted]	[redacted]

CV=cardiovascular; DVT=deep vein thrombosis; ITT=intention-to-treat; PE=pulmonary embolism; VTE=venous thromboembolism
Source: Table 28 of the CS[1]

Hospitalisation

The company conducted an analysis investigating the effect of apixaban 2.5mg versus placebo on the rate of all-cause hospitalisations. The results are presented in the CS[1] (Table 29, p77) and in Appendix 4 of this ERG report. The findings suggest that apixaban significantly reduces the likelihood of hospitalisation and increased the mean time to hospitalisation in comparison to placebo/no treatment.

Health related quality of life

No HRQoL data were collected during the AMPLIFY-EXT[37] trial. The ERG considers this to be a disappointing omission in the CS.[1]

4.6 Adverse events

The CS[1] reports the AEs relevant to the AMPLIFY[36] and AMPLIFY-EXT[37] trials on pages 113 to 127. The AEs of key interest are those related to bleeding events. In the CS,[1] the company reports the rates of different types of bleeding events. For clarity, the ERG describes each type of bleeding event in Table 15.

Table 15 Definition of bleeding events used in AMPLIFY and AMPLIFY-EXT trials

Event	Definition
Major bleeding (Taken from guidelines published by the International Society on Thrombosis and Haemostasis.[54])	Acute clinically overt bleeding accompanied by one or more of the following: • A decrease in haemoglobin of ≥2 grams per decilitre • A transfusion of 2 or more units of packed red blood cells • Bleeding that occurs in at least one of the following critical sites: intracranial, intraspinal intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, retroperitoneal • Bleeding that is fatal
Clinically relevant non-major bleeding	Acute clinically overt bleeding that consists of: • any bleeding compromising hemodynamics • any bleeding leading to hospitalization • subcutaneous haematoma larger than 25cm^2, or 100cm^2 if there was a traumatic cause • intramuscular haematoma documented by ultrasonography • epistaxis that lasted for more than 5 minutes, was repetitive or led to an intervention (e.g., packing or electrocoagulation) • gingival bleeding occurring spontaneously or lasting for more than 5 minutes • haematuria that was macroscopic and was spontaneous or lasted for more than 24 hours after instrumentation (e.g., catheter placement or surgery) of the urogenital tract • macroscopic gastrointestinal haemorrhage, including at least one episode of rectal blood loss • haemoptysis, if more than a few speckles in the sputum and not occurring within the context of PE • any other bleeding type considered to have clinical consequences for a patient such as medical intervention, the need for unscheduled contact with a physician, or temporary cessation of a study drug, or associated with pain or impairment of activities of daily life
Minor bleeding	All acute clinically overt bleeding events not meeting the criteria for either major bleeding or clinically relevant non-major bleeding
Fatal bleeding	A bleeding event that the independent adjudication committee determined was the primary cause of death or contributed directly to death

4.6.1 AMPLIFY

The ERG notes that the mean number of days of treatment in the apixaban arm is 154 and is 152 in the enoxaparin/warfarin arm.[38]

The company states that the safety endpoints and AE data are derived from patients during study treatment. Study treatment is defined as the time from the administration of the first treatment until 48 hours after the treatment was administered.

For the primary safety outcome of major bleeding a statistically significant reduction in major bleeding events is associated with apixaban compared with enoxaparin/warfarin (RR 0.31; 95% CI 0.17 to 0.55; p<0.001).

A K-M analysis of major bleeding in the AMPLIFY[36] trial is presented in Figure 19 of the CS[1] and indicates that the rate of events between apixaban and enoxaparin/warfarin separate at the beginning of the trial and that the separation is maintained across time, thus demonstrating that the difference between treatment with apixaban and enoxaparin/warfarin begins early and is maintained.

The CS[1] presents a summary of major bleeding events by anatomical site (Table 16) and reports that one patient in the apixaban arm and two patients in the enoxaparin/warfarin arm experienced fatal bleeds. The company emphasises the reduction in gastrointestinal bleeds associated with apixaban compared with enoxaparin/warfarin.

Table 16 Summary of major bleeding (non-fatal) by anatomical site (AMPLIFY trial)

	Apixaban N=2676 n (%)	**Enoxaparin/warfarin N=2689 n (%)**
Intracranial	3 (0.1)	6 (0.2)
Retroperitoneal	1 (<0.1)	3 (0.1)
Intraocular	0	2 (0.1)
Intra-articular	0	2 (0.1)
Intrathoracic	0	1 (<0.1)
Gastrointestinal	7 (0.3)	18 (0.7)
Intramuscular bleeding	0	5 (0.2)
Epistaxis	1 (<0.1)	1 (<0.1)
Urogenital bleeding	1 (<0.1)	3 (0.1)
Subcutaneous haematoma	1 (<0.1)	6 (0.2)

Source: Table 43 of the CS[1]

The company conducted analyses of the outcome of major bleeding across a range of subgroups including type of index event, male or female, age, level of renal impairment, weight, body mass index (BMI), extent of index event, use of LMWH or unfractionated

heparin. The results of the subgroup analyses are consistent with the safety outcomes of the overall population. The CS[1] reports that treatment by subgroup interactions with a p-value of <0.10 were subject to further investigation although no clinically important observations were noted.

The CS[1] reports that major bleeding events are consistent across patients with a PE and/or DVT and patients with only a DVT (Table 17). The ERG notes there is a greater percentage of major bleeding in the PE subgroup compared with the DVT only subgroup (2.8% and 1.4% respectively).

Table 17 Major bleeding by event type (AMPLIFY trial)

Event type	Apixaban n/N (%)	Enoxaparin/warfarin n/N (%)	Relative risk (95% CI)
PE (with or without DVT)	4/928 (0.4)	25/902 (2.8)	[redacted]
DVT subgroup	11/1738 (0.6)	24/1773 (1.4)	[redacted]

DVT=deep vein thrombosis; PE; pulmonary embolism
Source: Table 45 of the CS[1]

An analysis of the outcomes of major bleeding in patients with active cancer is provided in Table 46 of the CS[1]. As noted in Section 3 of this ERG report, it is unclear to the ERG why patients with cancer were eligible for inclusion in the AMPLIFY[36] trial. The company reports that the number of patients with cancer was small, but that the pre-specified subgroup analyses demonstrate consistency with the overall findings of the AMPLIFY[36] trial.

The company also conducted a post-hoc analysis of major bleeding and clinically relevant non-major bleeding at 3 months. The results demonstrated a statistically significantly lower risk for patients treated with apixaban compared with patients treated with enoxaparin/warfarin ([redacted]

Other bleeding outcomes

Secondary bleeding outcomes are presented in Table 18. Statistically significant differences in favour of apixaban compared to enoxaparin/warfarin are recorded across all of the outcomes.

Table 18 Secondary bleeding outcomes (AMPLIFY trial)

	Apixaban N=2676 n (%)	**Enoxaparin/warfarin N=2689 n (%)**	**Relative risk (95% CI)**	**p-value**
Major or CRNM bleeding	115 (4.3)	261 (9.7)	0.44 (0.36 to 0.55)	<0.001
CRNM bleeding	103 (3.8)	215 (8.0)	0.48 (0.38 to 0.60)	[redacted]
Minor bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Total bleeding	[redacted]	[redacted]	[redacted]	[redacted]

CRNM=clinically relevant non-major bleeding; RR= relative risk;
Source: Table 44 of the CS[1]

Other safety outcomes

The CS[1] summarises the type and frequency of the AEs recorded during the AMPLIFY[36] trial (Table 19). The ERG notes that the percentage of AEs and serious AEs (SAEs) is similar in both apixaban and enoxaparin/warfarin arms of the trial (67.1% versus 71.5% and 15.6% versus 15.2% respectively). The percentage of people discontinuing treatment due to AEs is also similar in both arms and is low (6.1% versus 7.4%). The percentage of deaths is comparable in both arms of the trial.

There are fewer AEs due to bleeding recorded in the apixaban arm than in the enoxaparin/warfarin (15.5% versus 25.8%). [redacted]

The CS[1] reports that the incidence of VTE-related complications during the AMPLIFY[36] trial was [redacted] The results of liver safety assessments did not indicate any cause for concern associated with the use of apixaban.

Table 19 Adverse events (AMPLIFY trial)

Event type	Apixaban N=2676 n/N (%)	Enoxaparin/warfarin N=2689 n/N (%)
Adverse events	1795 (67.1)	1923 (71.5)
Serious adverse events	417 (15.6)	410 (15.2)
Bleeding adverse events	415 (15.5)	695 (25.8)
Discontinuations due to adverse event	162 (6.1)	199 (7.4)
Deaths	[redacted]	[redacted]
Adverse events occurring in ≥5% of patients in either arm		
Headache	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]

Source: Table 48 of the CS[1]

In summary, the ERG agrees with the company that in comparison to patients in the enoxaparin/warfarin arm of the AMPLIFY[36] trial, patients treated with apixaban experienced statistically significantly fewer bleeding events, in terms of both major bleeding and for secondary measures of bleeding. The ERG also agrees that the overall incidence of AEs and SAE experienced by patients is similar for patients treated with apixaban and patients treated with enoxaparin/warfarin.

4.6.2 AMPLIFY-EXT

The CS[1] reports the safety outcomes only for the patients in the AMPLIFY-EXT[37] trial who were treated with 2.5mg twice daily apixaban compared with placebo/no treatment. The results for patients in the 5mg of apixaban twice daily arm of the AMPLIFY-EXT[37] trial are reported in the Appendices of the CS.[1] The ERG considers this appropriate as 2.5mg twice daily is the EMA[39] licensed dose of apixaban for the secondary prevention of VTE. The number of major bleeding events is low in both the apixaban and placebo/no treatment arms of the trial (2 versus 4) and the CS[1] reports that apixaban was not statistically significantly different to placebo/no treatment.

Secondary bleeding outcomes are summarised in the CS[1] (

Table 20). Across all outcomes, no statistically significant differences were observed in treatment with apixaban compared with placebo/no treatment.

Table 20 Secondary bleeding outcomes (AMPLIFY-EXT trial)

	Apixaban 2.5mg bd N=840 n(%)	**Placebo N=826 n(%)**	**Relative risk (95% CI)**	**p-value (for superiority)**
Major or CRNM bleeding	27 (3.2)	22 (2.7)	1.20 (0.69 to 2.10)	[redacted]
CRNM bleeding	25 (3.0)	19 (2.3)	1.29 (0.72 to 2.33)	[redacted]
Minor bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Total bleeding	[redacted]	[redacted]	[redacted]	[redacted]

* Hochberg adjusted p-value for superiority
CRNM=clinically relevant major bleeding; RR= relative risk; * Hochberg adjusted p-value for superiority
Source Table 50 of the CS[1]

Subgroup analyses (event type, gender, age, level of renal impairment, weight) for the composite outcome of major bleeding or CRNM bleeding are reported in Figure 24 of the CS.[1] The company reports that no clinically important differences were noted between the apixaban and placebo/no treatment arms of the trial. The ERG notes from the forest plot in the CS[1] that the risk of bleeding appears to be greater for people ≥75 years who were treated with apixaban; however, the number of events is small and the CIs are wide.

Other safety outcomes

The CS[1] summarises the type and frequency of the AEs recorded during the AMPLIFY-EXT[37] trial (Table 21). The ERG notes that the percentage of AEs and SAEs is similar in both apixaban and placebo/no treatment arms of the trial (71% versus 73.4% and 13.3% versus 19.1% respectively). The percentage of people discontinuing treatment due to AEs is lower in the apixaban arm compared to placebo/no treatment (8% versus 16.2%). The company reports that the difference in the discontinuation rate was due to higher numbers of VTE events in the placebo/no treatment arm. The percentage of deaths is greater in the placebo/no treatment arm compared with the apixaban arm (1.7% versus 0.8%).

Of the AEs that were experienced by ≥5% of patients in either arm, [redacted] The liver safety assessments did not indicate any cause for concern associated with the use of apixaban.

Table 21 Adverse events (AMPLIFY-EXT trial)

Event type	**Apixaban 2.5mg bd N=840 n(%)**	**Placebo N=826 n(%)**
Adverse events	596 (71.0)	606 (73.4)
Serious adverse events	112 (13.3)	158 (19.1)
Discontinuations due to adverse events	67 (8.0)	134 (16.2)
Adverse events occurring in ≥5% of patients in either arm		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Adverse events, n/N (%) – ITT population		
Deaths, through to end of intended treatment period n/N (%)	7/840 (0.8)	14/829 (1.7)

Bd=twice daily; ITT=intention to treat
Source: Table 51 of the CS[1]

In summary, the ERG agrees with the company that in the AMPLIFY-EXT[37] trial the rates of bleeding were low in both trial arms and were not statistically significantly different. The ERG also agrees that the overall incidence of AEs and SAEs experienced by patients is similar for those treated with apixaban and those in the placebo/no treatment arm. The number of discontinuations and deaths was greater in the placebo/no treatment arm than in the apixaban arm; the higher discontinuation rate in the placebo/no treatment arm was the result of more patients experiencing recurrence of VTE events.

4.7 Critique of the indirect evidence

4.7.1 Key points of the ERG critique of indirect evidence

- To allow the ERG to investigate the robustness of the company's RR estimates, the ERG requested that the company re-run both the initial treatment period and secondary prevention period NMAs using an alternative vague prior for the trial effect and asked for the analysis to treat the trial effect as random rather than fixed. The results of the company's original analyses and the analyses requested by the ERG are presented in this section
- The ERG is satisfied that the methodology used to conduct the initial treatment period NMA is appropriate and the results can be used to support the use of apixaban versus rivaroxaban and dabigatran in this setting
- The ERG considers the methods used to combine data in the secondary prevention period NMA to be inappropriate due to the different lengths of treatment periods and stated follow-up times of the included trials. This means that the results cannot be used to support the use of apixababn versus any active treatment in this setting

4.7.2 Included trials in the network meta-analyses and statistical approach

Sixteen trials in fourteen publications[36,37,55-66] were included in the review of the indirect evidence. The company performed NMAs using two networks of evidence; the first included trials which assessed anticoagulant therapy for the treatment of an initial VTE event (referred to as the "initial treatment period NMA"), and the second included trials which assessed extended anticoagulant therapy in patients who had already received treatment for an initial VTE event (referred to as the "secondary prevention period NMA").

In addition to the comparators specified in the scope issued by NICE,[16] the company considered dabigatran to be a relevant comparator and so included dabigatran in both the initial treatment period and secondary prevention period networks of evidence. For reasons outlined in Section 2, the ERG agrees that dabigatran is a relevant comparator.

Five trials in four publications[36,55,56,57] were included in the initial treatment period NMA, creating a network of evidence as shown in Figure 1. The remaining eleven trials in ten publications[37,58-66] were included in the secondary prevention period NMA, forming an evidence network as shown Figure 2.

The ERG did not identify any additional trials that met the company's eligibility criteria.

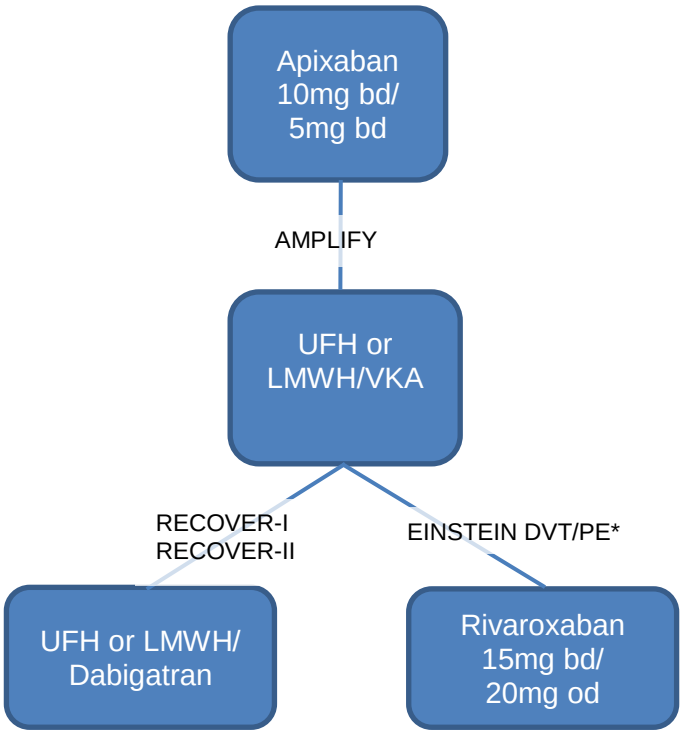

Figure 1 Network diagram for the initial treatment period NMA

bd=twice daily; LMWH=low molecular weight heparin; od=once daily; UFH=unfractionated heparin; VKA=vitamin K antagonist
*EINSTEIN pooled analysis[57] was used for the initial treatment period NMA
Source: Figure 10 of the CS[1]

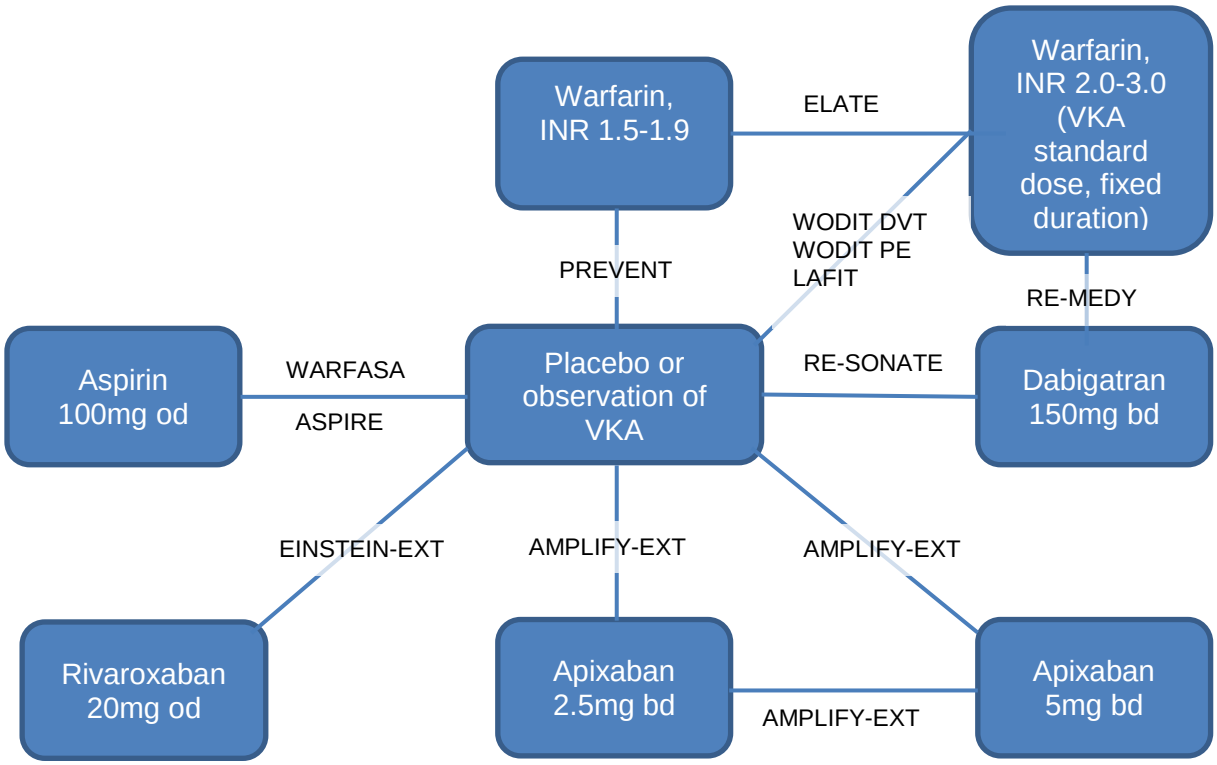

Figure 2 Network diagram for thte secondary prevention period NMA

bd=twice daily; INR=international normalised ratio; od=once daily; VKA=vitamin K antagonist
Source: Figure 11 of the CS[1]

The company states that no evidence was identified for the population of patients for whom treatment with a VKA would be unsuitable and therefore it was not possible to conduct an NMA in this population.

4.7.3 Treatment period NMA: overview of trials and statistical approach

The company performed NMAs for both efficacy and safety outcomes. Efficacy outcomes reported by all included trials were: recurrent-VTE or VTE-related death, non-fatal PE, DVT, VTE-related death, all-cause death, and overall discontinuation. Safety outcomes reported by all included trials were: major or CRNM bleeding, major bleeding, CRNM bleeding, IC bleeding, and other major bleeding. The company presented results only for certain key outcomes, and therefore the ERG has also focused on these key outcomes only.

The trials included in the initial treatment period NMA are summarised in Table 22. All trials included in the initial treatment period NMA were open-label, double blind RCTs.

Table 22: RCTs included in the initial treatment period NMA

Trial	Treatment (as described in trial)	Comparator (as described in trial)	Population used for analyses
AMPLIFY[36]	Apixaban 10mg bd (initial 7 days)/apixaban 5mg bd	Enoxaparin/warfarin	All efficacy analyses were based on an ITT population, i.e. patients who had an outcome reported at 6 months. Safety analyses were conducted for the on treatment population.
RE-COVER[55]	UFH or LMWH/dabigatran 150mg bd	UFH or LMWH/warfarin	Efficacy analyses were based on an mITT principle, i.e., patients who did not receive any study drug were excluded. Safety analyses were conducted for the on treatment population.
RE-COVER II[56]	UFH or LMWH/dabigatran 150mg bd	UFH or LMWH/warfarin	Efficacy analyses were based on an mITT principle, i.e., patients who did not receive any study drug were excluded. The safety population also consisted of all randomised patients who took ≥1 dose of study drug.
EINSTEIN DVT and PE pooled data set[57]	Rivaroxaban 15mg bd (initial 21 days)/rivaroxaban 20mg od	Enoxaparin/VKA (INR 2.0–3.0)	The primary efficacy analysis was based on the ITT principle. Safety analyses were conducted for all patients who received ≥1 dose of study drug.

bd=twice daily; INR=international normalised ratio; LMWH=low molecular weight heparin; od=once daily; UFH=unfractionated heparin; VKA=vitamin K antagonist; INR 2.0–3.0
Source: Table 30 of the CS[1]

The company assumed that the clinical effectiveness of all LMWH used in these trials was comparable. As discussed in Section 2 of this ERG report, the company is of the opinion that fondaparinux is not an appropriate comparator for this appraisal, and has not included fondaparinux in the network of evidence. The ERG is satisfied with the company's rationale.

The company reports that data from the EINSTEIN-PE and EINSTEIN-DVT trials were pooled,[57] to ensure that the results are applicable to a general VTE population. The ERG is satisfied that the pooling of results from these trials was performed adequately and is not a cause for concern with regards to this NMA.

The company uses data from the ITT population from the AMPLIFY[36] trial for efficacy outcomes, i.e. all patients were analysed according to the treatment they were originally assigned to, wherever possible. However, the ERG notes that majority of trials included in the network performed analyses using the modified ITT (mITT) population, i.e. patients with no outcome data were excluded from the analysis.

Data assumptions

The company lists several assumptions for the calculation of outcome event data (CS, p84). These assumptions were largely necessary due to inconsistency in the definitions of the outcomes reported across trials. The ERG is of the opinion that the assumptions made were reasonable and unlikely to affect the validity of the NMA results.

Sensitivity analyses

Sensitivity analyses were conducted to investigate the effect of the following adjustments on the results of the NMAs:

- using the mITT population instead of the ITT population
- using pooled data for RE-COVER[55] and RE-COVER II[56] which seemed to differ from the individual RE-COVER trials, in terms of the adjudication of events
- excluding dabigatran trials (RE-COVER[55] and RE-COVER II[56])

Statistical approach

The company used WinBUGS software and a Bayesian framework to implement Markov Chain Monte Carlo methods, in order to estimate the parameters of the model for the initial treatment period NMA. The company used a burn-in period of 50,000 simulations, and inferences were based on a further sample of 50,000 simulations, using three chains. The company ensured that convergence had been achieved by considering the Gelman-Rubin statistic.[67]

4.7.4 Secondary prevention period NMA: overview of trials and statistical approach

The company performed NMAs for both efficacy and safety outcomes. For each outcome, as many trials as possible were incorporated into the NMA. The company notes that trials did not consistently report the same outcomes and it was not possible for the company to carry

out an NMA using the primary outcome of the AMPLIFY-EXT[37] trial (recurrent VTE or all-cause death). NMAs were conducted for the following efficacy outcomes: recurrent-VTE or VTE-related death, non-fatal PE, DVT, VTE-related death, all-cause death, and overall discontinuation. NMAs were conducted for the following safety outcomes: major or CRNM bleeding, major bleeding, and CRNM bleeding. The company presented results only for certain key outcomes, and therefore the ERG has also focused on these key results only.

The trials included in the secondary prevention period NMA are summarised in Table 23. All trials included in the secondary prevention period NMA were open-label, double blind RCTs, which required patients to have at least 3 months of anticoagulation prior to treatment commencement.

Table 23: RCTs included in secondary prevention period NMA

Trial	Treatment (as described in the trial)	Comparator (as described in the trial)	Population used for analyses
AMPLIFY-EXT[37]	Apixaban 2.5mg bd/ 5mg bd	Placebo	All efficacy analyses included data from the ITT population. All safety analyses included data from patients during the time they were receiving treatment.
EINSTEIN-EXT[58]	Rivaroxaban 20mg od	Placebo	Primary efficacy analysis was performed on an ITT basis. The safety analysis included all patients who received the assigned study drug.
WARFASA[59]	Aspirin 100mg od	Placebo	The primary efficacy analysis was performed according to an mITT principle; all patients who received at least one dose of the assigned study drug after randomisation were included in the analysis. The safety analysis included all patients who received at least one dose of the study drug.
RE-SONATE[60]	Dabigatran 150mg bd	Placebo	For efficacy, an mTT analysis was performed with exclusion of patients who did not receive any dose of the study drug. All events during the initial treatment period were included in the safety analysis.
RE-MEDY[60]	Dabigatran 150mg bd	Warfarin (INR 2.0–3.0)	For efficacy, an mITT analysis was performed with exclusion of patients who did not receive any dose of the study drug. All events during the initia treatment period were included in the safety analysis.
ASPIRE[61]	Aspirin 100mg od	Placebo	Primary analysis used the ITT population.
LAFIT[62]	Warfarin (INR 2.0–3.0)	Placebo	Main efficacy and safety outcomes were reported for all randomised patients.
ELATE[63]	Warfarin (INR 1.5–1.9)	Warfarin (INR 2.0–3.0)	Main efficacy and safety outcomes reported for all randomised patients.
WODIT DVT[64]	VKA continuation	VKA discontinuation/ observation	Primary analysis used the ITT population.
WODIT PE[65]	VKA continuation	VKA discontinuation/ observation	Primary analysis used the ITT population.
PREVENT[66]	Warfarin (INR 1.5–1.9)	Placebo	Primary analysis used the ITT population.

bd=twice daily; INR=international normalised ratio; od=once daily; VKA=vitamin K antagonist
Source: Table 31 of the CS[1]

The company justifies including the low warfarin INR range treatments in the network of evidence, despite this low range not being regularly used in current clinical practice, as it provides an additional 'loop' of evidence, improving the reliability of the NMA treatment effect estimates. The ERG also notes that apixaban 5mg is not a relevant comparator for the appraisal. The inclusion of both of these treatments in the network of evidence does not concern the ERG, as they do provide additional indirect evidence. The company utilises

these studies to assess inconsistency between direct and indirect evidence from the treatment loops within the secondary prevention period network (see CS, p110-111). Assessing inconsistency in a NMA is an informative way of assessing the validity of the results from the NMA; if estimates of treatment effect differ greatly between the direct and indirect evidence, this suggests that the results from the NMA may not be valid.

In the secondary prevention period NMA, events were included from the planned treatment period only, and the NMA was designed to minimise the level of bias in the network from trials with an extended follow-up period. The exceptions to this were the ASPIRE[61] and ELATE[63] trials, in which outcome events were reported as those which took place during the follow-up period of each trial.

Data assumptions

The company lists several assumptions for the calculation of outcome event data (CS,[1] pp85-86). These assumptions were largely necessary due to the differences in the definitions of outcomes reported across the trials. The ERG is of the opinion that the assumptions related to outcome definitions made were reasonable and are unlikely to affect the validity of the NMA results.

Sensitivity analyses

Sensitivity analyses were conducted to investigate the effect of the following adjustments on the results of the NMAs:

- incorporating data from the treatment and follow-up period, as the primary analysis included events from the planned treatment period only
- excluding the WODIT DVT[64]/PE[65] trials, which had a considerably longer follow-up period (including a period when patients were not receiving treatment, and when the majority of primary outcome events occurred) than other trials in this NMA
- excluding dabigatran trials (RE-SONATE[60] and RE-MEDY[60])

Statistical approach

The company used WinBUGS software and a Bayesian framework to implement Markov Chain Monte Carlo methods, in order to estimate the parameters of the model for the secondary prevention period NMA. The company used a burn-in period of 100,000 simulations, and inferences were based on a further sample of 50,000 simulations, using three chains. A longer burn-in period was required than for the initial treatment period NMA, as many of the trials reported groups that experienced zero events, and so more iterations were required to achieve convergence. The company ensured that convergence had been achieved by considering the Gelman-Rubin statistic.[67]

4.7.5 Characteristics of the included trials

The characteristics of the trials included in the initial treatment period NMA and secondary prevention period NMA are summarised in Table 24 and Table 25.

The ERG is of the opinion that the key characteristics of the trials included in the initial treatment period NMA are similar enough to justify combining the results from these trials. The EINSTEIN[57] trials were the only trials to report results at time-points other than 6 months, as patients were treated for either 3, 6 or 12 months, depending on the recommendation provided by the physician. The ERG sought clinical advice as to whether this issue would greatly affect the comparability of the data from the included trials, and came to the conclusion that, as events are much more likely to occur in the first few months of treatment, it would be unlikely that there would be notable differences in the number of events observed between patients followed up at 3, 6 and 12 months. In addition, the majority of patients in both EINSTEIN-PE and EINSTEIN DVT trials[57] were followed up at 6 months (57% and 63%, respectively).

The ERG is more concerned about the comparability of trials in the secondary prevention period NMA as there are substantial differences between the time spent on treatment and the follow-up periods between the trials. This issue is discussed further in Section 4.8.3 of this ERG report, as the ERG is of the opinion that these differences render the results of the secondary prevention period NMA to be flawed.

Baseline patient characteristics for the trials included in the initial treatment period NMA and secondary prevention period NMA are summarised in Table 39 and Table 40 of the CS.[1] For the initial treatment period NMA, patient characteristics seem to be broadly comparable across trials, with the exception of the rates of index DVT and index PE within the EINSTEIN DVT/PE[57] trials. The ERG notes that a greater percentage of index events are PE events in both rivaroxaban and enoxaparin/VKA arms of the trials (58.3% and 58.4%, respectively), in comparison to the other trials within this network of evidence (percentage of patients with PE ranges from 21.2% to 25.2%). Subsequently, there are fewer patients with DVT in the EINSTEIN DVT/PE[57] trials than in the other included trials. For the secondary prevention period NMA, the trials are similar in terms of patient characteristics.

Table 24 Characteristics of trials included in the initial treatment period NMA

Trial & location	Primary outcomes	Secondary efficacy outcomes	Time on treatment
AMPLIFY[36] Randomised, double blind, non-inferiority trial International, multicentre	Efficacy 6 month incidence of the adjudicated composite of symptomatic, recurrent VTE or VTE-related death Safety Incidence during treatment period of adjudicated major bleeding.	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	6 months
RE-COVER[55] Randomised, double blind, non-inferiority trial International, multicentre	Efficacy 6-month incidence of recurrent symptomatic VTE and deaths related to VTE Safety Major bleeding	Efficacy Symptomatic DVT, symptomatic non-fatal PE, VTE-related death Safety Major or CRNM bleeding, any bleeding event	6 months
RE-COVER II[56] Randomised, double blind, non-inferiority trial International, multicentre	Efficacy 6-month incidence of recurrent symptomatic VTE and deaths related to VTE Safety Major bleeding	Efficacy Symptomatic DVT, symptomatic non-fatal PE, VTE-related death Safety Major or CRNM bleeding, any bleeding event	6 months
EINSTEIN PE[57] Randomised, open-label non-inferiority trial International, multicentre	Efficacy 3,6,12 month incidence of symptomatic recurrent venous thromboembolism Safety First major or CRNM	Efficacy and safety Major bleeding, death from any cause, vascular events and net clinical benefit (composite of primary efficacy outcome or major bleeding)	Outcomes measured at either 3, 6 or 12 months
EINSTEIN DVT[57] Randomised, open-label non-inferiority trial International, multicentre	Efficacy 3,6,12-month incidence of symptomatic recurrent venous thromboembolism Safety First major or CRNM	Efficacy and safety All-cause mortality, vascular events and net clinical benefit (composite of primary efficacy outcome or major bleeding)	Outcomes measured at either 3, 6 or 12 months

CRNM=clinically relevant non-major; DVT=deep vein thrombosis; PE=pulmonary embolism; VTE=venous thromboembolism
Source: Company clarification response

Table 25 Characteristics of trials included in secondary prevention period NMA

Trial & location	Primary outcomes	Secondary efficacy outcomes	Treatment and follow-up period
AMPLIFY-EXT[37] Randomised, double blind, placebo controlled trial International, multicentre	Efficacy Incidence of an adjudicated composite of symptomatic, recurrent VTE or all-cause death Safety Incidence during treatment period of adjudicated major bleeding.	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	Initial 6 to12 months treatment Trial: 12 months preventive period 30 day observation period
ASPIRE[61] Randomised, double blind, placebo controlled trial International, multicentre	Efficacy Recurrence of venous thromboembolism Safety Major or clinically relevant non-major bleeding	Efficacy and safety Major vascular events (composite of VTE, MI, stroke, or cardiovascular death) and a measure of the net clinical benefit (a reduction in the rate of the composite of VTE, MI, stroke, major bleeding, or death from any cause)	Initial treatment 6 to 24 weeks Trial: 2 to 4 years Mean: 37.2 months
EINSTEIN-EXT[58] Randomised, double-blind, placebo-controlled superiority trial International, multicentre	Efficacy Incidence of symptomatic recurrent VTE Safety Major bleeding	Efficacy and safety All-cause mortality and cardiovascular events	Initial 6 to 12 months treatment Trial: 6 to12 months treatment. One month observation period
LAFIT[62] Randomised, double-blind trial Multicentre(Canada and USA)	Efficacy Symptomatic, objectively confirmed recurrence of VTE during 24 months after randomisation Safety Major bleeding	Efficacy and safety Minor bleeding, all-cause death, biochemical abnormalities	3 months initial treatment. Trial: 24 months treatment. Mean: 10 months
PREVENT[66] Randomised, double blind trial Multicentre (Canada, USA and Switzerland)	Efficacy clinically relevant recurrent thromboembolic events	Efficacy Net clinical benefit (composite of recurrent VTE, major bleeding, and all-cause mortality) Safety Major hemorrhage, minor bleed or deaths	At least 3 months initial treatment. Duration of trial period not specified. Mean: 2.1 years
RE–SONATE[60] Randomised, double blind, placebo controlled trial International, multinational	Efficacy Recurrent symptomatic and objectively verified VTE or death associated with VTE or unexplained death Safety Major bleeding	Efficacy Symptomatic DVT, symptomatic non-fatal PE, unexplained death Safety Major or CRN bleeding event, any bleeding event, adverse	6 to 18 months initial treatment Trial: 6 months treatment

Trial & location	Primary outcomes	Secondary efficacy outcomes	Treatment and follow-up period
		events, acute coronary events (including cerebrovascular events)	
RE-MEDY[60] Randomised, double blind, active controlled trial International, multinational	Efficacy Recurrent or fatal thromboembolism Safety Major bleeding	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	3 to 12 months initial treatment Trial: 6 to 36 months
WARFASA[59] Randomised, double blind trial Multicentre (Italy, Austria)	Efficacy Symptomatic, objectively confirmed recurrence of VTE Safety Major bleeding	Efficacy Non-fatal MI Unstable angina Stroke TIA Acute ischaemia of the lower limbs Safety CRNM bleeding All-cause mortality	6 to 18 months initial treatment Trial: 2 years treatment with option of extending Median treatment period: 23.9 months, Median study period: 24.6 months
WODIT DVT[64] Randomised, open-label trial Multicentre (Italy)	Efficacy Recurrence of symptomatic, objectively confirmed recurrence of VTE during a follow-up period of ≥2 years after randomization Safety Major bleeding	Efficacy and safety Mortality, adverse events	3 months initial treatment Trial: 9 months treatment Observation period not specified Mean: 37.8 months in patients with recurrent VTE
WODIT PE[65] Multicentre (Italy)	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	Idiopathic 3 months initial treatment Trial: 9 months Provoked 3 months initial treatment Trial: 3 months Observation period not specified Mean: 33.8 months in patients with recurrent VTE
ELATE[63] Randomised, double blind trial Multicentre (Canada and USA)	Efficacy Recurrent VTE Safety Major bleeding	Efficacy and safety Major bleeding, any bleeding episode, all-cause mortality	3 months initial treatment Duration of trial period not specified. Mean: 2.4 years

CRNM=clinically relevant non-major; DVT=deep vein thrombosis; MI=myocardial infection; PE=pulmonary embolism VTE=venous thromboembolism Source: Table 3 of the company's clarification response

4.7.6 Quality assessment

The company conducted a quality assessment of each of the trials included in the two NMAs and results are presented in the CS[1] in Appendix 10.8. The assessments are summarised in Appendix 5. The ERG considers that the conclusions drawn by the company are valid and that the included trials are of good quality.

4.7.7 Individual trial findings

The company provides results from the individual trials from the initial treatment period NMA (CS, Appendix 6a) and the secondary prevention period NMA (CS, Appendix 6b). The ERG provides summary tables of these results in Appendix 6 of this ERG report.

4.8 Results of the network meta-analyses

The ERG has concerns about the methodology employed by the company to obtain estimates of treatment effect in the NMAs and these are discussed fully in Section 4.8.3 of this report. The ERG asked for the company to repeat the NMAs as part of the clarification process. The requested analyses were to use an alternative vague prior for the trial effect, treating the trial effect as random rather than fixed, in order to investigate the robustness of the estimated treatment effects. It is the results from this analysis which are presented in this ERG report.

The ERG did also request an analysis which included a more informative prior for the study effect, which the company conducted and submitted. However, after further discussion, and taking into consideration the company's concerns about the appropriateness of the informative prior analysis, the ERG decided that this analysis was not appropriate. The results from the informative prior analysis are not presented in this ERG report.

In the following results section, the main analysis for each NMA is referred to as the "base-case analysis". For each NMA, the results of the base-case analysis and its corresponding sensitivity analyses are presented, using both the company's original analysis method (referred to in the tables as "original analysis"), and the "alternative vague prior" analysis method requested by the ERG (referred to in the tables as "analysis requested by the ERG"). Statistically significant results are shown in bold.

4.8.1 Initial treatment period network meta-analysis results

Base-case analysis

The results from the base-case analysis for the initial treatment period NMA are provided in Table 26. There were no statistically significant differences between apixaban and any of the comparators in terms of the primary efficacy outcome of recurrent VTE or VTE-related death,

in either the original analysis or the alternative analysis requested by the ERG. There were no differences in the conclusions drawn for any of the safety outcomes when the alternative analysis method was used. The RRs for all the bleeding related outcomes were significantly reduced for apixaban in comparison to LMWH/VKA. Apixaban was shown to statistically significantly reduce the likelihood of major or CRNM bleeding in comparison to both dabigatran and rivaroxaban, to reduce the likelihood of major bleeding in comparison to dabigatran, and to reduce the likelihood of CRNM bleeding to rivaroxaban.

Table 26 Base-case analysis for initial treatment period NMA (6-month time point)

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*			
Original analysis	[redacted]	0.76 (0.46 to 1.27)	0.93 (0.59 to 1.46)
Analysis requested by ERG	[redacted]	[redacted]	[redacted]
Major or CRNM bleeding			
Original analysis	[redacted]	**0.69 (0.51 to 0.94)**	**0.47 (0.36 to 0.61)**
Analysis requested by ERG	[redacted]	[redacted]	[redacted]
Major bleeding			
Original analysis	[redacted]	**0.40 (0.19 to 0.81)**	0.55 (0.27 to 1.09)
Analysis requested by ERG	[redacted]	[redacted]	[redacted]
CRNM bleeding			
Original analysis	[redacted]	0.80 (0.57 to 1.12)	**0.47 (0.36 to 0.62)**
Analysis requested by ERG	[redacted]	[redacted]	[redacted]
Overall treatment discontinuation			
Original analysis	[redacted]	[redacted]	[redacted]
Analysis requested by ERG	[redacted]	[redacted]	[redacted]
All-cause mortality			
Original analysis	[redacted]	0.79 (0.44 to 1.41)	0.82 (0.50 to 1.34)
Analysis requested by ERG	[redacted]	[redacted]	[redacted]

CrI=credible interval; CRNM=clinically relevant non-major; ERG=Evidence Review Group; LMWH=low molecular weight heparin; RR=relative risk; vs=versus; VKA=vitamin K antagonist; VTE=venous thromboembolism
*VTE or VTE-related death outcome is composed of the sum of the incidences of non-fatal PE, DVT and VTE-related deaths
Source: Company clarification response

Sensitivity analysis: modified ITT population

The results from the sensitivity analysis using the mITT population for the initial treatment period NMA are provided in Table 27. The company's original analyses had shown that the results for the safety outcomes were not affected by changing from the base-case analysis to the sensitivity analysis including the mITT population (CS, Table 35, p90). Therefore, the company did not redo the analyses for the safety outcomes using the analysis method requested by the ERG, as it was assumed that the results from the safety outcomes would be very similar to those presented in the base-case analysis using the analysis method requested by the ERG.

The results show that there were no significant differences between apixaban and any of the relevant comparators in terms of the primary efficacy outcome, recurrent VTE or VTE-related death, when using the mITT population. These results are consistent with the results from the base-case analysis.

Table 27 Sensitivity analysis using mITT for initial treatment period NMA (6-month time point)

Outcome	Apixaban vs LMWH/VKA RR (95% CI)	Apixaban vs LMWH/dabigatran RR (95% CI)	Apixaban vs rivaroxaban RR (95% CI)
Recurrent VTE or VTE-related death - mITT population			
Original analysis	[redacted]	[redacted]	[redacted]
Analysis requested by ERG	[redacted]	[redacted]	[redacted]

CrI=credible interval; ERG=Evidence Review Group; mITT=modified intention-to-treat; LMWH=low molecular weight heparin; RR=relative risk; vs=versus; VKA=vitamin K antagonist; VTE=venous thromboembolism
Source: Company clarification response

Sensitivity analysis: pooled RE-COVER/RE-COVER II data set

The results from the sensitivity analysis using the pooled RE-COVER[55]/RE-COVER II[56] data set for the initial treatment period NMA are provided in Table 28. The company's original analyses had shown that the results for the primary efficacy outcome were not affected by changing from the base-case analysis to the sensitivity analysis using the pooled RE-COVER[55,56]/RE-COVER II data set (CS, Table 35, p90). The company explains in their response to the ERG's clarification letter that this was to be expected because the results from the pooled trials closely matched the sum of the reported data from the two individual trials.

The company did not redo the analyses for the primary efficacy outcome using the analysis method requested by the ERG, as it was assumed that the results for the primary efficacy outcome would be very similar to those presented in the base-case analysis, using the analysis method requested by the ERG.

The results from the sensitivity analysis using pooled RE-COVER[55]/RE-COVER II[56] data were consistent with those from the base-case analysis.

Table 28 Sensitivity analysis using RE-COVER/RE-COVER II pooled data for initial treatment period NMA (6-month time point)

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			
Original analysis	[redacted]	[redacted]	[redacted]
Analysis requested by ERG	[redacted]	[redacted]	[redacted]
Major bleeding			
Original analysis	[redacted]	[redacted]	[redacted]
Analysis requested by ERG	[redacted]	[redacted]	[redacted]
CRNM bleeding			
Original analysis	[redacted]	[redacted]	[redacted]
Analysis requested by ERG	[redacted]	[redacted]	[redacted]

CrI=credible interval; CRNM=clinically relevant non-major; ERG=Evidence Review Group; LMWH=low molecular weight heparin; RR=relative risk; vs=versus; VKA=vitamin K antagonist
Source: Company clarification response

Sensitivity analysis: excluding dabigatran trials (RE-COVER/RE-COVER II)

The results from the sensitivity analysis excluding dabigatran trials for the initial treatment period NMA are provided in Table 29. None of the conclusions drawn from this sensitivity analyses differed to those from the base-case analysis. Therefore, the ERG is further reassured that the inclusion of dabigatran is appropriate and unlikely to impact the conclusions drawn from the NMA.

Table 29 Sensitivity analysis excluding dabigatran trials for initial treatment period NMA (6-month timepoint)

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			
Original analysis	[redacted]	[redacted]	[redacted]
Analysis requested by ERG	[redacted]	[redacted]	[redacted]
Major bleeding			
Original analysis	[redacted]	[redacted]	[redacted]
Analysis requested by ERG	[redacted]	[redacted]	[redacted]
Major or CRNM bleeding			
Original analysis	[redacted]	[redacted]	[redacted]
Analysis requested by ERG	[redacted]	[redacted]	[redacted]
CRNM bleeding			
Original analysis	[redacted]	[redacted]	[redacted]
Analysis requested by ERG	[redacted]	[redacted]	[redacted]

CrI=credible interval; CRNM=clinically relevant non-major; ERG=Evidence Review Group; LMWH=low molecular weight heparin; RR=relative risk; vs=versus; VKA=vitamin K antagonist; VTE=venous thromboembolism
Source: Company clarification response

4.8.2 Secondary prevention network meta-analysis results

Base-case analysis

The results from the base-case analysis for the secondary prevention NMA are provided in Table 30. The company found that it was not possible to produce results for the recurrent VTE-related death outcome without applying continuity correction as requested by the ERG. Therefore, the estimates from the company's original analyses must be relied upon.

There were no significant differences between apixaban and dabigatran, rivaroxaban or VKA in terms of recurrent VTE or VTE-related death. Apixaban was shown to statistically significantly reduce the likelihood of recurrent VTE or VTE-related death in comparison to aspirin and placebo/no treatment.

With regards to the safety outcomes, apixaban was shown to statistically signficantly reduce the likelihood of major or CRNM bleeding (composite outcome) in comparison to dabigatran, rivaroxaban and VKA, and to reduce the likelihood of major bleeding and CRNM bleeding (as separate outcomes) in comparison to rivaroxaban and VKA. However, apixaban was only found to statistically significantly reduce the likelihood of major bleeding in comparison to rivaroxaban when using the treatment effect estimate from the company's original

analysis. When the ERG's requested analyses are conducted, this result was no longer statistically significant. There were no statistically significant differences between apixaban and aspirin or placebo/no treatment for any of the safety outcomes.

Table 30 Base-case analysis for the secondary prevention period NMA

Outcome	Apixaban 2.5mg bd vs dabigatran 150mg od RR (95% CrI)	Apixaban 2.5mg bd vs rivaroxaban 20mg od RR (95% CrI)	Apixaban 2.5mg bd vs VKA (INR 2.0–3.0) RR (95% CrI)	Apixaban 2.5mg bd vs aspirin 100mg od RR (95% CrI)	Apixaban 2.5mg bd vs placebo RR (95% CrI)
Recurrent VTE or VTE-related death*					
Original analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analysis requested by ERG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrent VTE-related death					
Original analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analysis requested by ERG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major or CRNM bleeding					
Original analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analysis requested by ERG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding					
Original analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analysis requested by ERG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleeding					
Original analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analysis requested by ERG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall treatment discontinuation					
Original analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analysis requested by ERG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All-cause mortality					
Original analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analysis requested by ERG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

bd=twice daily; CrI=credible interval; CRNM=clinically relevant non-major; ERG=Evidence Review Group; od=once daily; RR=relative risk; vs=versus; VKA=vitamin K antagonist; VTE=venous thromboembolism

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

Source: Company clarification response

Sensitivity analysis: ITT population

The results from the sensitivity analysis using the ITT population for the secondary prevention NMA are provided in Table 31. As the analyses for safety outcomes were based on the safety population, only the efficacy outcomes would be affected by changing from the population used in the base-case analysis to the ITT population (as shown in Table 38 of the CS[1]).

In the sensitivity analysis using the ITT population, apixaban was shown to statistically significantly reduce the likelihood of recurrent VTE or VTE-related death in comparison to LMWH/VKA. This is in contrast to the finding for this outcome from the base-case analysis, which showed that there were no statistically significant differences between apixaban and LMWH/VKA. All other results were consistent with those obtained from the base-case analysis.

Table 31 Sensitivity analysis using the ITT population for secondary prevention period NMA results

Outcome	Apixaban 2.5mg bd vs dabigatran 150mg od RR (95% CrI)	Apixaban 2.5mg bd vs rivaroxaban 20mg od RR (95% CrI)	Apixaban 2.5mg bd vs VKA (INR 2.0–3.0) RR (95% CrI)	Apixaban 2.5mg bd vsaspirin 100mg od RR (95% CrI)	Apixaban 2.5mg bd vs placebo RR (95% CrI)
Recurrent VTE or VTE-related death					
Original analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analysis requested by ERG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

bd=twice daily; CrI=credible interval; ERG=Evidence Review Group; od=once daily; RR=relative risk; VKA=vitamin K antagonist; vs;versus; VTE=venous thromboembolism
Source: Company clarification response

Sensitivity analysis: excluding WODIT DVT/PE trials

The results from the sensitivity analysis excluding the WODIT DVT/PE[64,65] trials for the secondary prevention period NMA are provided in Table 32. The results were consistent with those reported in the base-case analysis.

Table 32 Sensitivity analysis for secondary prevention period NMA results

Outcome	Apixaban 2.5mg bd versus dabigatran 150mg od RR (95% CrI)	Apixaban 2.5mg bd versus rivaroxaban 20mg od RR (95% CrI)	Apixaban 2.5mg bd versus VKA (INR 2.0–3.0) RR (95% CrI)	Apixaban 2.5mg bd versus aspirin 100mg od RR (95% CrI)	Apixaban 2.5mg bd versus placebo RR (95% CrI)
Recurrent VTE or VTE-related death					
Original analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analysis requested by ERG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding†					
Original analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analysis requested by ERG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

bd=twice daily; CrI=credible interval; ERG=Evidence Review Group; od=once daily; RR=relative risk; vs=versus; VKA=vitamin K antagonist; VTE=venous thromboembolism
† No continuity correction has been applied to the new results whereas it was necessary in the original analysis
Source: Company clarification response

Sensitivity analysis: excluding dabigatran trials (RE-SONATE /RE-MEDY)

The results from the sensitivity analysis excluding the dabigatran trials for the secondary prevention period NMA are provided in Table 33. Due to lack of data, results were not reported for CRNM bleeding or the composite outcome of major or CRNM bleeding. In contrast to the base-case analysis, there was no statistically significant difference between apixaban and VKA treatments in terms of major bleeding, although this result was only non-significant when using the company's original analysis. The results of the analysis requested by the ERG were consistent with the results from the base-case analysis. There were no other major differences between conclusions drawn from the base-case analysis and the results of the sensitivity analysis.

Table 33 Sensitivity analysis for secondary prevention period NMA results

Outcome	Apixaban 2.5mg bd vs rivaroxaban 20mg od RR (95% CrI)	Apixaban 2.5mg bd vs VKA (INR 2.0–3.0) RR (95% CrI)	Apixaban 2.5mg bd vs aspirin 100mg od RR (95% CrI)	Apixaban 2.5mg bd vs placebo RR (95% CrI)
Recurrent VTE or VTE-related death				
Original analysis	[redacted]	[redacted]	[redacted]	[redacted]
Analysis requested by the ERG	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding†				
Original analysis	[redacted]	[redacted]	[redacted]	[redacted]
Analysis requested by the ERG	[redacted]	[redacted]	[redacted]	[redacted]
Major or CRNM bleeding				
Original analysis	[redacted]	[redacted]	[redacted]	[redacted]
Analysis requested by the ERG	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleeding				
Original analysis	[redacted]	[redacted]	[redacted]	[redacted]
Analysis requested by the ERG	[redacted]	[redacted]	[redacted]	[redacted]

bd=twice daily; CrI=credible interval; CRNM=clinically relevant non-major; ERG=Evidence Review Group; od=once daily; RR=relative risk; vs=versus; VKA=vitamin K antagonist; VTE=venous thromboembolism
† No continuity correction has been applied to the new results whereas it was necessary in the original analysis
Source: Company clarification response

4.8.3 ERG critique of the network meta-analyses

The ERG is satisfied that the methodology used to conduct the initial treatment period NMA was appropriate, and that the indirect evidence provided by the company can be used to assess apixaban in terms of both efficacy and safety in comparison to relevant treatment comparators.

The ERG is of the opinion that the methods used to combine data in the secondary prevention period NMA are not appropriate due to the different lengths of treatment periods and stated follow-up times of the included trials. Time on treatment ranged from 6 months (RE-SONATE[60]) to 37.2 months (ASPIRE[61]) and follow-up times ranged from 10 months (LAFIT[62]) to 37.2 months (ASPIRE[61]). The company discusses both of these sources of heterogeneity in the CS[1] and explains that consultation with experts suggested that use of different treatment periods and follow-up times would not significantly impact the size of the relative treatment effects. The ERG does not agree that the outcome data from the studies included in the secondary prevention period NMA have been produced using sufficiently similar assumptions; the ERG considers that there are likely to be more events in studies with longer treatment periods and follow-up times than in studies with shorter treatment periods and follow-up times. This is a fundamental flaw in the secondary prevention period NMA and the ERG considers that the efficacy (and safety) of apixaban versus any active

comparator as secondary prevention is not yet confirmed and that the results of the secondary prevention period NMA analysis should be interpreted with caution. Therefore, the ERG considers that only the direct clinical effectiveness evidence for apixaban from the AMPLIFY-EXT[37] trial may be used to provide evidence for the use of apixaban as secondary prevention for recurrent VTE.

In addition, the ERG has concerns about the methodology used for the initial treatment period and secondary prevention period NMAs. The company applied continuity correction factors for instances of zero events for certain outcomes. This led to high estimates of RRs for some comparisons, which in turn were used in the economic model and so affected the size of the ICERs. For example, the company calculated the RR for major bleeding for apixaban versus rivaroxaban to be [redacted] in the secondary prevention period NMA, which the ERG considered to be extremely small.

In order to investigate the robustness of the company's estimates, the ERG asked for both the initial treatment period and secondary prevention period NMAs to be re-run using an alternative vague prior for the trial effect, and for the analysis to treat the trial effect as random rather than fixed. The company provided the requested analyses, and the ERG is satisfied that the results of the re-analysis yield less extreme estimates of underlying treatment effect than those provided in the company's original analyses, i.e. less likely to be overestimating or underestimating treatment effect. The new estimate for the RR for major bleeding for apixaban versus rivaroxaban in the secondary prevention period ([redacted]) is more acceptable than that provided in the company's original analysis. The results from the requested analyses were used in the ERG's calculations of ICERs.

Page superseded by erratum

A minor concern that the ERG has in relation to the initial treatment period NMA is that it is unclear whether the company included aspirin and no treatment in the network of evidence for this NMA. Tables 58, 61 and 63 in the CS[1] all show RRs for aspirin and no treatment versus apixaban for the initial treatment period. It is unclear to the ERG how these RRs were calculated and whether the initial treatment period NMA has also taken these treatments into consideration. The ERG has tried to replicate the company's findings from the initial treatment period NMA using the network of evidence as provided in Figure 10 of the CS,[1] but was unable to obtain the same results. In addition, the ERG is uncertain about how the estimates from the initial treatment period NMA were obtained used in the economic evaluation.

4.9 Conclusions of the clinical effectiveness section

The main source of clinical evidence described in the CS[1] is derived from two key RCTs that included two distinct patient populations. Patients in the AMPLIFY[36] trial required initial treatment for a VTE event. The AMPLIFY[36] trial compared apixaban versus enoxaparin/warfarin in adult patients with symptomatic proximal DVT or PE (with or without DVT) over a 6-month period. Patients recruited to the AMPLIFY-EXT[37] trial have symptomatic, proximal DVT or PE (with or without DVT) and were treated with standard anticoagulation therapy for 6 to 12 months without VTE recurrence. Patients in AMPLIFY-EXT[37] were considered to be at clinical equipoise meaning that the risks and benefits of extended anticoagulation treatment were uncertain.

The results of the AMPLIFY[36] trial demonstrate that for the initial treatment period of VTE apixaban is non-inferior to, but not superior to, treatment with enoxaparin/warfarin for the primary efficacy outcome of recurrent VTE or VTE-related death ($p<0.001$). This finding is consistent across a range of secondary outcomes and pre-specified subgroup analyses. A statistically significant reduction in major bleeding events is reported for apixaban-treated patients compared with enoxaparin/warfarin-treated patients (RR 0.31; 95% CI 0.17 to 0.55; $p<0.001$). This finding is consistent across a range of secondary outcomes and pre-specified subgroup analyses. The rate of AEs between the two arms of the trial is similar.

The results of the AMPLIFY-EXT[37] trial demonstrate that for patients at clinical equipoise, apixaban significantly reduces the risk of recurrent VTE or all-cause death compared to placebo/no treatment (RR 0.83; 95% CI 0.22 to 0.48; [redacted]). This finding is consistent across a range of secondary outcomes and pre-specified subgroup analyses. For the outcome of major bleeding, apixaban is not statistically significantly different compared to placebo/no treatment and this finding is consistent across a range of secondary outcomes and pre-specified subgroup analyses. The rate of AEs between the two arms of the trial is similar.

No HRQoL data were collected during either of the trials and therefore patients' experience of treatment with apixaban versus enoxaparin/warfarin or apixaban versus placebo/no treatment remains unknown.

Due to the absence of direct data for the comparisons of apixaban versus rivaroxaban and apixaban versus dabigatran for the initial treatment period of VTE, the company conducted an initial treatment period NMA using treatment with LMWH/VKA as the common link. For the assessment of treatments used as secondary prevention of VTE, there were also no

Page superseded by erratum

direct data and the company conducted a secondary prevention NMA to compare apixaban versus either rivaroxaban, dabigatran, VKA, aspirin and placebo/no treatment.

The results of the initial treatment period NMA demonstrated that there were no statistically significant differences between apixaban and any of the comparators in terms of the primary efficacy outcome of recurrent VTE or VTE-related death, in either the original analysis or the alternative analysis requested by the ERG via clarification. There were no differences in the conclusions drawn for any of the safety outcomes when the alternative analysis method was used. The RRs for all bleeding related outcomes were statistically significantly reduced for apixaban in comparison to LMWH/VKA. Apixaban was shown to statistically significantly reduce the likelihood of major or CRNM bleeding in comparison to both dabigatran and rivaroxaban, to reduce the likelihood of major bleeding in comparison to dabigatran, and to reduce the likelihood of CRNM bleeding in comparison to rivaroxaban. The ERG is satisfied with the results of the initial treatment period NMA after it was re-run by the company in response to the ERG request.

The results for the secondary prevention period NMA demonstrated that there were no significant differences between apixaban and dabigatran, rivaroxaban or VKA in terms of recurrent VTE or VTE-related death. Apixaban was shown to reduce the likelihood of recurrent VTE or VTE-related death in comparison to aspirin and placebo/no treatment. With regards to the safety outcomes, apixaban was shown to reduce the likelihood of major or CRNM bleeding (composite outcome) in comparison to dabigatran, rivaroxaban and VKA, and to reduce the likelihood of major bleeding and CRNM bleeding (as separate outcomes) in comparison to rivaroxaban and VKA. There were no statistically significant differences between apixaban and aspirin or placebo/no treatment for any of the safety outcomes.

The ERG considers that the methodology used in the secondary prevention treatment period NMA has serious flaws. The ERG is of the opinion that the methods used to combine data in the secondary prevention period NMA are not appropriate due to the different lengths of treatment periods and stated follow-up times of the included trials. The ERG does not agree that the outcome data from the studies included in this NMA have been produced using sufficiently similar assumptions; the ERG considers that there are likely to be more events in studies with longer treatment periods and follow-up times than in studies with shorter treatment periods and follow-up times. The ERG recommends that the results of the secondary prevention period NMA are treated with caution.

The results of the key apixaban trials[36,37] appear to be generalisable to the majority of patients treated in clinical practice in England and Wales, with the caveat that the patients in

both of the key trials are a younger cohort. This criticism extends to all the trials of NOACs that are included in the company's NMAs.

However, no data are presented in the CS[1] for a number of patient populations. These populations include:

- patients who require long-term or lifelong anticoagulation treatment. The treatment period in the AMPLIFY[36] trial was for a maximum of 6 months and in the AMPLIFY-EXT[37] trial, patients who were at clinical equipoise were treated for a further 12 months (following a pre-treatment period of 6 to 12 months)
- patients with distal only DVT
- patients with provoked DVT and no other risk factors for recurrence
- patients for whom treatment with a VKA is unsuitable
- patients with active cancer

The clinical effectiveness of apixaban in these patient groups is therefore unknown.

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5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured critique of the economic evidence submitted by Bristol Myers Squibb Pharmaceuticals Ltd and Pfizer Ltd in support of the use of apixaban for the treatment of DVT and PE, and the prevention of recurrent DVT and PE in adults. The two key components of the economic evidence presented in the CS[1] are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company also provided an electronic copy of their economic model (developed in Microsoft Excel).

Page superseded by erratum

5.2 ERG comment on company's review of cost effectiveness evidence

5.2.1 Objective of the company's cost effectiveness review

The company updated an existing systematic review conducted for the rivaroxaban NICE submission (TA287).[24] The TA287[24] review considered articles published between 1 July 2011 and 25 October 2015 and was an update and refinement of a review carried out to inform NICE CG144[20] guidance (Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing). The objective of the CG144[20] review was to identify "health economic evidence within published literature relevant to the review questions". The time period for the CG144[20] search had no lower limit and included articles published up until 1 August 2011.

Details of the cost effectiveness search strategies employed by the company are included in Appendix 10.33 of the CS.[1] Medline (via Ovid), Medline R-In Process (Ovid), EMBASE (Ovid), EconLit (EBSCO) and The Cochrane Library (incorporating the NHS Economic Evaluations Database (NHS EED) and the Health Technology Assessment (HTA) database were searched for published economic evaluations. The time horizon for the search was 25 October 2014 to 15 July 2013. Searches of grey literature and completed and on-going studies were also carried out. In addition, the NICE website was searched for potentially relevant company and ERG reports.

5.2.2 Eligibility criteria used in the study selection

The inclusion/exclusion criteria used in the study selection process are presented in Table 34. The ERG is satisfied that these criteria are relevant to the decision problem.

Table 34 Economic evaluation search inclusion/exclusion criteria

Category	Inclusion criteria	Exclusion criteria
Study type	Relevant economic study design: ○ Cost-utility analysis ○ Cost-benefit analysis ○ Cost effectiveness analysis ○ Cost-consequence analysis ○ Comparative cost analysis	
Outcomes	Costs: • Quality adjusted life years (QALYs) • Incremental costs and QALYs • Any other measure of effectiveness reported together with costs	
Population	Patients with suspected or confirmed PE or DVT	
Interventions	Any pharmaceutical for the treatment of VTE	
Publication type		• Unpublished reports • Abstract-only studies at full paper screening • Letters • Editorials • Reviews of economic evaluations (although reference lists of these will be checked)
Language		Non-English language articles.

Source: CS,[1] Table 52

5.2.3 Included and excluded studies

Although this search identified 12 studies that met the inclusion criteria none of the identified studies were directly relevant to the decision problem, i.e. they did not include apixaban. Furthermore, nine of the included studies were excluded at the full text review stage as they did not consider a UK population. The three identified studies were the two rivaroxaban NICE STAs (TA261[23] and TA287[24]) and a poster[68] which included evidence for the cost effectiveness of dabigatran versus placebo for the secondary prevention of recurrent DVT and PE.

5.2.4 Conclusions of the cost effectiveness review

The company concluded that the two rivaroxaban models that were presented as evidence to inform the two NICE STAs (TA261[23] and TA287[23]) were high quality and very informative.

However, the poster[68] considering the cost effectiveness of dabigatran was less informative due to limited reporting of relevant data.

5.3 ERG critique of the company's literature review

Apixaban only received a full marketing authorisation from the EMA for the treatment of DVT and PE and prevention of recurrent DVT and/or PE in adults in July 2014. As this date coincides with the date of the final searches carried out by the company, a lack of economic evaluations of direct relevance to the decision problem is not unexpected. The ERG is, therefore, satisfied that company's search strategy and stated inclusion/exclusion criteria did not lead to any relevant studies being missed.

The ERG acknowledges that the company has carried out a series of literature reviews to inform the parameterisation of the model and that these are reported at appropriate points in the CS;[1] the ERG considers this information to be helpful.

5.4 Summary and critique of the company's submitted economic evaluation by the ERG

5.4.1 NICE reference case checklist

Table 35 NICE Reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Yes – although the use of a single model to carry out two distinct evaluations (short-term treatment and long-term prevention) is questionable
Comparator(s)	Alternative therapies routinely used in the NHS	Yes
Perspective costs	NHS and Personal Social Services	Partial - only NHS costs were included in the model
Perspective benefits	All health effects on individuals	Yes, health effects to the individual are captured via QALYs
Form of economic evaluation	Cost effectiveness analysis	Cost effectiveness analysis
Time horizon	Sufficient to capture differences in costs and outcomes	Lifetime horizon was used (up to 100 years of age)
Synthesis of evidence on outcomes	Systematic review	Yes
Outcome measure	Quality adjusted life years (QALYs)	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes
Benefit valuation	Time-trade off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	Benefits and costs were discounted at the 3.5% rate
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	All QALYs estimated by the model have the same weight
Sensitivity analysis	Probabilistic sensitivity analysis	Deterministic, scenario and probabilistic sensitivity analyses were undertaken by the company

QALY=quality adjusted life year; HRQoL=health related quality of life

Table 36 Critical appraisal checklist for the economic analysis completed by ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?		Two distinct questions are posed, relating to early post-event treatment and lomg-term secondary prevention. It is questionable whether the submitted decision model accurately accommodates both issues within a single model
Was a comprehensive description of the competing alternatives given?	Yes	-
Was the effectiveness of the programme or services established?	Partially	The AMPLIFY[36] trial indicates non-inferiority vs conventional therapy in reducing recurrent VTE events, but superiority in reducing incidence of major bleeding. The AMPLIFY-EXT[37] trial demonstrated superiority in reducing recurrent VTE events vs placebo, but not for reducing bleeding events. Relative effectiveness and safety depend on use of network meta-analyses, which are of questionable validity
Were all the important and relevant costs and consequences for each alternative identified?	Yes	-
Were costs and consequences measured accurately in appropriate physical units?	Yes	Generally in agreement with practice in similar recent appraisals
Were the cost and consequences valued credibly?	Uncertain	Key effectiveness and safety model parameters could not be validated as the relevant trial evidence was not made available to the ERG
Were costs and consequences adjusted for differential timing?	Yes	-
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	ICERs were calculated correctly
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Deterministic, scenario and probabilistic sensitivity analyses were undertaken
Did the presentation and discussion of study results include all issues of concern to users?	Yes	-

QALY=quality adjusted life year; HRQoL=health related quality of life; ERG=evidence review group; ICERs=incremental cost effectiveness analysis

5.4.2 Description of the company's economic model

The company's cost effectiveness model is a Markov state transition model which comprises 13 health states. The 11 main health states are: index PE, index DVT, recurrent PE, recurrent DVT, CTEPH, IC bleed, non-IC major bleed, CRNM bleed, PE off treatment, DVT off treatment and death; whilst two further health states, PE second-line and DVT second-line, are only used in sensitivity analyses. Patients enter the model having experienced either an index PE or index DVT. At each cycle, patients are at risk of experiencing a recurrent DVT or recurrent PE event, IC bleed, non-IC major bleed, CRNM bleed, CTEPH, treatment discontinuation or death. A constant proportion of patients within the DVT health states were assumed to experience PTS.

The possible patient routes through the model are as displayed in Figure 3 and the Markov model health states are described in Table 37.

The model was developed in Microsoft Excel. It uses a 3-month cycle length, includes a half-cycle correction and the time horizon is up to 65 years. Health effects are measured in quality adjusted life years (QALYs). The company reports that their modelling approach is consistent with the approach adopted in earlier rivaroxaban NICE submissions (TA261 and TA287).[23,24]

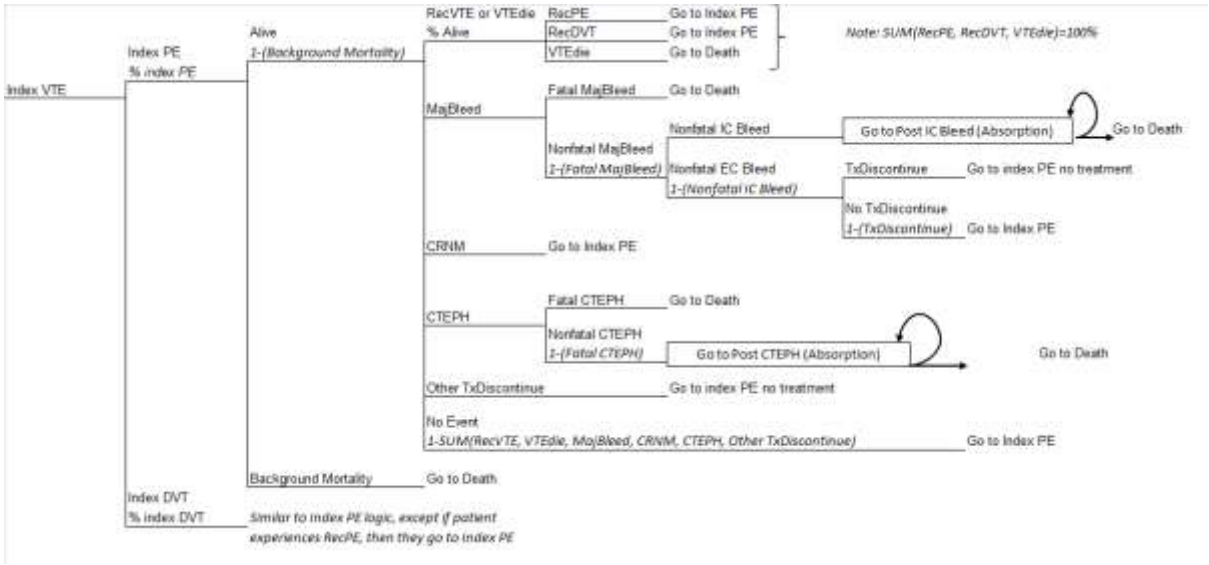

Figure 3 Schematic of company's model

CRNM bleed=clinically relevant non-major bleed; CTEPH=chronic thromboembolic pulmonary hypertension; DVT=deep vein thrombosis; IC=intracranial; MajBleed=major bleed; PE=pulmonary embolism; RecDVT=recurrent deep vein thrombosis; RecPE=recurrent pulmonary embolism; RecVTE=recurrent venous thromboembolism; TxDiscontinue=treatment discontinuation; VTE=venous thromboembolism; VTEdie=death from venous thromboembolis

Source: CS,[1] Figure 26

Table 37 Markov model health states

Health state	Description
Index PE	Patients who enter the model having experienced an index PE event or who entered with an index DVT event and subsequently experienced a recurrent symptomatic PE event.
Index DVT	Patients who enter the model having experienced an index DVT event.
Recurrent PE	Patients who experience a non-fatal recurrent symptomatic PE enter this state for one cycle length before moving to the index PE health state.
Recurrent DVT	Patients who experience a non-fatal recurrent symptomatic DVT enter this state for one cycle length before moving back to the index VTE health state they were in before the recurrent event.
CTEPH	Patients who experience non-fatal CTEPH transition to a semi-absorbing post CTEPH health state and remain in this state unless they die.
IC bleed	Patients who experience a non-fatal IC bleed transition to a semi-absorbing post IC bleed health state and remain in this state unless they die.
Non-IC major bleed	Patients who experience a non-fatal non-IC major bleed transition to this transient health state, where they incur a disutility and acute care costs. Patients remaining on their current anticoagulation return to the index VTE health state. Patients discontinuing treatment transition to either the second-line VTE health state (sensitivity analysis) or the off treatment VTE health state (base case analysis).
CRNM bleed	Patients who experience a CRNM bleed transition to this transient health state, incurring a disutility and acute care costs. Patients transition back to the index VTE health state.
PE second-line treatment	In the base case, patients who discontinue first-line treatment move directly to the off treatment health states. In sensitivity analyses patients who discontinue first-line treatment are able to move to the second-line treatment health states. The events modelled in the second-line treatment health states are identical to those in the first-line health states.
DVT second-line treatment	
PE off treatment	Patients originating from the index PE health state enter this health state after permanently discontinuing treatment. The events modelled in this health state are identical to the first- and second-line treatment health states without the option for further treatment switching.
DVT off treatment	Patients originating from the index DVT health state enter this health state after permanently discontinuing treatment. The events modelled in this health state are identical to the first- and second-line treatment health states without the option for further treatment switching.
Death	Patients enter the death state due to background mortality, death due to a recurrent symptomatic VTE event, fatal major bleeding, or fatal CTEPH.

CRNM= clinically relevant non-major; CTEPH= chronic thromboembolic pulmonary hypertension; DVT= deep vein thrombosis; IC=intracranial; PE=pulmonary embolism; VTE=venous thromboembolism
Source: CS,[1] Table 54

The model considers two scenarios: 6-month treatment duration and lifelong treatment duration. The company reports that these durations were chosen on the basis of advice from experts that was included in NICE CG144[20] and because the majority of NOAC trials report at these timepoints. The company recognised that some patients may only require 3 months of treatment and so a 3-month treatment period was considered in a scenario analysis.

5.4.3 Population

The company states that the base-case population reflects the licensed population, i.e. patients who require anticoagulation for treatment of an index VTE event up to 6 months and subsequent lifelong therapy for the prevention of recurrent VTE events. Specifically, and

based on the AMPLIFY[36] trial population, the population included in the economic analyses comprises [redacted] female, [redacted] males, patients are assumed to weigh 84.6kg and be [redacted] years of age. Patients enter the model having experienced either an index PE ([redacted]) or an index DVT ([redacted]).[36]

5.4.4 Interventions and comparators

The company's base-case economic evaluation compares treatment with apixaban with the current standard of care (LMWH/VKA) as well as with rivaroxaban and with LMWH/dabigatran. The interventions are implemented in the model in accordance with their UK marketing authorisations and doses (Table 38).

Table 38 Daily treatment schedule for the drugs considered in the economic analyses

	Induction length	Induction length concomitant LMWH	Induction dose	Long-term dose (post induction to 6 months)	Extended dose (beyond 6 months)
Apixaban	7 days		20mg	10mg	5mg
Rivaroxaban	21 days		30mg	20mg	20mg
Dabigatran	5 days	5.00 days	N/A	300mg	300mg
VKA (LMWH regimen)	7.64 days	7.64 days	6mg	6mg	6mg
LMWH monotherapy	91 days		1.5mg/kg	1.5mg/kg	1.5mg/kg
Aspirin					100mg

LMWH=low molecular weight heparin; VKA=vitamin K antagonist
Source: Company model[1]

5.4.5 Perspective, time horizon and discounting

The company states that the economic evaluation is undertaken from the perspective of the NHS and Personal Social Services. The model considers a period of up to a maximum of 65 years. Both costs and outcomes are discounted at 3.5% in line with the NICE Methods Guide to Technology Appraisal.[42]

5.4.6 Treatment effectiveness and extrapolation

A description of each of the health states in the company's Markov model is included in the CS[1] and reproduced in Table 37 of this ERG report.

Risks of clinical events for patients treated with apixaban or LMWH/VKA in the first 6 months were derived from the AMPLIFY[36] trial; whilst risks for patients treated with apixaban or who receive no treatment after the initial 6-month period were derived from AMPLIFY-EXT.[37] Risks for all efficacy endpoints were derived from analyses of ITT data; whilst risks for safety endpoints (i.e. bleeding) were derived from analysing data relating to the treated population.

For all other NOACs (rivaroxaban, LMWH/dabigatran, VKA and aspirin), RRs for efficacy and AEs, were generated by the company's two NMAs.[1] The calculated RRs were applied to absolute risks extracted from AMPLIFY[36] and AMPLIFY-EXT[37] trial data. Absolute and RRs for recurrent VTE and VTE related death are presented in Table 39 and Table 40 whilst those for major bleeding are presented in Table 41 and Table 42. Based on a pooled analysis of randomised trials of patients who received anticoagulant therapy for 6 months,[69] the base-case assumption was that 13.46% of major bleeds would be fatal and, of the remaining non-fatal bleeds, 13.97% would be IC bleeds. The proportion of non-IC major bleeds was calculated as the remainder of non-fatal major bleeds that were not IC bleeds.

Table 39 Absolute risks for recurrent VTE and VTE-related death

6-month treatment duration	**Apixaban (95% CI)**	**LMWH/VKA (95% CI)**
0–3 months	[redacted]	[redacted]
3–6 months	[redacted]	[redacted]
Lifelong treatment duration	**Apixaban (95% CI)**	**Placebo (95% CI)**
6–9 months	[redacted]	[redacted]
9–12 months	[redacted]	[redacted]
12–15 months	[redacted]	[redacted]
15–18 months	[redacted]	[redacted]

CI=confidence Interval; LMWH=low molecular weight heparin; VKA=vitamin K antagonist
Source: CS,[1] Table 57

Table 40 Relative risks of recurrent VTE or VTE-related death

	6-month treatment duration[a]		**Lifelong treatment duration[b]**	
	RR vs apixaban	**95% CI**	**RR vs apixaban**	**95% CI**
LMWH/VKA	[redacted]	[redacted]	[redacted]	[redacted]
Rivaroxaban	1.08[d]	0.69 to 1.69[d]	[redacted]	[redacted]
LMWH/dabigatran	1.31[70]	0.79 to 2.16[70]	[redacted]	[redacted]
No treatment*	[redacted]	[redacted]	[redacted]	[redacted]
Aspirin[c]	[redacted]	[redacted]	[redacted]	[redacted]

CI=confidence Interval; LMWH=low molecular weight heparin; RR=relative risk; VKA=vitamin K antagonist
a NMA1
b NMA2
c 6-month relative risk used only for second-line treatment
Source CS,[1] Table 58

Table 41 Event rates for major bleeding

6-month treatment duration	Apixaban (95% CI)	LMWH/VKA (95% CI)
Event rate (95% CI)		
0–3 months	[redacted]	[redacted]
3–6 months	[redacted]	[redacted]
Lifelong treatment duration	**Apixaban (95% CI)**	**Placebo (95% CI)**
>6 months	[redacted]	[redacted]

CI=confidence Interval; LMWH=low molecular weight heparin; RR=relative risk; VKA=vitamin K antagonist
Source: CS,[1] Table 61

Table 42 Relative risks of major bleeds

	6-month treatment duration[a]		Lifelong treatment duration[b]	
	RR vs apixaban	(95% CI)	RR vs apixaban	(95% CI)
LMWH/VKA	[redacted]	[redacted]	[redacted]	[redacted]
Rivaroxaban	1.83[†]	0.92 to 3.76[†]	[redacted]	[redacted]
LMWH/dabigatran	2.51[70]	1.23 to 5.34[70†]	[redacted]	[redacted]
No treatment*	[redacted]	[redacted]	[redacted]	[redacted]
Aspirin	[redacted]	[redacted]	[redacted]	[redacted]

CI=confidence Interval; LMWH=low molecular weight heparin; RR=relative risk; VKA=vitamin K antagonist
a NMA1
b NMA2
c 6-month relative risk used only for second-line treatment
Source CS,[1] Table 61

A constant risk of CTEPH was applied in the model following a PE event. The model also assumed a constant prevalence of severe PTS amongst patients with DVT. The company notes that this is a simplified approach similar to that used in the rivaroxaban model[23,24] and is likely to underestimate patient risk in the first 5 years but overestimate it thereafter.

Details of the risks for CRNM bleeding and severe PTS are provided in the CS[1] (pp156-7).

Treatment discontinuation

Treatment discontinuation related assumptions used in the model following bleeding events were as follows:

- CRNM bleed - treatment interrupted for 2 days
- IC bleed - treatment discontinued treatment permanently
- non-IC major bleed - [redacted] of patients discontinued treatment permanently. Remainder interrupted treatment for 14 days

In the base case, the event rate for treatment discontinuation unrelated to the modelled events was obtained from the AMPLIFY[36] and AMPLIFY-EXT[37] trials for apixaban and LMWH/VKA. For the other model comparators, discontinuation rates for events unrelated to modelled events were obtained from the two NMAs carried out by the company.

Risks of recurrent VTE and bleed events in patients who had discontinued treatment (i.e. those in the post-CTEPH and post-IC health states) were based on data from the placebo arm of the AMPLIFY-EXT[37] trial. The risks of recurrent VTE events beyond the end of the AMPLIFY-EXT[37] trial were based on those reported in a prospective cohort study.[4]

Other deaths

In the base case, deaths from causes unrelated to VTE recurrences, VTE complications or bleeding were modelled as age- and sex-dependent background general mortality rates based on data from the Office of National Statistics 2010-2012.[71] These background rates were adjusted by a hazard ratio (4.41 [95% CI 3.63 to 5.36])[72] to reflect the excess mortality associated with a diagnosis of VTE. The risk of death was assumed to be equal across treatments. However, patients entering the non-fatal IC bleed and CTEPH semi-absorbing health states were modelled as having a higher risk of mortality, HR 2.6 (95% CI 2.2 to 3.0)[73] and HR 1.3 (95% CI 0.98 to 1.73)[74] respectively

Health related quality of life

No HRQoL data were collected in either the AMPLIFY[36] or AMPLIFY-EXT[37] trials. In the model a baseline utility (0.825) was applied to all patients. The company reports that this figure was based on a UK population-average score from Kind et al[75] and was updated upon the occurrence of an IC bleed and CTEPH (permanent changes). In addition, utility decrements were added to the baseline utility for PE, DVT, non-IC major bleed, CRNM bleed or severe PTS events. Model utility scores for baseline, IC bleed, and CTEPH are presented in .

Table 43 and utility decrements associated with clinical events and those associated with the use of anticoagulants are presented in Table 44.

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Table 43 Summary of model quality of life values for baseline, IC bleed and CTEPH

Utility scores for baseline, IC bleed, and CTEPH	Utility score	Utility measurement	Source	Duration	Source
Baseline utility	0.8224	EQ-5D	Kind et al1998[75] (NICE TA261;[23] NICE TA287[24])		
IC bleed					
Acute care period	0.33	TTO	Locadia et al 2004[76] (NICE TA261;[23] NICE TA287[24])	91 days	Locadia et al 2004[76]
Post-acute care	0.61	EQ-5D	Pickard et al 2004;[77] (NICE TA287[24])	Beyond 91 days	
CTEPH					
Acute care period	0.65	EQ-5D	Ghofrani et al 2013[78]	30 days	Ghofrani et al 2013[78]
Post-acute care	0.65			Beyond 30 days	

AC=anticoagulant; CRNM=clinically relevant non-major; CTEPH=chronic thromboembolic pulmonary hypertension; DVT=deep vein thrombosis; IC=intracranial; LMWH=low molecular weight heparin; PE=pulmonary embolism; PTS=post-thrombotic syndrome; SG=standard gamble; TTO=time trade-off; VKA=vitamin K antagonist
Source: CS[1] Table 67

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Table 44 Model utility decrements associated with clinical events and use of anticoagulants

Utility decrements associated with clinical events and use of ACs	Utility decrement	Utility measurement	Source	Duration	Source
PE	-0.32	TTO	Locadia et al 2004[76] (NICE TA261[23]; NICE TA287[24])	30 days	Hogg et al 2013[79]
DVT	-0.11				
Bleeding					
Major non-IC bleed	-0.30	TTO	Locadia et al 2004[76] (NICE TA261[23]; NICE TA287[24])	30 days	Expert opinion
CRNM bleed	-0.0054	EQ-5D	Sullivan et al 2011[80]	2 days	Dorian et al 2014[81]
Severe PTS	-0.07	SG	Lenert et al 1997[82] (NICE TA261;[23] NICE TA287[24])	Throughout	Lenert et al 1997[82]
Anticoagulation					
Apixaban	-0.002	TTO	Gage et al 1996[83]	Whilst on treatment	Gage et al 1996[83]
Rivaroxaban	-0.002				
LMWH/dabigatran	-0.002				
LMWH/VKA	-0.013				
Aspirin	-0.002				

AC=anticoagulant; CRNM=clinically relevant non-major; CTEPH=chronic thromboembolic pulmonary hypertension; DVT=deep vein thrombosis; IC=intracranial; LMWH=low molecular weight heparin; PE=pulmonary embolism; PTS=post-thrombotic syndrome; SG=standard gamble; TTO=time trade-off; VKA=vitamin K antagonist
Source: CS,[1] Table 67

5.4.7 Resources and costs

Drug acquisition costs

A summary of the modelled daily drug costs for each comparator can be found in Table 45.

It is noted in the CS[1] that enoxaparin is the most widely used LMWH in England and Wales for VTE treatment and that, therefore, this drug was used in the model to represent LMWH treatment. However, the dose used in the AMPLIFY[36] trial was 2mg/kg whereas the recommended dose in the UK is 1mg/kg. The lower (UK) dose has been used by the company in their model.

Table 45 Daily drug costs used in the company model

	Unit size	Unit cost	Daily cost (induction)	Daily cost long-term (post induction to 6 months)	Daily cost extended period (beyond 6 months)
Apixaban[84]	2.5mg	£1.10	£4.40	£2.20	£2.20
	5mg				
Rivaroxaban[84]	15mg	£2.10	£4.20	£2.10	£2.10
	20mg				
Dabigatran[84]	150mg	£1.10		£2.20	£2.20
LMWH[a84]	300mg	£21.33	£9.02		
VKA[b85]	6mg	£0.009	£0.009	£0.009	£0.009
Aspirin[c85]	75mg	£0.004			£0.005

LMWH=low molecular weight heparin; VKA=vitamin K antagonist
* See Table 38
a Multi-dose vial
b 5mg and 1mg unit prices added
c 75mg gastroresistant packsize 56
Source: Company model[1]

Administration and monitoring costs

Within the model it is assumed that 92% of patients taking LMWH would self-inject and the remainder would need to be injected by a health professional (note that this assumption was used in previous NICE submissions).[23,24] All patients initiating LMWH were assigned a one-off training cost of £17[86] (based on half an hour spent with a nurse at a GP practice). For those requiring professional administration of the injection a cost, equivalent to 15.5 minutes contact with a nurse at a GP practice (£8.78),[86] was applied. These costs were only applied to the proportion of patients treated as outpatients for index and recurrent events – it was assumed that costs for inpatients would be included in hospital charges.

The model includes a number of assumptions relating to who carries out the INR monitoring and where it is carried out (GP or a nurse in the primary care setting, or in the secondary care setting). It was assumed that six monitoring visits would be required in the first 3

months followed by three visits every 3 months.[87] The resulting annual cost of monitoring in the first year of the model was £319.19 with the cost in subsequent years being £252.52.

No other administration or monitoring costs were included in the model.

Health state costs

The cost of treating VTE was included in the model. Events were assumed to be treated in the outpatient setting for 69% of DVT patients and 17% of PE patients, with the remainder being treated as inpatients. This assumption is in line with that used in the rivaroxaban NICE submissions.[23,24] The cost of treating PE was estimated as £1,525.72 and the cost of treating DVT was estimated as £747.18. These costs were calculated using NHS Reference Costs (2012-13) (Codes DZ09D-DZ09H).[88]

Resource use in the outpatient setting wasobtained from earlier economic evaluations [23,24] which, in turn, were based on NICE Clinical Guideline 92.[3] Costs were extracted from NHS Reference Costs (2012-13),[88] except for the cost of D-dimer test which was obtained from the TA287).[24] Treatment for a DVT event was assumed to comprise a Doppler ultrasound, a D-dimer test, and an emergency room visit (total £194.93). The cost of treating a PE event was assumed to comprise a computer tomography pulmonary angiogram (CTPA), a chest X-ray, an echocardiogram, a D-dimer test and an emergency room visit (total £323.94).

Adverse events costs

The costs of AEs are summarised in Table 46 and Table 47 for the 6-month and lifelong treatment models respectively. In the case of non-fatal bleeds and CTEPH, maintenance costs were applied until death. Based on information in NICE Clinical Guideline 92,[3] treating an acute CTEPH event was assumed to include a chest x-ray, lung function test, walk test, ECG, echocardiogram, blood tests, CT lung scan and right-heart catheter study. In addition, 9.6% of patients received a pulmonary endocarterectomy (PEA).

In line with previous NICE submissions,[23,24] two different maintenance costs were specified for IC bleed, one for the first 3 months after the acute event (14 days of stroke rehabilitation) and one for subsequent 3-month periods.[89]

In TA261[23] the cost of severe PTS was assumed to comprise three vascular surgery outpatient visits in the first year and two GP visits annually thereafter.[90] In the company's model PTS has the potential to occur in PE patients who have a recurrent DVT but the Markov structure of the model makes it impossible to track the incidence of PTS in the first year. However, the company has shown the results to be robust to varying the cost of PTS in one-way sensitivity analyses.

Table 46 Adverse events costs (acute)

	Cost	Lower interval	Upper interval	NHS Reference Costs[88] codes
Semi-absorbing health states				
IC bleed	£2,589.48	£1,689.11	£3,154.86	Codes AA23C-AA23G. Elective, non-elective, regular day or night admissions, day cases
CTEPH	£1,251.46	£1,009.08	£1,426.56	Codes AA23C-AA23G. Elective, non-elective, regular day or night admissions, day cases Codes DAPF, DZ45Z, DZ32Z, EA47Z, RA60A, DAPS05, RA10Z, EA36H, REHABL1-3 admitted patient care and other
Transient health states				
Non-IC major bleed	£1,064.08	£802.21	£1,239.77	Codes FZ38G-H, FZ38J-N, FZ38P, FZ24G-H and FZ24J
CRNM bleed	£137.81	£119.17	£152.66	Code VB07Z
Fatal events				
Fatal major bleed	£2,589.48	£1,689.11	£3,154.86	Codes AA23C-AA23G. Elective, non-elective, regular day or night admissions, day cases
Fatal CTEPH	£1,251.46	£1,009.08	£1,426.56	Assumed to be the same as CTEPH
VTE-related death	£1,525.72	£1,141.53	£1,787.63	Assumed to be the same as non-fatal pulmonary embolism event

CRNM=clinically relevant non-major; CTEPH=chronic thromboembolic pulmonary hypertension; IC=intracranial; VTE=venous thromboembolism Source: CS,[1] Table 76

Table 47 Adverse event costs (maintenance)

	Mean cost	Lower interval	Upper interval	NHS Reference Costs[88] codes
First 3-month cycle following acute care				
IC bleed	£4,692.13	£3,914.32	£5,565.39	National Schedule of Reference Costs Year 2012-2013;[88] VC04Z, RH Assumed 14 days of stroke rehabilitation similarly to TA261.[91]
CTEPH	£4,232.34	£2,962.64	£5,502.04	Advised by experts that the long term maintenance costs would be also be applied in the first 3 months, NICE CG92[3] inflated using PSSRU indices.[86]
Long term (per 3-month cycle)				
IC bleed[c]	£680.53	£478.64	£905.58	Luengo Fernandez et al[89] inflated using PSSRU[86] indices and an exchange rate of 0.64 to convert from US dollars.[86]
CTEPH[d]	£4,232.34	£2,962.64	£5,502.04	NICE CG92[3] inflated using PSSRU indices.[86]
PTS[e]	£188.92	£132.24	£245.60	NICE CG92,[3] as advised by experts.

CTEPH=chronic thromboembolic pulmonary hypertension; IC=intracranial; PTS=post-thrombotic syndrome
Source CS,[1] Table 77

5.4.8 Model validation

The company reports that a number of steps were taken to validate and quality assure the model, namely:

- clinical face validity was established by presenting the initial model concept, the Markov diagram and final model structure to key opinion leaders attending an advisory board
- technical accuracy was determined by carrying out extreme-value sensitivity analyses to check for logical consistency
- two independent external experts undertook a quality check which included validating the logical structure of the model, mathematical formulae, sequences of calculations and the values of model inputs
- predictive validity was checked by comparing key outcomes to the source data

5.4.9 Results included in the company's model

The base-case and incremental cost effectiveness results (6-month treatment duration) generated by the company's economic model are presented in Table 48 and Table 49 respectively. The ICER for apixaban versus LMWH/VKA is estimated by the company to be £2,406 per QALY gained. When compared with either rivaroxaban or LMWH/dabigatran apixaban is dominant.

Table 48 Company's base-case cost effectiveness results for apixaban versus each comparator: 6-month treatment duration

Technolog-ies	Total costs (£)	Total LYG	Total QALY	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£) per LY gained	ICER (£) per QALY gained
Apixaban	£5,034.96	10.323	8.422	-	-	-	-	-
LMWH/VKA	£4,954.94	10.292	8.389	£80.02	0.031	0.033	£2,570	£2,406
Rivaroxaban	£5,069.16	10.311	8.412	-£34.20	0.012	0.010	Dominant	Dominant
LMWH/ dabigatran	£5,100.37	10.293	8.396	-£65.41	0.030	0.026	Dominant	Dominant

Inc=incremental; ICER=incremental cost effectiveness ratio; LMWH=low molecular weight heparin; LY=life year; QALY=quality-adjusted life year; VKA=vitamin K antagonist
Source: CS,[1] Table 80

Table 49 Company's base-case incremental analysis: 6 month treatment duration

Technolog-ies	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£) per LY gained	ICER (£) per QALY gained
LMWH/VKA	£4,954.94	8.389	-	-	-	-
Apixaban	£5,034.96	8.422	£80.02	0.033	£2,405.53	£2,405.53
Rivaroxaban	£5,069.16	8.412	£114.22	0.023	£5,016.99	Dominated
LMWH/ dabigatran	£5,100.37	8.396	£145.43	0.007	£19,782.46	Dominated

Inc=incremental; ICER=incremental cost effectiveness ratio; LMWH=low molecular weight heparin; LY=life year; QALY=quality-adjusted life year; VKA=vitamin K antagonist
Source: CS,[1] Table 81

The base-case and incremental cost effectiveness results (lifelong treatment duration) generated by the company's economic model are presented in Table 50 and Table 51 respectively. The ICER for apixaban versus LMWH/VKA is estimated by the company to be £16,676 per QALY gained, whilst the ICERs per QALY gained for apixaban compared with rivaroxaban and LMWH/dabigatran are £809 and £5,058 per QALY gained respectively.

Table 50 Base-case cost effectiveness results for apixaban versus each comparator: lifelong treatment duration

Technolog -ies	Total costs (£)	Total LYG	Total QALY	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£) per LY gained	ICER (£) per QALY gained
Apixaban	£9,497.37	10.635	8.673	-	-	-	-	-
LMWH/VKA	£6,136.28	10.481	8.472	£3,361.09	0.154	0.201	£21,803	£16,676
Rivaroxaban	£9,013.16	9.981	8.075	£484.21	0.654	0.598	£741	£809
LMWH/ dabigatran	£9,083.28	10.544	8.591	£414.09	0.091	0.082	£4,540	£5,058

Inc=incremental; ICER=incremental cost effectiveness ratio; LMWH=low molecular weight heparin; LY=life year; QALY=quality-adjusted life year; VKA=vitamin K antagonist
Source: CS,[1] Table 83

Table 51 Base case incremental analysis: lifelong treatment duration

Technologi es	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£) per LY gained	ICER (£) per QALY gained
LMWH/VKA	£6,136.28	8.472	-	-	-	-
Rivaroxaban	£9,013.16	8.075	£2,876.88	-0.397	Dominated	Dominated
LMWH/ dabigatran	£9,083.28	8.591	£2,947.00	0.120	£24,621.57	Extendedly dominated
Apixaban	£9,497.37	8.673	£3,361.09	0.202	£16,675.53	£16,675.53

Inc=incremental; ICER=incremental cost effectiveness ratio; LMWH=low molecular weight heparin; LY=life year; QALY=quality-adjusted life year; VKA=vitamin K antagonist
Source: CS,[1] Table 84

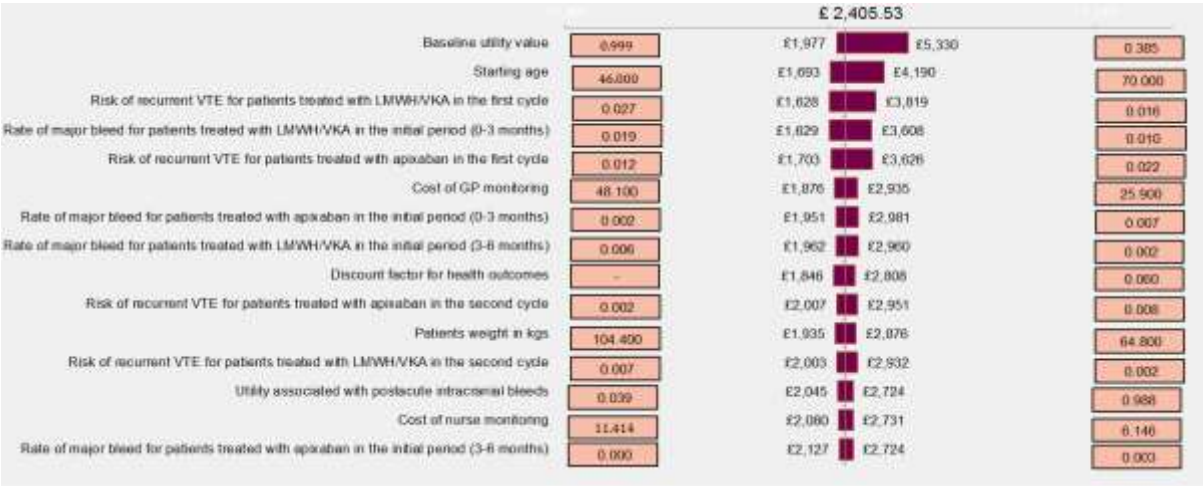
In addition, the company undertook an analysis in which lifelong apixaban treatment was compared with LMWH/VKA for 6 months followed by no treatment for the remaining lifetime. The aim of this analysis was to reflect costs and outcomes for the subgroup of patients who would benefit from lifelong treatment with an anticoagulant but who may not currently be receiving treatment due to bleeding risk; a group for whom there is currently no therapeutic option. The company's model generated an ICER per QALY gained of £17,917 for this analysis.

5.4.10 Sensitivity analyses

Deterministic sensitivity analyses – 6 month treatment period

Univariate deterministic sensitivity analysis was performed by varying each parameter according to the 95% CIs and standard deviations where applicable, while holding all other parameters constant.

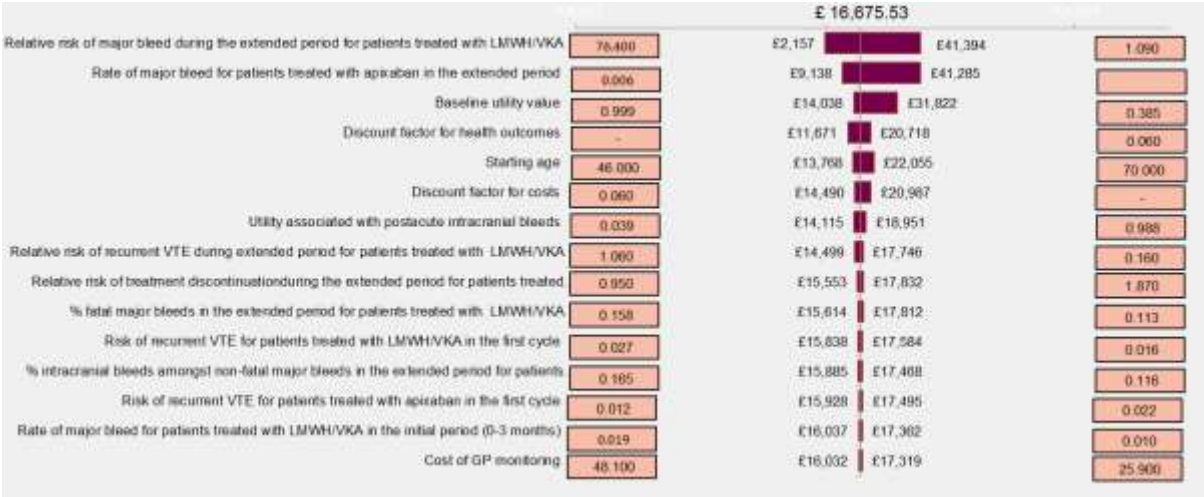
For the 6-month time period, the ICER for the comparison of apixaban vs LMWH/VKA varied between £1,628 and £5,330 per QALY gained (see Figure 4). The highest ICER per QALY gained (£5,330) resulted from decreasing the baseline utility value from 0.825 to 0.385.



Source: CS,[1] Figure 29

Figure 4: Tornado diagram illustrating results from univariate sensitivity analysis for incremental cost per QALY gained vs LMWH/VKA (index VTE, 6-month treatment duration)

For the lifelong treatment period, the ICER per QALY gained for the comparison of apixaban versus LMWH/VKA varied from £2,157 to £41,394 (see Figure 5). The three scenarios resulting in an ICER above £30,000 per QALY gained were: reducing the RR of major bleeding for LMWH/VKA vs apixaban to [redacted] ([redacted] in the base case), setting the risk of major bleeding for apixaban to 0 (i.e. no difference between the two drugs in terms of major bleed outcomes) and reducing the baseline utility value to 0.385



Source: CS,[1] Figure 34

Figure 5: Tornado diagram illustrating results from univariate sensitivity analysis for incremental cost per QALY gained vs LMWH/VKA (index VTE, lifelong treatment duration)

Probabilistic sensitivity analyses

The company undertook probabilistic sensitivity analyses (PSA) to derive the mean ICERs per QALY gained for apixaban vs the three comparators considered in this appraisal (LMWH/VKA, rivaroxaban and LMWH/dabigatran).

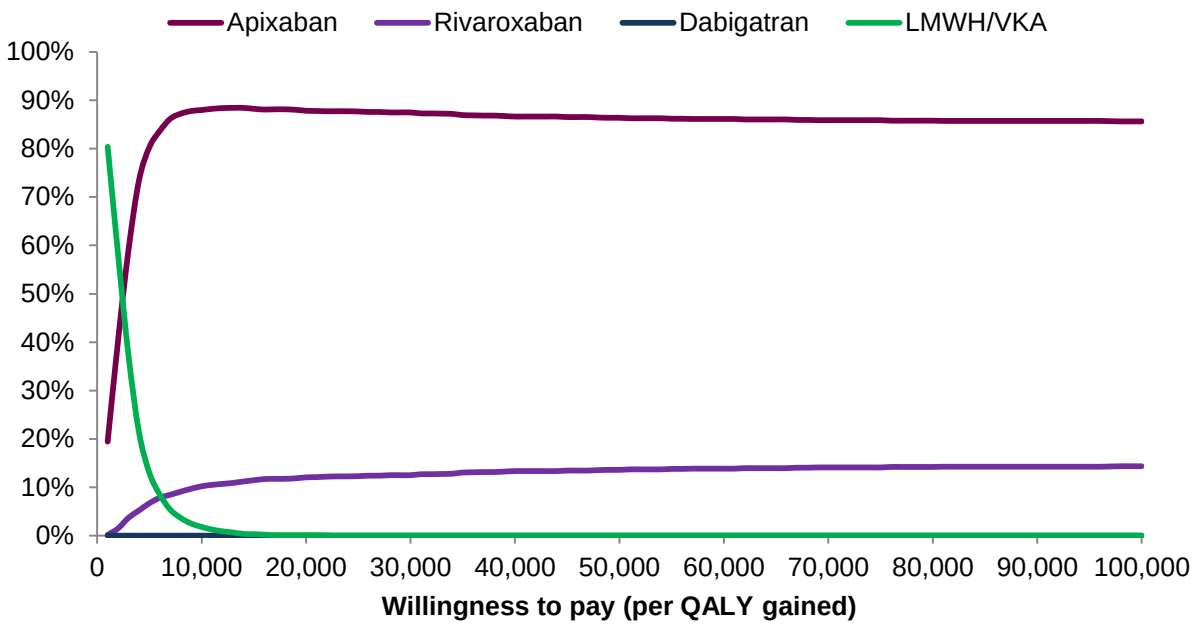
When considering the 6-month time period, the comparison of apixaban versus LMWH/VKA resulted in an ICER of less than £20,000 per QALY gained in 100% of runs. When considering the lifelong time period, this comparison was shown to be 54% cost effective at a threshold of £20,000 and 77% cost effective at a threshold of £30,000. Results for all comparisons are shown in Table 52 with cost effectiveness acceptability curves displayed in Figure 41

Figure 6 and Figure 7.

Table 52 Proportion of runs resulting in which the comparison resulted in apixaban being cost effective

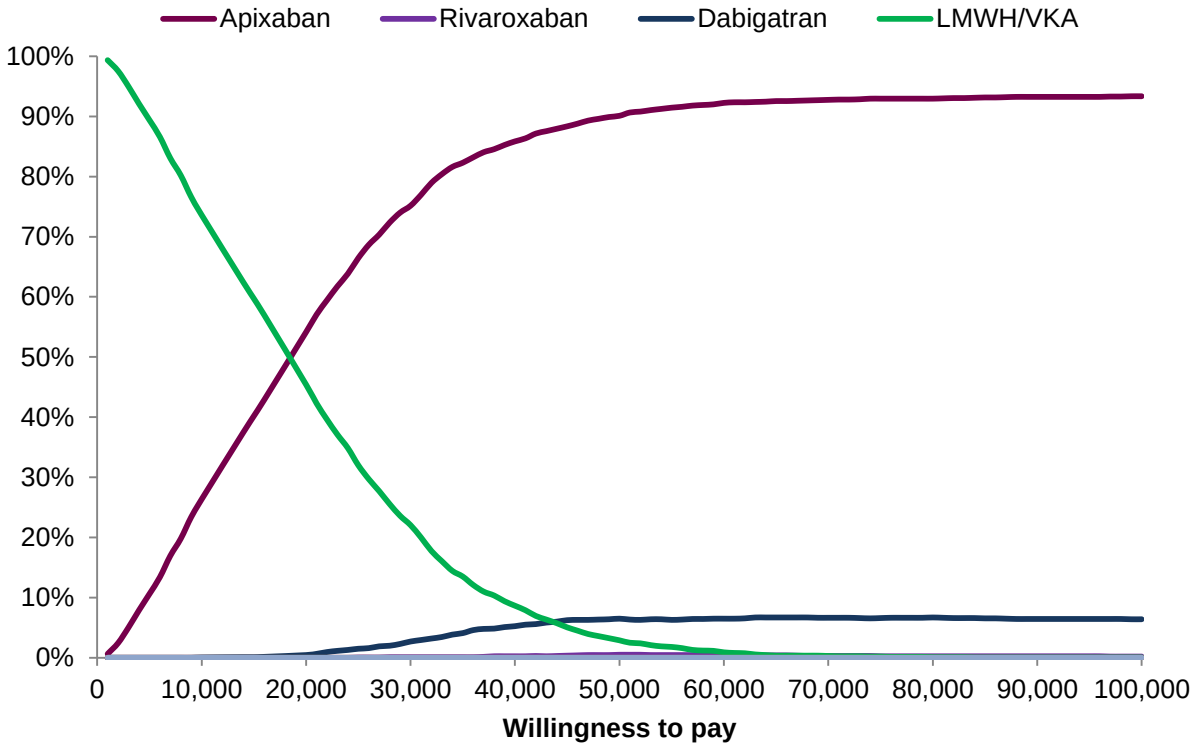
	6-month treatment	Lifelong treatment	
	ICER per QALY gained threshold		
	< £20,000	<£20,000	< £30,000
LMWH/VKA	100%	54%	77%
Rivaroxaban	85%	96%	98%
LMWH/dabigatran	98%	86%	89%

ICER=incremental cost effectiveness ratio; LMWH=low molecular weight heparin; QALY=quality-adjusted life year
Source: CS,[1]p208



LMWH=low molecular weight heparin; QALY=quality adjusted life year; VKA=vitamin K antagonist
Source: CS[1] Figure 41

Figure 6 Multi-way cost effectiveness acceptability curve, index VTE, 6-month treatment duration



LMWH=low molecular weight heparin; QALY=quality adjusted life year; VKA=vitamin K antagonist
Source: CS[1] Figure 45

Figure 7 Multi-way cost effectiveness acceptability curve, index VTE, lifelong treatment duration

Scenario analyses

The company also undertook 30 different scenario analyses for each of the treatment strategies considered in the base case (i.e. 6-month treatment, lifelong treatment and apixaban versus LMWH/VKA/no treatment for remaining lifetime). The scenario analyses explored how varying factors including distribution/risk of events, utility values, time on treatment, cost of care and population characteristics might affect the results of the economic evaluation. The results of these scenario analyses are displayed in Tables 87 to 93 in the CS.[1]

The company concluded that for all scenario analyses that considered treatment durations of either 3, 6 or 18 months, apixaban was dominant or cost effective at a willingness to pay threshold of £20,000 per QALY gained compared to LMWH/VKA, rivaroxaban and LMWH/dabigatron.

For scenario analyses conducted with a lifelong treatment duration, apixaban was cost effective at a willingness to pay threshold of £20,000 per QALY gained versus LMWH/VKA in all but three scenarios (utility decrements for all treatments set to equal those of VKA, use of a treatment dependent distribution of fatal bleeds and non-fatal IC bleeds and use of lower INR monitoring resource). In addition, apixaban was dominant or cost effective at a willingness to pay threshold of £20,000 per QALY gained in all scenarios when compared to LMWH/VKA, rivaroxaban and LMWH/dabigatran.

5.5 Detailed critique of company's economic model

5.5.1 Model structure and design

Trial populations

The design of the company model includes the initial treatment of the index VTE event for the first 3-6 months, as well as subsequent preventive treatment with apixaban, or no preventive treatment over the remaining lifetime of surviving patients. Model variables are calibrated with data taken from the AMPLIFY[36] and AMPLIFY-EXT[37] clinical trials. This approach to model design is problematic since the populations included in the two trials[36,37] are clearly dissimilar. The recruitment criteria for AMPLIFY-EXT[37] explicitly exclude patients surviving a recurrent VTE event during earlier treatment of their index event. Moreover, only a third of AMPLIFY-EXT[37] patients were recruited from AMPLIFY,[36] of whom, presumably, half had previously received apixaban (i.e. a sixth of the total cohort).

This has implications for modelling the cost effectiveness of long-term preventive treatment with apixaban, since the model begins with a pure AMPLIFY[36] population then applies long-term outcome effectiveness parameters derived from a very mixed population from which all patients surviving a prior recurrent VTE have been excluded. This essential incompatibility of the two parts of the model seriously compromises the results of the long-term preventive assessment of apixaban. The results of the assessment of short-term apixaban treatment may also be called into question if the parameters drawn from AMPLIFY-EXT[37] to represent long-term survival cannot be shown to be relevant to the AMPLIFY[36] population.

Ideally, two distinct decision models should be available, each based exclusively on a single trial; short-term use of apixaban versus comparators using AMPLIFY[36] data, and long-term use of apixaban versus no treatment using AMPLIFY-EXT[37] data. The ERG has devised a model modification (rebase prevention model) to improve the long-term assessment results by effectively excluding the first two 3-month model cycles of the submitted model. This is adequate to reflect the experience of those patients (one-third) who received 6 months initial treatment in the AMPLIFY[36] trial before joining AMPLIFY-EXT[37], but may not give accurate results for other AMPLIFY-EXT[37] patients who may have received active treatment for up to 12 months following their index VTE event.

Age, sex and index event

The submitted model uses a Markov state-transition structure to project the expected experience of a mixed cohort of male and female patients of varying ages (18-99 in the AMPLIFY[36] clinical trial) and who may have experienced either an index DVT alone or an

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index PE with or without DVT. In general, differences in age or sex are not taken into account in any of the main model parameters, other than through the use of UK national life tables to represent background (i.e. all other causes) mortality through calculation of a weighted average age-specific mortality rate. Unfortunately this is inaccurately calculated since the overall sex ratio of any incident cohort varies over time (mortality rates for females being lower than those for males) so that an incident cohort of 20 year olds with [redacted] males will contain only 31.1% males at 100 years of age. As a consequence, a simple weighted cohort averaging of age-specific mortality rates over a whole lifetime leads to an over-estimation of cohort mortality rates by up to 4% per annum.

Ideally, the model should be constructed with multiple age/sex/VTE type specific parallel models aggregated to an overall result. However, the existing model can be used to assess the impact of including the age/sex/VTE type population structure on the estimated ICERs by carrying out multiple runs of the model for separate age/sex/VTE type subgroups of the AMPLIFY[36] trial population, and then creating an overall weighted average result. Since the submitted model systematically overestimates mortality rates, taking account of age and sex tends to increase slightly the gains in both survival and QALYs.

When preventive apixaban is compared with LMWH/VKA the base-case long-term ICER reduces from £16,676 to £15,137 per QALY gained. Similarly, the ICER for apixaban versus rivaroxaban reduces from £809 to £627 per QALY gained, and the ICER for apixaban versus dabigatran reduces from £5,058 to £4,441 per QALY gained. By contrast, when only short-term apixaban use is assessed versus LMWH/VKA, the ICER increases from £2,406 to £2,454 per QALY gained.

In principle, other model parameters should also be differentiated by age and/or sex as well as by type of index VTE event. However, the data to carry out these refinements are not currently available to the ERG.

Recurrent VTE events

The model structure adopted by the company incorporates features intended to avoid complexity and duplication of features when projecting patients' long-term experience. The methods employed incorporate implicit assumptions which warrant careful examination.

At first sight two distinct populations are represented by parallel sub-models of very similar structure which distinguish between patients by their index event (PE+/-DVT versus DVT only). However, these sub-models are in fact linked; it is assumed that experiencing a PE event at any time has more serious consequences than experiencing a DVT event. To reflect this assumption, index DVT patients who suffer a subsequent PE event are removed from the DVT sub-model and permanently transferred to the PE sub-model. However, index PE patients suffering any number of subsequent DVT events remain in the PE sub-model indefinitely. Therefore, over time there is a steady transfer of patients between the separate cohorts, a factor which must be carefully considered when interpreting model results.

A closely related feature of the company model is that any patient who suffers a non-fatal VTE event without permanent AEs (i.e. bleeding, PTS or CTEPH) is returned to the pool of index PE or DVT patients after one cycle of event-related treatment. This implicitly assumes that the risk of a first recurrent VTE event is the same as the conditional risk of experiencing a second or third VTE event. No evidence is offered in support of this assumption. Published evidence of recurrence risks with long-term follow-up is rare. However, in 1995 Beyth and colleagues[92] reported on 6 to 8 years follow-up of 124 DVT patients to ascertain the incidence of recurrent VTE events and mortality. Of the 124 patients, 18 (14.5%) suffered a first recurrent event (15 DVT and 3 PE), but six of these (33.3%) suffered at least one subsequent VTE event. The RR of second recurrence, compared with first recurrent, therefore increased significantly (RR 2.1, p=0.02). This finding was supported by the authors' Cox proportional hazards modelling that indicated that the risk of a first recurrence was significantly related to a baseline prior history of VTE (relative hazard 2.9, p=0.03).

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The natural consequence of the company model design is, therefore, that long-term estimates of future VTE events (including deaths) will be increasingly underestimated, resulting in understated event costs and disutilities, and overestimated cohort survival. The company acknowledges this limitation in their model and considers that its effect is to understate the advantage from apixaban treatment through reduced risk of bleeding events. The ERG recognises this argument in relation to long-term apixaban treatment, but considers it of limited applicability to the assessment of short-term apixaban use. However, there is no obvious model modification available to the ERG that would correct this important

weakness in model structure; the only reliable approach would be to redesign the model completely to incorporate progressively increasing VTE recurrence rates by introducing several additional patient states for those experiencing second and subsequent recurrent events.

5.5.2 Long-term mortality rates

In the submitted model, background mortality is applied to reflect deaths due to all causes other than VTE-related events as a function of age and gender. Based on a study describing the survival of patients suffering venous embolism by Flinterman et al,[72] a single overall risk ratio has been estimated by the ERG and applied to uplift all general population mortality risks irrespective of age and gender, to reflect increased mortality risks from causes unrelated to VTE.

However, this does not take into account the fact that the risks of recurrent VTE events and of mortality from all causes increase progressively with each additional VTE event. A paper by Klok et al[93] compared outcomes for PE and non-PE patients for up to 5.5 years. This showed that in the long-term (3+ years) mortality rates in all patients increased and accelerated over time. Patients with PE showed higher mortality rates than non-PE patients, and the long-term mortality hazard ratio (PE versus non-PE) increased by 2.7% per year.

Beyth et al[92] reported an analysis of mortality in non-cancer DVT patients indicating a statistically significant higher long-term mortality risk for patients aged 75 years or over, and for those with prior history of stroke (long-term hazard ratio 5.4). In addition, the long-term risk of recurrent VTE was three times greater for patients younger than 65 years who had a previous history of VTE.

Also, stroke and IC haemorrhage events can result in the development or worsening of disability, which is known to be associated with increased subsequent mortality. In the NICE appraisal of clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of Technology Appraisal No. 90[94]) it was found that risks of all types of stroke, MIs, other vascular deaths and non-vascular deaths (i.e. background deaths) increased with age, and were also increased if the patient had suffered prior serious stroke-related disability (modified Rankin score 3+). The risk of suffering a new haemorrhagic stroke multiplied by 1.93 due to existing disability, and the risk of non-vascular death multiplied by 1.87. In addition, it was found that the odds ratio for fatality from MI and stroke events increased by 2.44 for a second event and by 5.56 for a third event. There is,

Page superseded by erratum

therefore, good reason to expect that the RR risk applied to standard life-table mortality risks may increase over time as additional VTE events accumulate among the 'at risk' population.

The impact on the model of increasing recurrent event incidence, fatality rates and general mortality rates over time would be to increase the net cost of further events while also reducing the average survival estimates in both trial arms and thereby proportionately reducing the estimated survival gain and incremental QALYs attributable to treatment with apixaban. The net effect on cost effectiveness of incorporating these time-varying risk parameters into the submitted economic model is difficult to anticipate without much more detailed analysis of the AMPLIFY[36] and AMPLIFY-EXT[37] trial data together with data from longer-term trials of apixaban and comparator products.

Page superseded by erratum

5.5.3 Treatment costs

The cost of anti-thromboembolic therapies is calculated in the company's model for each 3-month cycle based on the average number of patients alive and on treatment during the cycle (i.e. the number of patients incurring costs is estimated as the average of those patients on treatment at the beginning of the cycle and those remaining on treatment at the end of the cycle). This method of calculation is inaccurate for both the first cycle and for subsequent cycles.

The first cycle cost includes the initial treatment of the DVT/PE event which generally lasts only a few days (5, 7-8 or a maximum of 21 days); all VTE patients entering the model incur this cost in full. After this initial phase, patients move to continuing therapy for the rest of the first cycle, using prescribed medication sufficient to treat them for the remainder of the first cycle. However, the company's model assumes that those patients discontinuing treatment at any time during the first cycle incur this cost only for half a cycle. The ERG considers that this understates the true cost since oral medications prescribed early in the cycle cannot be returned and must be discarded. The cost incurred for treatment in the first 3 months is more accurately estimated using the full number of patients who begin treatment.

For second and subsequent cycles of extended treatment, the ERG considers it reasonable to assume that all patients remaining on long-term medication would receive repeat prescriptions quarterly. The only exception would be for patients receiving LMWH monotherapy who require regular injections. In this case it would be more appropriate to calculate medication and administration costs averaged across each cycle (including the first cycle).

Applying these model modifications produces small increases in the long-term base-case ICER for apixaban versus LMWH/VKA or LMWH monotherapy (+£367 or +£79 per QALY gained) and small reductions in the ICER for apixaban versus rivaroxaban or dabigatran (-£9 or -£49 per QALY gained respectively).

5.5.4 Population utility values

The company model provides two options for applying population EQ-5D utility values to the cohort of patients:

- in the base-case analysis, a single average EQ-5D value is used for all patients and is considered static over time (i.e. patients surviving until age 100 years are still accorded the same utility value as at any earlier age)
- alternatively, five EQ-5D values are used to represent the utility experienced by all patients (males and females combined) within 10 year age-bands from 50-59 up to 90+ years

These values are referenced by the company to an article published by Kind et al[75] in 1998. However, the Kindet al paper[75] does not include any utility values. The original source document for this UK national survey is the Centre for Health Economics (CHE) Discussion Paper 172[95] published in 1999. Table A in that document provides mean EQ-5D index values by sex and for seven 10-year age bands (under 25, 25-34 up to 65-74, and 75+ years), together with the standard deviation and responder count in each category.

There are two important differences between the utility parameter values in the company model and the original source document:

- the mean values do not match those published, and are ascribed to different age-bands
- the standard error figures in the company model are in fact standard deviations

The consequence of these errors is that mean utility values are incorrect, having been attributed to patients at the wrong ages, and also that the uncertainty associated with these utility parameters are seriously overstated (by more than 17 times in individual age-bands, and by 58 times for the overall utility estimate) calling into question the results of the PSA. These same errors apply even when only a single overall utility value is applied independent of age. The model results are further flawed by failing to recognise that mean utility in the general population decreases significantly over a lifetime.

The ERG has considered four possible options for estimating the value for the population utility:

1) The company model fixed mean value (0.825)
2) A fixed mean value consistent with Measurement and Valuation of Health Survey (MVH[95]) values (0.823)
3) The company model age-related values
4) Age-related values consistent with MVH values

The estimated ICER increases steadily as options two, three and four are selected, ranging from the company's long-term base-case result for apixaban versus LMWH/VKA (£16,676 per QALY gained) to £17,516 per QALY gained for option four, the ERG's preferred method.

5.5.5 Discounting method

The submitted model applies discounting at a different rate for every 3-month model cycle based on the time elapsed. By convention in the UK, in line with the use of annual public sector budgets, discounting is applied annually considering the first 12-month period as involving current costs and each subsequent 12-month period requiring discounting for an additional year's delay. In some models with extended survival and multiple future events, the choice of discounting method may have a large impact on the size of the modelled ICERs. However, using annual discounting in the company model for this appraisal has only a minor effect, increasing the estimated long-term base-case ICERs by £0-6 per QALY gained.

5.5.6 Body weight

The cost of LMWH treatment is based on a daily dose of 1.5mg/kg of body weight. In the company model the mean body weight is 84.6kg as reported for the AMPLIFY[36] trial population. However, this is noticeably higher than the mean adult population weight of 77.4kg reported from the Health Survey for England for 2012.[96] Applying this lower value affects treatment costs for all regimens during induction therapy for the index VTE event, and long-term preventive costs where LMWH (monotherapy or with VKA) is used. The base-case estimated ICER for short-term treatment with apixaban versus LMWH/VKA increases from £2,406 to £2,577 per QALY gained. For long-term preventive treatment with apixaban the base-case estimated ICER versus LMWH/VKA increases from £16,676 to £16,704 per QALY gained.

5.5.7 Revised relative risks

The company was asked during the clarification process to undertake alternative NMA calculations for selected model variables (see Clarification letter). These are discussed in detail in Section 4.8 of this ERG report. The resultant RR values estimated by the company for VTE recurrence and related deaths, major bleeding and CRNM have been applied as model revisions by the ERG. However, the ERG has continuing concerns relating to the estimation of RR parameters for major bleeding and CRNM derived from the secondary prevention period NMA. Model results are especially sensitive to these variables, and some parameter estimates in the company's base-case model appear excessively large (e.g. RR of [redacted] for major bleeding for rivaroxaban versus apixaban). As previously discussed, this may be related to the wide range of follow-up periods in the included trials. The ERG carried out two additional analyses using a Poisson assumption (relating risk to the time of follow-up exposure), using Bayesian and non-Bayesian methods (Appendix 7 of this ERG report).

The company's base-case ICER is reliant on the original company model RR parameters. Using the results of the analysis method requested by the ERG in the clarification process and the two Poisson-based methods, a range of alternative parameter value sets are available. The impact of these alternatives on cost effectiveness estimates are compared in Section 6.

5.5.8 Time-to-event analysis and projective model coefficients

The submitted model uses parameter values derived from the AMPLIFY[36] and AMPLIFY-EXT[37] clinical trials to represent the various AEs suffered by VTE patients during the trial follow-up periods (i.e. recurrent VTE events, VTE related fatality, death from other causes, major bleeding events, CRNM events, IC bleeding, CTPH and PTS), as well as treatment duration. The sources for these model parameters are described in the model as "AMPLIFY/AMPLIFY-EXT secondary analysis" but without any supporting information describing the original evidence or the analytic methods used to generate the values used.

As neither the trial publications[36,37] nor the related CSRs[47,52] provide relevant information, the ERG submitted a set of 12 clarification requests for K-M time-to-event analysis relating to the main model variables used to populate the model. The ERG intended to use this information to address three important issues:

- to validate the model parameter values against the original data

Page superseded by erratum

- to assess whether temporal trends in the risk of key events are consistent with the modellers' general assumption that risks evident in the last 3-month cycle of AMPLIFY-EXT[37] follow-up can be projected indefinitely at a constant level
- to formulate alternative projective hazard functions, where varying hazard trends are evident in any of the time-to-event variables, as a basis for providing revised ICER per QALY gained estimates

Of the 12 analyses requested by the ERG, the company supplied only two. The two analyses relate to overall survival and time to treatment discontinuation in the AMPLIFY trial.[36] As the ERG received the analyses 8 days prior to the submission date for the ERG report, the time available for the ERG to assess the data was limited. A brief discussion of the data is presented in this section.

Page superseded by erratum

Time to treatment discontinuation

Examination of the time to treatment discontinuation results by the ERG from the AMPLIFY[36] trial has revealed that an important error has been made in calibrating this feature of the company model. The rate of discontinuation of treatment in the two 3-month cycles of the model has been estimated as though the duration of the trial was 12 months, rather than the true duration of 6 months. As a consequence, the calculated rate used in the model is only half the true rate of discontinuation.

This finding confirms the ERG belief that all similar model parameters should be independently validated against the original trial data. Without access to the requested K-M analyses, it is not possible for the ERG to determine whether or not this calculation error has been repeated across the whole range of time-to-event model variables, rendering the calculated ICERs wholly unreliable.

Time to death from any cause

The ERG has undertaken a preliminary examination of the overall survival K-M results from the AMPLIFY[36] trial (time to death from any cause), focussing attention on the larger index DVT cohort.

It is clear that a survival advantage for apixaban-treated index DVT patients is established in the first few weeks of the trial, which is evidenced by the separation of the two survival curves (Figure 8). However, after a short time the two curves appear to follow a parallel course. Figure 8 also shows a straightforward 2-phase survival model fitted to the trial data, using separate exponential functions for the initial 'separation' period, followed by a common long-term exponential model used in both arms. This can be confirmed by time-shifting the comparator plot forward until the curves cross (arrows on Figure 9). This occurs when a shift of 46 days is used, at which point the long-term trends of the time trial arms are indistinguishable. This shows that the long term survival prognosis is the same beyond this point, indicating that the full mean survival benefit has been established and is preserved thereafter.

Using the area under curve (AUC) method, the advantage up to the point of convergence in Figure 9 is confirmed as 45.8 days. **The company's base-case short-term model results indicate an undiscounted survival advantage for apixaban of only 15.6 days, suggesting that the submitted model is incorrectly calibrated from the AMPLIFY[36] trial data.**

[redacted]

Figure 8 Time to death from any cause – 2-phase model fitted to index DVT data (AMPLIFY trial)

[redacted]

Figure 9 Time to death from any cause – results for index DVT patients (AMPLIFY trial)

5.5.9 Cost effectiveness summary

The ERG has reviewed the decision model submitted by the company and has identified a number of areas of concern:

- The decision problem encompasses two distinct assessments based on results from two clinical trials[36,37] in quite different populations. The model design attempts to encompass both assessments within one structure, despite the evident incompatibility of the two sets of evidence. It is the ERG's view that two separate models should have been developed to avoid compromising either assessment.
- The company acknowledges that no attempt has been made to incorporate the impact of accumulating history of recurrent VTE events through increasing future risks (including background mortality), as is attested in the literature. This is likely to lead to exaggerated estimates of long-term health gains for apixaban.
- The model structure operates on the assumption that all patients begin with the same average age, and that background mortality rates are adequately represented by a simple weighted average of life-table values. The ERG has demonstrated that this is inappropriate and leads to biased results which tend to overstate estimated ICERs per QALY gained.
- In the model, treatment costs have been underestimated, incorrect UK utility values have been employed, and an excessive mean body weight estimate for a UK population has been used.
- The ERG notes that the company's INR monitoring costs are in line with previous NICE appraisals of rivaroxaban[23,24]and dabigatran[25] and do not significantly impact the size of the ERG's estimated ICERs.
- The method used to derive hazard ratios for the long-term secondary preventive treatment period comparisons has been shown to yield unrealistic values in some instances, tending to improve the estimated ICERs per QALY gained in favour of apixaban. Alternative approaches considered by the ERG have been shown to produce very different ICERs per QALY gained in some cases, indicating substantial unresolved uncertainty.
- The company only provided two of the requested 12 time-to-event analyses requested by the ERG. One of these revealed a significant error in calculating the risk of treatment discontinuation, and the other showed a significant difference between survival gain estimated by the model and that shown in the AMPLIFY[36] trial results. The ERG considers that it is likely that other discrepancies and errors

Page superseded by erratum

may remain undetected in the model but this cannot be confirmed without access to the other ten analyses of trial data (from both the AMPLIFY[36] and AMPLIFY-EXT[37] studies) requested by the ERG.

- The derivation of key model parameter values is not transparent (often referenced as 'AMPLIFY/AMPLIFY-EXT secondary analysis'), and substantiating evidence for important assumptions concerning the long-term level of key risk variables has not been provided.
- Results of sensitivity analyses show that the main drivers of cost effectiveness are baseline utility and starting age (6-month model) and baseline utility and risk of major bleed (lifelong model). Starting age should be a parameter for which there is general agreement. The ERG considers that there is uncertainty around the most plausible baseline utility as no HRQOL data were collected during the trials.[36,37]

In summary, the ERG considers that the company model (even with the amendments/corrections proposed by the ERG) does not provide a reliable basis for estimating the relative cost effectiveness of apixaban for the treatment and secondary prevention of DVT and/or PE.

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

The various model amendments and corrections implemented by the ERG to rectify problems described earlier in this report are exemplified in Table 53-59. These feature six specific model changes (R1 to R6) using the ERG preferred alternative parameter values or formulae and three alternative methods of calculating hazard ratios from the secondary prevention period NMA which are presented as incremental changes to the company's base-case analysis (S1 to S3) and as a component of three illustrative scenarios (B to D). The model amendments made by the ERG are described in Appendix 8 of this ERG report.

In addition, the ERG carried out a scenario analysis. The analysis assumes that the three NOACs (rivaroxaban, dabigatran and apixaban) are equally effective and expose patients to equivalent risks of major bleeding and CRNM when used for secondary prevention of recurrent VTE events. This ERG analysis represents an alternative approach to estimating the cost effectiveness of apixaban versus other treatments when used for 3 to 6 months following an index VTE event. The results are shown in Table 60.

It should be noted that the magnitude of individual parameters can have a disproportionate influence on cost effectiveness results; as shown in Table 60, there is a 3-fold difference in the size of the ICER due to a change in a single major bleeding parameter value.

In the absence of the K-M data analysis results requested from the company by the ERG, it is not known whether any of the results reported in Table 53-60 will require major revision in the light of the missing information.

Table 53 Cost effectiveness results for apixaban vs LMWH/VKA with ERG revisions to company's long-term base-case comparison

Model scenarios & ERG revisions	Apixaban			LMWH/VKA			Incremental			ICER	ICER
	Cost	QALYs	Life	Cost	QALYs	Life years	Cost	QALYs	Life	£/QALY	Change
***A.* Company's base-case**	**£9,497**	**8.673**	**14.181**	**£6,136**	**8.472**	**13.942**	**£3,361**	**0.202**	**0.239**	**£16,676**	-
R1. Age/sex modelling	£9,617	8.425	15.243	£6,580	8.224	14.953	£3,038	0.201	0.291	£15,137	**- £1,538**
R2. Treatment costs	£9,576	8.673	14.181	£6.141	8.472	13.942	£3,435	0.202	0.239	£17,043	**+ £368**
R3. Age-varying MVH utility	£9,497	8.294	14.181	£6,136	8.102	13.942	£3,361	0.192	0.239	£17,516	**+ £841**
R4. Discounting method	£9,609	8.785	14.181	£6,204	8.581	13.942	£3,405	0.204	0.239	£16,671	**+ £4**
R5. Body weight	£9,496	8.673	14.181	£6,129	8.472	13.942	£3,367	0.202	0.239	£16,704	**+ £28**
R6. Rebase prevention model	£8,842	8.725	14.265	£5,241	8.538	14.051	£3,601	0.187	0.214	£19,283	**+ £2,607**
S1. HRs requested by ERG	£9,498	8.673	14.181	£6,174	8.449	13.903	£3,324	0.224	0.179	£14,837	**- £1,839**
S2. HRs – ERG Poisson (Bayesian)	£9,498	8.673	14.181	£6,089	8.505	13.999	£3,409	0.169	0.117	£20,227	**+ £3,552**
S3. HRs – ERG Poisson (non-Bayesian)	£9,498	8.673	14.181	£5,993	8.562	14.099	£3,504	0.111	0.053	£31,501	**+ £14,825**
***B.* R1-R6 + S1**	**£9,147**	**8.493**	**15.334**	**£5,797**	**8.282**	**15.017**	**£3,350**	**0.212**	**0.317**	**£15,837**	**- £838**
***C.* R1-R6 + S2**	**£9,147**	**8.493**	**15.334**	**£5,700**	**8,345**	**15.143**	**£3,447**	**0.148**	**0.191**	**£23,224**	**+ £6,549**
***D.* R1-R6 + S3**	**£9,147**	**8.493**	**15.334**	**£5,590**	**8.411**	**15.275**	**£3,557**	**0.083**	**0.059**	**£42,918**	**+ £26,242**

Costs and QALYs discounted; life years undiscounted; HR=hazard ratio; MVH=Measurement and Valuation of Health survey; QALYs=quality adjusted life years

Table 54 Cost effectiveness results for apixaban vs rivaroxaban with ERG revisions to company's long-term base-case comparison

Model scenarios & ERG revisions	Apixaban			Rivaroxaban			Incremental			ICER	ICER
	Cost	QALYs	Life	Cost	QALYs	Life	Cost	QALYs	Life	£/QALY	Change
***A*. Company's base-case**	**£9,497**	**8.673**	**14.181**	**£9,013**	**8.075**	**13.179**	**£484**	**0.598**	**1.002**	**£809**	-
R1. Age/sex modelling	£9,617	8.425	15.243	£9,243	7.827	14.093	£374	0.597	1.150	£627	**- £183**
R2. Treatment costs	£9,576	8.673	14.181	£9,098	8.075	13.179	£479	0.598	1.002	£800	**- £9**
R3. Age-varying MVH utility	£9,497	8.294	14.181	£9,013	7.735	13.179	£484	0.558	1.002	£867	**+ £58**
R4. Discounting method	£9,609	8.785	14.181	£9,119	8.179	13.179	£491	0.606	1.002	£810	**+ £0**
R5. Body weight	£9,496	8.673	14.181	£9,012	8.075	13.179	£484	0.598	1.002	£810	**+ £1**
R6. Rebase prevention model	£8,842	8.725	14.265	£8,261	8.068	13.175	£581	0.657	1.090	£885	**+ £76**
S1. HRs requested by ERG	£9,497	8.673	14.181	£8,261	8.539	13.948	£672	0.134	0.232	£5,025	**+ £4,216**
S2. HRs – ERG Poisson (Bayesian)	£9,497	8.673	14.181	£8,824	8.576	14.010	£674	0.097	0.109	£6,938	**+ £6,129**
S3. HRs – ERG Poisson (non-Bayesian)	£9,497	8.673	14.181	£8,812	8.597	14.045	£685	0.076	0.135	£8,981	**+ £8,171**
***B.* R1-R6 + S1**	**£9,147**	**8.493**	**15.334**	**£8,428**	**8.346**	**15.028**	**£719**	**0.148**	**0.306**	**£4,869**	**+ £4,059**
***C.* R1-R6 + S2**	**£9,147**	**8.493**	**15.334**	**£8,420**	**8.386**	**15.108**	**£727**	**0.107**	**0.226**	**£6,801**	**+ £5,991**
***D.* R1-R6 + S3**	**£9,147**	**8.493**	**15.334**	**£8,405**	**8.410**	**15.153**	**£742**	**0.084**	**0.181**	**£8,875**	**+ £8,066**

Costs and QALYs discounted; life years undiscounted; HR=hazard ratio; MVH=Measurement and Valuation of Health survey; QALY=quality adjusted life years

Table 55 Cost effectiveness results for apixaban vs LMWH/dabigatran with ERG revisions to company's long-term base-case comparison

Model scenarios & ERG revisions	Apixaban			LMWH/dabigatran			Incremental			ICER	ICER
	Cost	QALYs	Life	Cost	QALYs	Life	Cost	QALYs	Life	£/QALY	Change
***A.* Company's base-case**	**£9,497**	**8.673**	**14.181**	**£9,083**	**8.591**	**14.041**	**£414**	**0.082**	**0.140**	**£5,058**	-
R1. Age/sex modelling	£9,617	8.425	15.243	£9,237	8.339	15.070	£379	0.086	0.173	£4,441	**- £617**
R2. Treatment costs	£9,576	8.673	14.181	£9,166	8.591	14.041	£410	0.082	0.140	£5,009	**- £49**
R3. Age-varying MVH utility	£9,497	8.294	14.181	£9,083	8.217	14.041	£414	0.076	0.140	£5,425	**+ £366**
R4. Discounting method	£9,609	8.785	14.181	£9,189	8.702	14.041	£420	0.083	0.140	£5,064	**+ £6**
R5. Body weight	£9,496	8.673	14.181	£9,078	8.591	14.041	£418	0.082	0.140	£5,104	**+ £46**
R6. Rebase prevention model	£8,842	8.725	14.265	£8,378	8.665	14.160	£465	0.060	0.105	£7,758	**+ £2,700**
S1. HRs requested by ERG	£9,498	8.673	14.181	£9,079	8.598	14.052	£419	0.075	0.128	£5,617	**+ £554**
S2. HRs – ERG Poisson (Bayesian)	£9,498	8.673	14.181	£9,078	8.618	14.086	£419	0.055	0.095	£7,624	**+ £2,566**
S3. HRs – ERG Poisson (non-Bayesian)	£9,498	8.673	14.181	£9,075	8.629	14.104	£423	0.044	0.077	£9,532	**+ £4,473**
***B.* R1-R6 + S1**	**£9,147**	**8.493**	**15.334**	**£8,710**	**8.429**	**15.196**	**£437**	**0.064**	**0.138**	**£6,801**	**+ £1,743**
***C.* R1-R6 + S2**	**£9,147**	**8.493**	**15.334**	**£8,707**	**8.452**	**15.241**	**£440**	**0.042**	**0.093**	**£10,573**	**+ £5,515**
***D.* R1-R6 + S3**	**£9,147**	**8.493**	**15.334**	**£8,701**	**8.464**	**15.265**	**£446**	**0.029**	**0.069**	**£15,149**	**+ £10,091**

Costs and QALYs discounted; life years undiscounted; HR=hazard ratio; MVH=Measurement and Valuation of Health survey; QALY=quality adjusted life year

Table 56 Cost effectiveness results for apixaban vs LMWH/VKA followed by no treatment with ERG revisions to company's long-term base-case comparison

Model scenarios & ERG revisions	Apixaban			LMWH/VKA			Incremental			ICER	ICER
	Cost	QALYs	Life	Cost	QALYs	Life	Cost	QALYs	Life	£/QALY	Change
***A.* Company's base-case**	**£9,497**	**8.673**	**14.181**	**£4,892**	**8.416**	**13.720**	**£4,606**	**0.257**	**0.461**	**£17,917**	-
R1. Age/sex modelling	£9,617	8.425	15.243	£5,525	8.158	14.688	£4,092	0.267	0.555	£15,353	**- £2,565**
R2. Treatment costs	£9,576	8.673	14.181	£4,896	8.416	13.720	£4,680	0.257	0.461	£18,207	**+ £290**
R3. Age-varying MVH utility	£9,497	8.652	14.181	£4,892	8.396	13.720	£4,606	0.256	0.461	£17,965	**+ £48**
R4. Discounting method	£9,609	8.785	14.181	£4,943	8.524	13.720	£4,667	0.260	0.461	£17,920	**+ £3**
R5. Body weight	£9,496	8.673	14.181	£4,884	8.416	13.720	£4,613	0.257	0.461	£17,944	**+ £27**
R6. Rebase prevention model	£8,842	8.725	14.265	£3,859	8.474	13.803	£4,983	0.251	0.372	£19,876	**+ £1,959**
S1. HRs requested by ERG	£9,498	8.673	14.181	£4,892	8.416	13.720	£4,606	0.257	0.460	£17,936	**+ £18**
S2. HRs – ERG Poisson (Bayesian)	£9,498	8.673	14.181	£4,892	8.416	13.720	£4,606	0.257	0.460	£17,936	**+ £18**
S3. HRs – ERG Poisson (non-Bayesian)	£9,498	8.673	14.181	£4,892	8.416	13.720	£4,606	0.257	0.460	£17,936	**+ £18**
***B.* R1-R6 + S1**	**£9,147**	**8.493**	**15.334**	**£4,556**	**8.234**	**14.775**	**£4,591**	**0.256**	**0.558**	**£17,700**	**- £217**
***C.* R1-R6 + S2**	**£9,147**	**8.493**	**15.334**	**£4,556**	**8.234**	**14.775**	**£4,591**	**0.256**	**0.558**	**£17,700**	**- £217**
***D.* R1-R6 + S3**	**£9,147**	**8.493**	**15.334**	**£4,556**	**8.234**	**14.775**	**£4,591**	**0.256**	**0.558**	**£17,700**	**- £217**

Costs and QALYs discounted; life years undiscounted; HR=hazard ratio; MVH=Measurement and Valuation of Health survey; QALY=quality adjusted life year

Table 57 Cost effectiveness results for apixaban vs LMWH/VKA with ERG revisions to company's short-term base-case comparison

Model scenarios & ERG revisions	Apixaban			LMWH/VKA			Incremental			ICER	ICER
	Cost	QALYs	Life	Cost	QALYs	Life years	Cost	QALYs	Life	£/QALY	Change
***A.* Company's base-case**	**£5,035**	**8.422**	**13.720**	**£4,955**	**8.389**	**13.677**	**£80**	**0.033**	**0.043**	**£2,406**	-
R1. Age/sex modelling	£5,669	8.164	14.687	£5,591	8.132	14.642	£78	0.032	0.044	£2,454	**+ £48**
R2. Treatment costs	£5,044	8.422	13.720	£4,959	8.389	13.677	£84	0.033	0.043	£2,538	**+ £132**
R3. Age-varying MVH utility	£5,035	8.402	13.720	£4,955	8.369	13.677	£80	0.033	0.043	£2,412	**+ £6**
R4. Discounting method	£5,088	8.530	13.720	£5,007	8.497	13.677	£81	0.034	0.043	£2,397	**- £8**
R5. Body weight	£5,032	8.422	13.720	£4,947	8.389	13.677	£86	0.033	0.043	£2,577	**+ £171**
R6. Rebase prevention model	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
S1. HRs requested by ERG	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
S2. HRs – ERG Poisson (Bayesian)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
S3. HRs – ERG Poisson (non-Bayesian)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
***B.* R1-R5**	**£5,739**	**8.184**	**14.687**	**£5,648**	**8.153**	**14.642**	**£90**	**0.032**	**0.044**	**£2,850**	**+ £444**

Costs and QALYs discounted; life years undiscounted; HR=hazard ratio; MVH=Measurement and Valuation of Health survey; QALY=quality adjusted life year

Table 58 Cost effectiveness results for apixaban vs rivaroxaban with ERG revisions to company's short-term base-case comparison

Model scenarios & ERG revisions	Apixaban			Rivaroxaban			Incremental			ICER	ICER
	Cost	QALYs	Life years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change
***A.* Company's base-case**	**£5,035**	**8.422**	**13.720**	**£5,069**	**8.412**	**13.704**	**- £34**	**0.010**	**0.016**	**-£3,258 (Dominant)**	-
R1. Age/sex modelling	£5,669	8.164	14.687	£5,703	8.154	14.670	- £34	0.010	0.017	-£3,448 (Dominant)	**- £190**
R2. Treatment costs	£5,044	8.422	13.720	£5,081	8.412	13.704	- £37	0.010	0.017	-£3,512 (Dominant)	**- £254**
R3. Age-varying MVH utility	£5,035	8.057	13.720	£5,069	8.047	13.704	- £34	0.010	0.016	-£3,443 (Dominant)	**- £185**
R4. Discounting method	£5,088	8.530	13.720	£5,122	8.520	13.704	- £34	0.011	0.016	-£3,229	**+ £29**
R5. Body weight	£5,032	8.422	13.720	£5,067	8.412	13.704	- £34	0.010	0.016	-£3,258	**£0**
R6. Rebase prevention model	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
S1. HRs requested by ERG	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
S2. HRs – ERG Poisson (Bayesian)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
S3. HRs – ERG Poisson (non-Bayesian)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
***B.* R1-R5**	**£5,739**	**8.184**	**14.687**	**£5,776**	**8.112**	**14.670**	**-£37**	**0.010**	**0.017**	**-£3,729 (Dominant)**	**- £471**

Costs and QALYs discounted; life years undiscounted; HR=hazard ratio; MVH=Measurement and Valuation of Health survey; QALY=quality adjusted life year

Table 59 Cost effectiveness results for apixaban vs LMWH/dabigatran with ERG revisions to company's short-term base-case comparison

Model scenarios & ERG revisions	Apixaban			Dabigatran			Incremental			ICER	ICER
	Cost	QALYs	Life	Cost	QALYs	Life	Cost	QALYs	Life	£/QALY	Change
***A.* Company's base-case**	**£5,035**	**8.422**	**13.720**	**£5,100**	**8.396**	**13.680**	**- £65**	**0.026**	**0.040**	**-£2,524 (Dominant)**	-
R1. Age/sex modelling	£5,669	8.164	14.687	£5,735	8.139	14.645	- £66	0.025	0.042	-£2,689 (Dominant)	**- £145**
R2. Treatment costs	£5,044	8.422	13.720	£5,112	8.396	13.680	- £68	0.026	0.040	-£2,641 (Dominant)	**- £117**
R3. Age-varying MVH utility	£5,035	8.057	13.720	£5,100	8.032	13.680	- £65	0.025	0.040	-£2,662 (Dominant)	**- £138**
R4. Discounting method	£5,088	8.530	13.720	£5,153	8.504	13.680	- £66	0.026	0.040	-£2,505 (Dominant)	**+ £19**
R5. Body weight	£5,032	8.422	13.720	£5,094	8.396	13.680	- £62	0.026	0.040	-£2,380 (Dominant)	**+ £144**
R6. Rebase prevention model	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
S1. HRs requested by ERG	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
S2. HRs – ERG Poisson (Bayesian)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
S3. HRs – ERG Poisson (non-Bayesian)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
***B.* R1-R5**	**£5,739**	**8.184**	**14.687**	**£5,804**	**8.160**	**14.645**	**- £66**	**0.025**	**0.042**	**-£2,668 (Dominant)**	**- £143**

Costs and QALYs discounted; life years undiscounted; HR=hazard ratio; MVH=Measurement and Valuation of Health survey; QALY=quality adjusted life year

Table 60 Scenario analysis assuming equal efficacy and bleeding risks for all NOACs in secondary prevention. Cost effectiveness results for initial treatment with apixaban vs rivaroxaban and apixaban vs dabigatran with ERG revisions R1-R5 applied

Model scenario	**Apixaban**			**Comparator**			**Incremental**			**ICER**	**ICER**
	Cost	**QALYs**	**Life**	**Cost**	**QALYs**	**Life**	**Cost**	**QALYs**	**Life**	**£/QALY**	**Change**
Rivaroxaban as comparator											
Company base case	£9,497	8.673	14.181	£9,013	8.075	13.179	£484	0.598	1.002	**£809**	-
Equal efficacy & bleeding risks	£9,812	8.444	15.243	£9,107	8.411	15.167	£705	0.032	0.077	**£21,798**	**+ £20,988**
Dabigatran as comparator											
Company base case	£9,497	8.673	14.181	£9,083	8.591	14.041	£414	0.082	0.140	**£5,058**	-
Equal efficacy & bleeding risks	£9,812	8.444	15.243	£9,404	8.399	15.149	£408	0.045	0.094	**£9,139**	**+ 4,080**

Costs and QALYs discounted; life years undiscounted; HR=hazard ratio; MVH=Measurement and Valuation of Health survey; QALY=quality adjusted life year

7 END OF LIFE

NICE has set out supplementary advice[97] that should be taken into account by the AC when appraising treatments that may be life-extending for patients with a short life expectancy. This advice only applies if a treatment fulfils the following three criteria:

1. The treatment is indicated for patients with a short life expectancy, normally less than 24 months
2. There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment
3. The treatment is licensed or otherwise indicated, for small patient populations.

The CS[1] includes the following points:

1. The company model generates an estimates that the mean undiscounted survival for patients is between 13 and 14 years
2. The company model generates survival gains of about 3 months for some comparisons; however, these figures do not seem to be borne out by the results of the AMPLIFY[36,37] trials
3. The company estimates that there will be 58,392 incident patients in England and Wales who will begin treatment for VTE in 2015, rising to 60,045 in 2019

The ERG, therefore, considers that the company has correctly not put forward a case for apixaban to be considered under the NICE end of life criteria.

8 OVERALL CONCLUSIONS

The company provided a detailed submission that partially addressed the NICE scope; the ERG notes that the company did not provide any clinical effectiveness data to support the use of apixaban in patients who definitely required long-term treatment with an anticoagulant.

This STA was complicated by the fact that evidence from two trials[36,37] was presented by the company for two populations, who were followed for two different time periods and who received two different doses of apixaban (Table 61).

Table 61 Evidence presented by the company

	AMPLIFY[36]	**AMPLIFY-EXT[37]**
Population	Adult patients with an unprovoked index event or a provoked index event with a risk of recurrence. The index event being symptomatic, proximal DVT or PE (with or without DVT)	Adult patients with symptomatic, proximal DVT or PE (with or without DVT): • Who had been treated for 6 to 12 months with standard anticoagulant therapy, or had competed the AMPLIFY study • Who had not had a symptomatic recurrence during prior anti-coagulation therapy • For whom there was clinical equipoise about the continuation or cessation of anticoagulant therapy
Time period	Up to 6 months following the index event	12 months following a post index treatment period of 6 to 12 months
Apixaban dose	10mg twice daily for 7 days, then 5mg twice daily for 6 months	2.5mg twice daily for 12 months

8.1 Direct evidence

The key clinical evidence for the efficacy and safety of apixaban was derived from two good quality RCTs. Data from the AMPLIFY[36] trial provided supporting evidence for the use of apixaban in patients for the 6-month period following an index event. Data from AMPLIFY-EXT[37] provided information, over a 12-month period, for patients for whom it was unclear whether extended anticoagulant therapy would be beneficial (i.e. clinical equipoise). The direct evidence from AMPLIFY[36] suggests that, for the initial treatment period of VTE, apixaban is non-inferior to enoxaparin/warfarin for the primary composite outcome of VTE or VTE-related death. Similarly, over a 12-month period, the direct evidence from AMPLIFY-EXT[37] supports the use of apixaban rather than placebo/no treatment for the secondary prevention of symptomatic, recurrent VTE or all-cause mortality in a population of patients for whom the risks and benefits of extended anticoagulant therapy are uncertain.

8.1.1 Issues relating to study populations

The ERG has some concerns about whether the populations recruited to AMPLIFY[36] and AMPLIFY-EXT[37] represent patients routinely treated in the NHS. In particular, the mean age of patients participating in AMPLIFY[36] and AMPLIFY-EXT[37] was approximately 57 years and almost two-thirds of the patients were male. This contrasts with findings from a recent cohort study[17] which suggested that the mean age of patients in the UK with unprovoked VTE was 64 years and just over half of the patients were female.

According to the results of one of the company's subgroup analyses, patients ≥ 75 years of age who are in receipt of apixaban may have an increased RR of bleeding events compared to those in receipt of placebo/no treatment.[37] The ERG supports the EMA recommendation[38] that patients ≥75 years of age are under-represented in the AMPLIFY-EXT[37] trial and that more data are required to describe the efficacy and safety profile of apixaban for this vulnerable patient group.

The inclusion criteria for both AMPLIFY[36] and AMPLIFY-EXT[37] led to the exclusion of patients with a provoked index event without risk of recurrence and to the exclusion of patients with distal DVT. Patients in these subgroups may have a lower risk of VTE recurrence and may be more likely to require shorter treatment periods than patients who took part in the AMPLIFY[36,37] trials.

The ERG is aware that the EMA[38] was satisfied that, having been shown to be clinically effective in patients at higher risk of recurrence, apixaban is also likely to be effective in patients who are at a lower risk of recurrence. The ERG has some concerns about this assumption as no clinical data are available from the AMPLIFY[36] trials to support the use of apixaban in patients with a provoked index event without risk of recurrence or in patients with distal DVT.

NOACs have a potentially important role to play in the management of cancer patients. However, the ERG notes that apixaban is not currently licensed[39] in Europe for use in patients with active cancer. Patients with active cancer and for whom treatment with LMWH was planned were excluded from the AMPLIFY[36,37] trials, although baseline data show that a small number of patients actually participated in these trials. However, no clinical data are available from the AMPLIFY[36,37] trials to support the use of apixaban in patients with active cancer.

The NICE scope listed two key patient populations to be considered via subgroup analyses: (i) patients who require a limited period of anticoagulation (3–6 months) and (ii) patients who

require long-term anticoagulation (usually lifelong). The scope also stated that, if the evidence allowed, patients for whom the risks and benefits of long-term anticoagulation are uncertain should also be considered via subgroup analysis. In the CS,[1] only patients who required a limited period of anticoagulation and patients whose need for long-term anticoagulation is uncertain were considered. No clinical data are therefore available from the AMPLIFY[36,37] trials to support the explicit use of apixaban in patients who definitely require long-term anticoagulation (i.e. high risk patients). The ERG notes that previous NICE guidance[23-25] has not distinguished between patients who definitely need long-term treatment and patients whose need for treatment is uncertain.

The ERG has some comments on the company's analyses that are reliant on data from AMPLIFY-EXT.[37] In this trial the clinical equipoise population is poorly defined and so the extent to which the trial population is truly representative of patients for whom the risks and benefits of long-term treatment with an anticoagulant are uncertain is unknown. Clinical advisors to the ERG are of the opinion that clinical equipoise patients may be difficult to identify in clinical practice. The size of this population relative to the size of the population known to definitely require long-term treatment because of the presence of risk factors (including a recurrent VTE, thrombophilia or immobility) is unclear. If the patients in this subgroup are truly representative of patients for whom the benefits of long-term treatment could be considered to be uncertain, then the results of the AMPLIFY-EXT[37] trial demonstrate that, over a 12-month period, treatment with apixaban compared to placebo/no treatment is clinically effective.

8.1.2 Outcome data

No HRQoL data were available from either the AMPLIFY[36] or AMPLIFY-EXT[37] trials. This means there is no clear evidence of patient experience of treatment with apixaban compared with enoxaparin/warfarin or placebo/no treatment. Similarly, no direct evidence was available for the incidence or risks of PTS or CTEPH.

8.2 Indirect evidence

As there was no direct evidence available to compare the efficacy and safety of apixaban with rivaroxaban or dabigatran in the first 6 months after an index event or with rivaroxaban, dabigatran or VKA as secondary prevention, the company carried out two NMAs. The results of both the initial treatment period and the secondary prevention period NMAs demonstrate that there is no significant difference in efficacy when apixaban is compared with dabigatran, rivaroxaban or VKA in patients who received apixaban as initial treatment or as secondary prevention. The ERG is satisfied with the methods used in the initial treatment period NMA.

The ERG, however, is not confident that the methods used in the secondary prevention period NMA are robust and considers that the results from this NMA are not credible.

8.2.1 Issues relating to NMA methodology

The ERG was unable to reproduce the results of either the company's initial treatment period or the company's secondary prevention period NMA using the information included in the CS.[1] The ERG notes that the information about the comparators included in the initial treatment period NMA that is presented in the clinical section of the CS[1] is not the same as the information that is presented in the economics section. Specifically there are results for two additional comparators (no treatment and aspirin) listed in Table 58 of the economics section. The legend for Table 58 is not sufficiently detailed to allow understanding of any additional assumptions/analyses that have been carried out by the company to explain this discrepancy.

There were small numbers of events for many of the outcomes reported in the AMPLIFY[36,37] trials and this led to wide confidence intervals for many of the RR estimates resulting from both initial treatment period NMA and the secondary prevention period NMA.

The ERG has an additional major concern about the methodology and assumptions underpinning the secondary prevention period NMA. There is marked variation in the lengths of the included trial treatment periods (before recruitment into the trial, the trial treatment period and also of the observation period after the end of treatment). However, the number of events, and hence RRs, for these different periods were used in the analyses as if all of the trials had the same follow-up period. To illustrate, in AMPLIFY-EXT[37] apixaban is used for a 12-month treatment period following an initial treatment period of 6 to 12 months; in other trials[2-4,6,8,15,36,37,78,82] the initial treatment period varies from 3 to 18 months and the trial treatment period varies from 6 months to longer than 2 years. The advice given to the company was that the RRs between different treatment options were not likely to differ over time. However, recent evidence from Martinez et al[17] demonstrates that the risk of recurrence is highest in the first 6 months after an index event but then falls progressively between 6 months and 4 years, at which point it plateaus. The trials included in the secondary prevention period NMA[37,58-66] evaluate the effects of different therapies at different time-points during this decline in risk and the ERG is not aware of any data to justify the assumption that a comparison of the results of these trials is valid.

8.2.2 Economic model

The ERG's critique of the company's submitted economic model was severely hampered by a lack of information. This lack of information meant that the ERG was unable to verify key

Page superseded by erratum

model parameters. Although the company was asked, via the clarification process, to carry out a series of 12 K-M analyses, only two analyses were provided. Examination of these data revealed issues with both the company's calculation of the risk of treatment discontinuation, and a significant difference between the survival gain estimated by the model and that shown by the AMPLIFY[36] trial results. The fact that there are outstanding issues relating to the parameters that had been estimated from both of the provided data sets raises concern that there may be other issues relating to the ten analyses carried for which no results were made available to the ERG.

The company created one model, combining the risks and benefits resulting from treatment with apixaban over an initial treatment period of 6 months with those associated with long-term secondary prevention. Risks of VTE-related events calculated from AMPLIFY[36] data were used to estimate risks in the initial 6-month period, whilst risks for VTE-related events calculated from AMPLIFY-EXT[37] data were used to estimate long-term risks beyond 6 months. As previously discussed, the population in AMPLIFY-EXT[37] only represents patients for whom there is uncertainty regarding the risks and benefits of treatment as patients who had a recurrent VTE within 6 months of an index event were excluded from this trial. The ERG considers that the risks of recurrent events for the whole population receiving apixaban are, therefore, likely to have been underestimated in the company's economic model.

Furthermore, it is not clear whether the RRs for the comparator treatments described in the CS[1] are valid for patients who definitely require lifelong treatment (i.e. patients at overall higher risk of VTE recurrence). From the information in the CS,[1] it appears that the RRs for the comparator treatments are mainly derived from data relating to the clinical equipoise population (AMPLIFY-EXT[37] and EINSTEIN-EXT[58]). This is an important consideration as these RRs are used in the economic model to generate the (lifelong) ICERs per QALY gained. This means that the company's economic model may yield an ICER that is not relevant to all patients who require lifelong treatment, including those with persistent factors who are at higher risk of recurrence.

The results from the company's secondary prevention period NMA were used as the basis for assessing lifelong use of apixaban in the economic model despite some values being unrealistic and despite the follow-up data for apixaban only being available for 12 months. The ERG also had minor concerns about the modelling of background mortality risk, treatment costs, utility and the discounting methods used in the model.

The ERG acknowledges that their adjustments to the company's model had minimal effects on the sizes of the ICERs per QALY gained. However, the ERG is very concerned that their

Page superseded by erratum

critique was restricted by the failure of the company to provide requested data. Unfortunately, the currently available cost effectiveness estimates cannot be considered robust unless the ERG is given the opportunity to check the parameter estimates and assumptions used in the company model.

8.3 Implications for research

Due to the paucity of long-term evidence for both the continued benefit and safety of treatment with NOACs, close monitoring and surveillance of patients undergoing treatment with NOACs is necessary.

In addition, access to, support and best use of currently available clinical data from patient registries and hospital audits should be encouraged in order to explore the substantial uncertainty around key clinical issues for patients with VTE.

A robust study of quality of life in patients treated with NOACs compared to patients treated with warfarin would be welcome.

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10 APPENDICES

APPENDIX 1

Eligibility criteria AMPLIFYand AMPLIFY-EXT

Eligibility criteria in the AMPLIFY and AMPLIFY-EXT RCTs

Trial Acronym	Inclusion criteria	Exclusion criteria
AMPLIFY[36]	Target Population Patients who had an unprovoked index event or a provoked index event with a risk for recurrence Patients who had acute, symptomatic, proximal DVT with evidence of proximal thrombosis that involved at least the popliteal vein or a more proximal vein, demonstrated by imaging with compression ultrasound, or ascending contrast venography Or Patients who had acute symptomatic PE with evidence of thrombosis demonstrated by imaging showing: An intraluminal filling defect in segmental or more proximal branches on spiral computed tomography scan, or An intraluminal filling defect or a sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram, or A perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scan Age and Sex Men and women, aged 18 years or over Women of childbearing potential must have been	Sex and Reproductive Status Pregnancy or breastfeeding Target Disease Exceptions: Less than 6 months of anticoagulation planned for the most recent DVT or PE (index event) Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the concurrent episode of VTE Active bleeding, or high risk for bleeding, contraindicating treatment with LMWH and a VKA Patients with cancer who were treated for ≥6 months with LMWH therapy Patients with contraindications according to the local prescribing information of enoxaparin or warfarin Medical History and Concurrent Diseases: Patients with indications for long-term treatment with a VKA, such as: Mechanical valve Atrial fibrillation or atrial flutter with moderate to high risk of systemic thromboembolism Active and clinically significant liver disease (e.g. hepatorenal syndrome) Life expectancy <6 months Bacterial endocarditis Uncontrolled hypertension: systolic blood pressure (BP) >180 mm Hg or diastolic BP >100 mm Hg Physical and Laboratory Test Findings: Platelet count <100,000/mm^3 Haemoglobin <9 g/dL Serum creatinine >2.5mg/dL (221 µmol/L) Calculated creatinine clearance <25 ml/min Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) >2 times upper limit of normal

Trial Acronym	Inclusion criteria	Exclusion criteria
	using an adequate method of contraception to avoid pregnancy throughout the trial in such a manner that the risk of pregnancy was minimised	(ULN) Total bilirubin >1.5 times ULN (unless an alternative causative factor was identified [e.g. Gilbert's syndrome]) Allergies and Adverse Drug Reactions: Heparin induced thrombocytopaenia Allergic reaction to UFH, LMWH, fondaparinux or any VKA. Prohibited Treatments and/or Therapies: DVT or PE treatment with more than 2 doses of fondaparinux or a LMWH that was labelled for once daily (od) dosing, or more than 3 doses of a LMWH that was labelled for twice daily (bd) dosing, or continuous infusion of UFH for more than 36 hours, before the first administration of trial drug; and/or DVT or PE treatment with more than 2 doses of oral VKA therapy before the first administration of trial drug Treatment with apixaban in a previous clinical trial Patients who required acetylsalicylic acid (ASA) >165mg/day at randomisation Patients who required dual antiplatelet therapy (such as ASA plus clopidogrel or ASA plus ticlopidine) at randomisation. Patients who transitioned from dual antiplatelet therapy to monotherapy prior to randomisation were eligible for the trial
AMPLIFY-EXT[37]	Target population: Patients who had an objectively documented index event of symptomatic, proximal thrombosis, demonstrated by imaging with CUS, including grey-scale colour-coded Doppler, or ascending contrast venography Symptomatic PE with evidence of thrombosis demonstrated by imaging as follows: An intraluminal filling defect in segmental or more proximal branches on a spiral CT scan; or An intraluminal filling defect or a sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram; or A perfusion defect of at least 75% of a segment with a local normal ventilation result (high-	Sex and Reproductive Status: Pregnancy or breastfeeding Medical History and Concurrent Diseases: Patients with a provoked index event without the existence of a persistent risk factor More than 12 months of anticoagulation planned for the most recent DVT or PE (index event) Patients with indications for long-term treatment with a VKA, such as: Mechanical valve Atrial fibrillation or atrial flutter with moderate to high risk of systemic thromboembolism Multiple episodes of unprovoked DVT or PE Documented anti-phospholipid antibodies, AT III deficiency, protein C deficiency, protein S deficiency, homozygous factor V Leiden, or homozygous prothrombin gene mutation. Patients with cancer who were treated indefinitely with anticoagulation therapy Active and clinically significant liver disease (e.g. hepatorenal syndrome) Life expectancy <12 months Bacterial endocarditis Uncontrolled hypertension: systolic blood pressure (BP) >180 mm Hg or diastolic BP >100 mm Hg

Trial Acronym	Inclusion criteria	Exclusion criteria
	probability) on ventilation/perfusion lung scan 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[36] trial Had not had a symptomatic recurrence during prior anticoagulant therapy There was clinical equipoise about the continuation or cessation of anticoagulant therapy Age and sex: Men and women, aged 18 years or over Women of childbearing potential must have been using an adequate method of contraception to avoid pregnancy throughout the trial in such a manner that the risk of pregnancy was minimised	Physical and Laboratory Test Findings: Platelet count <100,000/mm^3 Haemoglobin <9 g/dL Serum creatinine >2.5mg/dL (221 µmol/L) Calculated creatinine clearance <25 ml/min Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) >2 times upper limit of normal (ULN) Total bilirubin >1.5 times ULN (unless an alternative causative factor was identified [e.g. Gilbert's syndrome]) Prohibited Treatments and/or Therapies: Patients requiring acetylsalicylic acid (ASA) >165mg/day at randomisation Patients who required dual antiplatelet therapy (such as ASA plus clopidogrel or ASA plus ticlopidine) at randomisation. Patients who transitioned from dual antiplatelet therapy to monotherapy prior to randomisation were eligible for the trial Patients who had used any oral direct factor Xa inhibitor, any oral direct thrombin inhibitor, or any investigational antithrombotic agent during the period between the onset of the index event to randomisation. Patients who participated in the AMPLIFY[36] trial could have participated in this trial and were exempt from this exclusion

ALT=alanine aminotransferase; ASA=acetylsalicylic acid; AST=aspartate aminotransferase; AT=antithrombin; bd=twice daily; BP=blood pressure; CUS=compression ultrasonography; DVT=deep vein thrombosis; LMWH=low molecular weight heparin; No.=number; PE=pulmonary embolism; UFH=unfractionated heparin; ULN=upper limit of normal; VKA; vitamin K Antagonist; VTE=venous thromboembolism
Source: Table 8 of the CS[1]

APPENDIX 2

Outcome measures in the AMPLIFY and AMPLIFY-EXT trials

Primary and secondary outcomes in AMPLIFY and AMPLIFY-EXT RCTs

Trial	Primary outcome(s)	Secondary outcome(s)	Outcome measures
AMPLIFY[36]	**Efficacy** 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 (6 months). **Safety** Incidence during treatment period of adjudicated major bleeding.	**Efficacy** Incidence of the following adjudicated events: symptomatic non-fatal PE symptomatic non-fatal DVT composite of recurrent symptomatic VTE or all-cause death composite of recurrent symptomatic VTE or CV-related death composite of recurrent symptomatic VTE, VTE-related death or major bleeding composite of recurrent symptomatic VTE, myocardial infarction, stroke, CV-related death, major bleeding, CRNM bleeding VTE-related death CV-related death All-cause death Time to first occurrence of: Adjudicated composite of recurrent symptomatic VTE and all-cause death Adjudicated composite of recurrent symptomatic VTE and VTE-related death **Safety** Incidence of the following adjudicated events: composite of major or CRNM bleeding minor bleeding composite of major, CRNM bleeding, or minor bleeding (total adjudicated bleeding) CRNM bleeding	**PE** was judged to occur where symptoms of PE were present along with one of the following findings: Intraluminal filling defect Sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram Perfusion defect of at least 75% **DVT** was judged to occur where symptoms of DVT were present along with one of the following findings: Abnormal CUS Intraluminal filling defect **Bleeding** was defined according to ISTH guidelines : Major bleeding: Clinically overt bleeding accompanied by a decrease in haemoglobin of ≥2 g/dL and/or transfusion of ≥2 units of packed red blood cells Bleeding that occurred in a critical site Bleeding that was fatal CRNM bleeding – clinically overt bleeding that did not satisfy the criteria for major bleeding and that led to either: Hospital admission Physician guided medical or surgical treatment A change in antithrombotic therapy All acute clinically overt bleeding events not meeting criteria for major bleeding or clinically relevant non-major bleeding were classified as minor bleeding

Trial	Primary outcome(s)	Secondary outcome(s)	Outcome measures
		Time to first occurrence during treatment period of: Adjudicated major bleeding Adjudicated composite of major or CRNM bleeding **Additional analyses** 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: 7 days 21 days 3 months Rate of all-cause hospitalisations Time from randomisation to first hospitalisation	Hospitalisations were captured by dedicated case report forms. Patients were censored at death, loss to follow-up (<2.5% in all treatment arms), or end of trial, whichever came first.
AMPLIFY-EXT[37]	**Efficacy** Incidence of an adjudicated composite of symptomatic, recurrent VTE (non-fatal DVT or non-fatal PE) or all-cause death occurring at any time from randomisation until the end of the originally intended treatment period (6 months). **Safety** Incidence during treatment period of adjudicated major bleeding.	**Efficacy** Incidence of the following adjudicated events: Symptomatic non-fatal PE Symptomatic non-fatal DVT Composite of recurrent symptomatic recurrent VTE or VTE-related death Composite of recurrent symptomatic VTE or CV-related death VTE-related death CV-related death All-cause death Time to first occurrence of: Adjudicated composite of symptomatic, recurrent VTE or all-cause death Adjudicated composite of symptomatic, recurrent VTE or VTE-related death **Safety** Incidence during treatment period of:	As for AMPLIFY[36]

Trial	Primary outcome(s)	Secondary outcome(s)	Outcome measures
		Adjudicated composite of major and CRNM bleeding Adjudicated minor bleeding Adjudicated major, CRNM, or minor bleeding (total adjudicated bleeding) Time to first occurrence during treatment period of: Adjudicated major bleed Adjudicated composite of major and CRNM bleeding **Additional analyses** Rate of all-cause hospitalisations Time from randomisation to first hospitalisation	

AE=adverse event; CRNM=clinically relevant non-major; CUS=compression ultrasonography; CV=cardiovascular; DVT=deep vein thrombosis; ISTH=International Society on Thrombosis and Haemostasis; No.=number; PE=pulmonary embolism; VTE=venous thromboembolism
Source: Table 11 of the CS[1]

Appendix 3

Company's quality assessment for the AMPLIFY trials

Company's quality assessment results (AMPLIFY and AMPLIFY-EXT)

Assessment criteria	AMPLIFY[36]	AMPLIFY-EXT[37]
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the trial in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

Source: Table 17 of the CS[1]

APPENDIX 4
Post-hoc analyses from the AMPLIFY and AMPLIFY-EXT trials

Post-hoc analysis of recurrent VTE or VTE-related death at early timepoints (AMPLIFY efficacy evaluable population)

	Apixaban	Enoxaparin/warfarin	RR (95% CI)	p-value for non-inferiority
Recurrent VTE or VTE-related death, n/N (%)				
7 days	18/2661 (0.68)	23/2676 (0.86)	0.79 (0.43 to 1.46)	0.0033
21 days	29/2652 (1.09)	35/2667 (1.31)	0.83 (0.51 to 1.36)	0.0008
3 months	[redacted]	[redacted]	[redacted]	[redacted]

CI=Confidence interval; RR=relative risk; VTE=Venous thromboembolism
Efficacy evaluable population included data for patients in the intention-to-treat population for whom the outcome status at the investigated timepoint was documented.
Source: Table 23 of the CS[1]

Summary of hospitalisation outcomes (AMPLIFY[36])

	Apixaban N=2676	Enoxaparin/ warfarin N=2689	HR (95% CI)	p-value
Hospitalisation outcomes				
Number of patients hospitalised during intended 6 month treatment period	153	190	0.81 (0.65 to 1.00)	p=0.048
Rate of hospitalisation per year	11.1%	13.8%	-	-
Rate of hospitalisation in the first 30 days after VTE index event	2.3%	3.4%	0.68 (0.49 to 0.94)	p=0.019
Median time to first hospitalisation (days)	63.0	34.5	-	-

CI=confidence interval; HR=hazard ratio; VTE=venous thromboembolism
Analysis is based on the safety population (those patients who received at least one dose of trial medication)
Source: Table 24 of the CS[1]

Summary of hospitalisation outcomes (AMPLIFY-EXT)

	Apixaban N=840	Placebo N=829	HR (95% CI)	p-value
Hospitalisation outcomes				
Number of patients hospitalised during intended 12 month treatment period	42	62	0.65 (0.44 to 0.96)	p=0.030
Rate of hospitalisation per year	4.8%	7.5%	-	-
Mean time to first hospitalisation (days)	196.9	153.7	-	-

CI=confidence interval; HR=hazard ratio
Analysis performed on the intention-to-treat (ITT) population
Source: Table 29 of the CS[1]

APPENDIX 5

The company's quality assessment of trials included in the initial treatment and secondary prevention period NMAs

Results of the company's quality assessment of trials included in the initial treatment period NMA

Trial question	RECOVER[55]	EINSTEIN-PE[45]	EINSTEIN-DVT[44]	RECOVER-II[56]
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Not clear	Not clear	Not clear
Were the groups similar at the outset of the trial in terms of prognostic factors, for example severity of disease?	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Yes/No	No	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	No

Source: Appendix 5 of the CS[1]

Results of the company's quality assessment of trials included in the secondary prevention period NMA

Trial question	EINSTEIN-EXT[58]	WARFASA[59]	RE-SONATE[60]	RE-MEDY[60]	ASPIRE[61]	LAFIT[62]	ELATE[63]	WODIT DVT[64]	PREVENT[66]	WODIT PE[65]
Was randomisation carried out appropriately?	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Not clear
Was the concealment of treatment allocation adequate?	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear
Were the groups similar at the outset of the trial in terms of prognostic factors, for example severity of disease?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes/No	Yes	Yes/No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No	No	No	No	No	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No	No	No	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes

Source: Appendix 5 of the CS[1]
YES/NO= blinding procedures were implemented in some, but not all aspects of the trial.

APPENDIX 6

Efficacy outcomes of initial treatment period NMA and secondary prevention period NMA.

Key efficacy outcomes from trials included in the initial treatment period NMA

Trial	Intervention and comparator	Recurrent VTE or VTE-related death[c]		Overall treatment discontinuation		All-cause mortality	
		No. of events/n	RR[†] (95% CI)	No. of events/n	RR (95% CI)	No. of events/n	RR (95% CI)
AMPLIFY[36],[a]	Apixaban 5mg bd	59/2691	0.84 (0.59 to 1.17)	377/2691	0.92 (0.81 to 1.04)	41/2691	0.79 (0.53 to 1.19)
	Enoxaparin/warfarin INR 2.0-3.0	71/2704		413/2704		52/2704	
RE-COVER[55],[b]	UFH or LMWH/dabigatran 150mg bd	30/1274	1.10 (0.66 to 1.85)	204/1274	1.11 (0.92 to 1.33)	21/1274	0.99 (0.55 to 1.81)
	UFH or LMWH/warfarin INR 2.0-3.0	27/1265		183/1265		21/1265	
RE-COVER II[56],[b]	UFH or LMWH/dabigatran 150mg bd	30/1279	1.08 (0.65 to 1.80)	188/1279	1.04 (0.86 to 1.26)	25/1279	1.01 (0.58 to 1.75)
	UFH or LMWH/warfarin INR 2.0-3.0	28/1289		182/1289		25/1289	
EINSTEIN DVT & PE pooled[57],[a]	Rivaroxaban 15mg bd/20mg od	86/4150	0.90 (0.68 to 1.20)	454/4150	0.84 (0.74 to 0.94)	96/4150	0.97 (0.73 to 1.27)
	Enoxaparin/VKA	95/4131		541/4131		99/4131	

bd=twice daily; CI=confidence interval; INR=international normalised ratio; od=once daily; RR=relative risk; HR=hazard ratio; LMWH=low molecular weight heparin; VKA=vitamin K antagonist; VTE=venous thromboembolism; ITT=intention-to-treat; UFH=unfractionated heparin

[a]ITT population used for efficacy analysis.

[b]ITT population (randomly assigned patients who received ≥1 dose of trial drug). Events occurring within 6 months post randomisation were counted as events in the analysis regardless of early discontinuation of trial drug.

[c]Outcome reported as: 'first recurrent VTE or VTE-related death' in AMPLIFY;[36] 'VTE or related death during the trial period' (data also reported for events during the trial period plus an additional 30-day follow-up) in RE-COVER; 'VTE or related death during 6 months' (data also reported for events during the trial period plus an additional 30-day follow-up) in RE-COVER-II; 'first-recurrent VTE' in EINSTEIN DVT & PE pooled.

[†]Calculated from the reported raw data (AMPLIFY[36] trial reports RR for certain outcomes; remaining trials report HR).

Source: Appendix 6a of the CS[1]

Key safety outcomes from trials included in the treatment period NMA

Trial	Intervention and comparator	Major or CRNM bleeding		Major bleeding event		CRNM bleeding[e]	
		No. of events/n	RR (95% CI)	No. of events/n	RR (95% CI)	No. of events/n	RR (95% CI)
AMPLIFY[36],[a]	Apixaban 5mg bd	115/2676	0.44 (0.36 to 0.55)	15/2676	0.31 (0.17 to 0.55)	103/2676	0.48 (0.38 to 0.61)
	Enoxaparin/warfarin INR 2.0-3.0	261/2689		49/2689		215/2689	
RE-COVER[55],[b]	UFH or LMWH/dabigatran 150mg bd	71/1273	0.64 (0.48 to 0.85)	20/1273	0.83 (0.46 to 1.49)	51/1273	0.58 (0.42 to 0.82)
	UFH or LMWH/warfarin INR 2.0-3.0	111/1266		24/1266		87/1266	
RE-COVER II[56],[c]	UFH or LMWH/dabigatran 150mg bd	64/1280	0.63 (0.47 to 0.86)	15/1280	0.69 (0.36 to 1.32)	49/1280	0.62 (0.44 to 0.87)
	UFH or LMWH/warfarin INR 2.0-3.0	102/1288		22/1288		80/1288	
EINSTEIN DVT & PE pooled[57],[d]	Rivaroxaban 15mg bd/20mg od	388/4130	0.94 (0.82 to 1.07)	40/4130	0.55 (0.38 to 0.81)	354/4130	1.02 (0.89 to 1.18)
	Enoxaparin/VKA	412/4116		72/4116		346/4116	

bd=twice daily; CI=confidence interval; CRNM=clinically relevant non-major; INR=international normalised ratio; od=once daily; RR=relative risk; LMWH=low molecular weight heparin; VKA=vitamin K antagonist; UFH=unfractionated heparin

aSafety population used for safety analyses; defined as data obtained from patients during the trial treatment, defined as time from the administration of the first dose until 48 hours after the last dose was administered.

bSafety analysis of bleeding events was performed on the basis of the number of patients treated with dabigatran or warfarin rather than the number assigned to treatment. Events that occurred during the 6-month treatment period plus a 6-day washout period were included.

cSafety analysis of bleeding events was performed on the basis of the number of patients treated with dabigatran or warfarin rather than the number assigned to treatment. Events that occurred during the 6-month treatment period plus a 6-day washout period were included.

dSafety population defined as all patients who received trial drug (included in analysis if events occurred during treatment or within 2 days after discontinuation of the trial drug)

eCalculated as "'major or CRNM bleeding event' - 'major bleeding event'" in RE-COVER, RE-COVER II, and reported as 'non-major clinically relevant bleeding (all events, not just the first event)' in EINSTEIN DVT & PE POOLED.

Source: Appendix 6a of the CS[1]

Key efficacy outcomes from trials included in the secondary prevention period NMA

Trial	Intervention and comparator	Recurrent VTE or VTE-related death[e]		VTE-related death[f]		Overall treatment discontinuation		All-cause mortality	
		No. of events/ n	RR (95% CI)	No. of events/ n	RR (95% CI)	No. of events/n	RR (95% CI)	No. of events/ n	RR (95% CI)
AMPLIFY-EXT[37,a]	Apixaban 2.5mg bd	14/840	0.19 (0.11 to 0.33)	2/840	[redacted]	114/840	0.60 (0.48 to 0.74)	7/840	[redacted]
	Placebo	73/829		7/829		188/829		14/829	
EINSTEIN-EXT[58a]	Rivaroxaban 20mg od	8/602	0.19 (0.09 to 0.40)	1/602	0.99 (0.06 to 15.74)	76/602	0.81 (0.61 to 1.07)	1/602	0.49 (0.05 to 5.43)
	Placebo	42/594		1/594		93/594		2/594	
WARFASA[59b]	Aspirin 100mg od	23/205	0.57 (0.35 to 0.91)	NR	NR	16/205	1.03 (0.52 to 2.02)	NR	NR
	Placebo	39/197		NR		15/197		NR	
RESONATE[60c]	Dabigatran 150mg bd	3/681	0.08 (0.02 to 0.25)	0*/681	0.97 (0.02 to 48.92)	71/681	0.70 (0.52 to 0.93)	NR	NR
	Placebo	37/662		0*/662		99/662		NR	
REMEDY[60c]	Dabigatran 150mg bd	26/1430	1.44 (0.79 to 2.62)	1/1430	1 (0.06 to 15.93)	276/1430	0.98 (0.84 to 1.14)	17/1430	0.89 (0.47 to 1.71)
	Warfarin INR 2.0-3.0	18/1426		1/1426		281/1426		19/1426	
ASPIRE[61d]	Aspirin 100mg od	57/411	0.78 (0.57 to 1.07)	1/411	1 (0.06 to 15.93)	117/411	0.89 (0.72 to 1.09)	16/411	0.89 (0.46 to 1.72)
	Placebo	73/411		1/411		132/411		18/411	
LAFIT[62d]	Warfarin INR 2.0-3.0	1/79	0.06 (0.01 to 0.45)	0*/79	0.35 (0.01 to 8.47)	14/79	1.13 (0.57 to 2.25)	1/79	0.35 (0.04 to 3.30)
	Placebo	17/83		1/83		13/83		3/83	
ELATE[63d]	Warfarin INR 1.5-1.9	16/369	2.67 (1.06 to 6.74)	1/369	0.5 (0.05 to 5.49)	84/369	1.45 (1.07 to 1.96)	16/369	2.00 (0.87 to 4.62)
	Warfarin INR 2.0-3.0	6/369		2/369		58/369		8/369	

WODIT DVT[64a]	VKA continuation	1/134	0.09 (0.012 to 0.69)	0*/134	0.99 (0.02 to 49.66)	NR	NR	NR	NR
	VKA discontinuation / observation	11/133		0*/133		NR		NR	
PREVENT[66d]	Warfarin INR 1.5-1.9	14/255	0.38 (0.21 to 0.68)	0*/255	0.2 (0.01 to 4.11)	64/255	1.13 (0.83 to 1.55)	4/255	0.50 (0.15 to 1.63)
	Placebo	37/253		2/253		56/253		8/253	
WODIT PE[65]	VKA continuation	NR	NR	NR	NR	NR	NR	NR	NR
	VKA discontinuation / observation	NR		NR		NR		NR	

bd=twice daily; CI=confidence interval; INR=international normalised ratio; od=once daily; RR=relative risk; VKA=vitamin K antagonist; VTE=venous thromboembolism; ITT=intention-to-treat
[a] ITT population used for efficacy analyses.
[b] Modified ITT population used for efficacy analyses (all patients who received at least one dose of the assigned trial drug post randomisation).
[c] Modified ITT population used for efficacy analyses (excluding patients who did not receive any dose of the trial drug).
[d] All randomised patients used in efficacy analyses.
[e] Outcome reported as 'recurrent VTE' in EINSTEIN-EXT, ELATE and PREVENT; 'recurrent VTE episodes' in WARFASA; 'recurrent or fatal VTE or unexplained death' in RE-SONATE; 'recurrent VTE (composite of symptomatic, objectively confirmed DVT, non-fatal PE, or fatal PE)' in ASPIRE; 'VTE' in LAFIT; 'risk of VTE recurrence during the first 9 months of follow-up' in WODIT-DVT
[f] Outcome reported as 'death unexplained, PE could not be ruled out' in AMPLIFY-EXT;[37] calculated from 'fatal PE' and 'recurrent VTE: PE cannot be ruled out' in EINSTEIN-EXT; 'death from any cause: PE' in ASPIRE; RESONATE specified that 'there were no cases of objectively verified fatal PE or of any other deaths'; LAFIT states that 'one of the three deaths in the placebo group was reported as due to PE'; ELATE states the number of fatal PE events out of the recurrent VTE episodes; WODIT states that 'all episodes of recurrent VTE were idiopathic, and none were fatal'; PREVENT state that 'two deaths in the placebo group were due to fatal PE'.
*There were insufficient patient / trial data to ensure the WinBUGS model converged without applying a continuity correction. Therefore, where zero outcome events were reported, a correction of 0.5 was added as per the Cochrane Handbook.
Source: Appendix 6b of the CS[1]

Key safety outcomes from trials included in the secondary prevention period NMA

Trial	Intervention and comparator	Major or CRNM bleeding[a]		Major bleeding event		CRNM bleeding[b]	
		No. of events/n	RR (95% CI)	No. of events/n	RR (95% CI)	No. of events/n	RR (95% CI)
AMPLIFY-EXT[37i]	Apixaban 2.5mg bd	27/840	1.21 (0.69 to 2.10)	2/840	0.49 (0.09 to 2.68)	25/840	1.29 (0.72 to 2.33)
	Placebo	22/826		4/826		19/826	
EINSTEIN-EXT[58v]	Rivaroxaban 20mg od	36/598	5.07 (2.28 to 11.31)	4/598	8.88 (0.48 to 164.57)	32/598	4.51 (2.01 to 10.14)
	Placebo	7/590		0*/590		7/590	
WARFASA[59vi]	Aspirin 100mg od	4/205	0.96 (0.24 to 3.79)	1/205	0.96 (0.06 to 15.26)	3/205	0.96 (0.20 to 4.71)
	Placebo	4/197		1/197		3/197	
RESONATE[60iii]	Dabigatran 150mg bd	36/684	2.89 (1.52 to 5.51)	2/684	4.82 (0.23 to 100.16)	34/684	2.73 (1.43 to 5.23)
	Placebo	12/659		0*/659		12/659	
REMEDY[60iv]	Dabigatran 150mg bd	80/1430	0.55 (0.42 to 0.72)	13/1430	0.52 (0.27 to 1.01)	67/1430	0.56 (0.42 to 0.74)
	Warfarin INR 2.0-3.0	145/1426		25/1426		120/1426	
ASPIRE[61ii]	Aspirin 100mg od	14/411	1.75 (0.74 to 4.13)	8/411	1.33 (0.47 to 3.81)	6/411	3.00 (0.61 to 14.78)
	Placebo	8/411		6/411		2/411	
LAFIT[62ii]	Warfarin INR 2.0-3.0	NR	NR	3/79	7.35 (0.39 to 140.09)	NR	NR
	Placebo	NR		0*/83		NR	
ELATE[63ii]	Warfarin INR 1.5-1.9	NR	NR	9/369	1.13 (0.44 to 2.88)	NR	NR
	Warfarin INR 2.0-3.0	NR		8/369		NR	

WODIT DVT[64ii]	VKA continuation	NR	NR	4/134	1.99 (0.37 to 10.66)	NR	NR
	VKA discontinuation / observation	NR		2/133		NR	
PREVENT[66ii]	Warfarin INR 1.5-1.9	NR	NR	5/255	2.48 (0.49 to 12.67)	NR	NR
	Placebo	NR		2/253		NR	
WODIT PE[65ii]	VKA continuation	NR	NR	3/165	2.93 (0.31 to 27.85)	NR	NR
	VKA discontinuation / observation	NR		1/161		NR	

bd=twice daily; CI=confidence interval; CRNM=clinically relevant non-major; INR=international normalised ratio; od=once daily; RR=relative risk; VKA=vitamin K antagonist; VTE=venous thromboembolism

[a] Outcome calculated from addition of major bleed and CRNM bleeding in ASPIRE; reported as 'major bleeding events' in RESONATE and REMEDY; reported as 'first major or CRNM bleeding' in EINSTEIN-EXT.

[b] Outcome calculated by subtracting major bleed from 'major or CRNM bleeding' in REMEDY and RESONATE.

[i] Safety analyses included data from patients during the time they were receiving treatment, defined as the time between administration of the first dose of a trial drug and 48 hours after administration of the last dose.

[ii] Safety analyses included all randomised patients

[iii] Safety analyses included 684 patients who received dabigatran and 659 who received placebo. Three patients in the placebo group mistakenly received dabigatran throughout the trial.

[iv] Safety analyses were based on the treatment period and a 3-day washout period after the end of treatment.

[v] Safety analyses included all patients who received the assigned trial drug. Bleeding events were included in the analysis if they occurred during treatment or within 2 days after discontinuation of the trial drug.

[vi] Safety analyses included all patients who received at least one dose of the trial drug.

*There were insufficient patient / trial data to ensure the WinBUGS model converged without applying a continuity correction. Therefore, where zero outcome events were reported, a correction of 0.5 was added as per the Cochrane Handbook.

Source: Appendix 6b of the CS[1]

Appendix 7

Poisson rate modelling as an alternative approach to generating RRs for major and CRNM bleeds during the prevention period

Background

The original prevention period NMA presented by the company considered a fixed trial effect, random treatment effect model for assessing relative risks of bleeding events. The ERG considered that this model was inappropriate due both to the presence of zero counts for some treatment arms of some trials and because some of the treatments were only included in a single trial. In particular, the model parameters were only estimable if continuity corrections were applied for the zero counts. In addition, results were sensitive to the value of the continuity correction that was applied.

The ERG requested an alternative analysis which was based on a random trial effect and a fixed treatment effect. This model had the advantage that it required fewer input parameters. It generated less extreme, and more plausible, estimates, particularly for treatment with rivaroxaban.

A further issue was the fact that the company's prevention period NMA combined data from trials with differing durations of follow-up and no adjustment was made to take the differences into account. This approach effectively assumes that the risk of a bleeding event at 6 months following treatment for a VTE is the same as the risk at 36 months after the index event. and is likely to cause systematic bias unless it can be assumed that the vast majority of events occur at the start of the preventative period. Several trials in the network involving warfarin had much longer mean follow-up times (e.g. ASPIRE[61] = 37 months, WARFASA=24[59] months) than the 12 months follow-up in the AMPLIFY-EXT[37] trial. As a consequence, there is a potential for the relative risk of bleeding associated with warfarin treatment to be overstated when compared with treatment with apixaban.

Without detailed data on the timing of bleeding events in individual trials, adjusting for differing study lengths requires the assumption that the rate of bleeding events for a given treatment is constant with respect to time during the whole of preventative treatment. If the incidence rates of bleeding events decrease with time then there is potential for the Poisson this method to under-estimate the risks derived from studies with a longer follow-up period. There is, therefore, some possibility that the Poisson method underestimates the relative risk of bleeding events associated with treatment with warfarin compared to treatment with apixaban. Nevertheless, the method provides a way of presenting estimates based on

assumptions that are at least as, if not more, realistic than those used in the company's original prevention period NMA.

Methods

Fixed effects

Assume the number of major bleeding events for treatment i in trial j is Poisson distributed with mean $\mu_0 \times RR_i \times PY_{ij}$, where μ_0 is the rate of events per year for the baseline treatment (here apixaban 2.5mg), RR_i is the treatment effect of treatment i compared to the baseline (RR = 1 for apixaban) and PY_{ij} is the total person-years of follow-up for treatment i in trial j.

Random effects

For the random treatment effects model the number of events conditional on trial effect φ_j is Poisson with mean $\mu_0 \times RR_i \times PY_{ij} \times \varphi_j$, where the trial effects are log-normally distributed with log-mean 0 and an estimated variance. For the Bayesian analysis, a U[0,2] prior is specified for the log-standard deviation. In each case PY_{ij} is estimated by taking the "Time on treatment" figure for the respective trials from Table 41 of the company's submission and multiplying by the number of patients in the respective arm of the trial.

Major bleeding

Data for the number of events and as well as those for the number of patients are taken from Table 22 of the Appendix to the company's submission.

Bayesian analysis

Results generated using WinBUGS from 50000 samples following a burn-in of 50000 are shown in **Error! Reference source not found.**. The model assumes fixed treatment effects nd random trial effect.

Table 62 Major bleed results (Bayesian analysis)

Treatment	Rate ratio (Posterior Median)	95% Credible interval	
		Lower limit	Upper limit
Apixaban (2.5mg)	1	-	-
Rivaroxaban	5.04	0.80	48.38
Dabigatran	3.10	0.71	24.32
LMWH/VKA (INR 2-3)	5.79	1.48	43.91
Aspirin	2.61	0.54	20.49
No treatment/Placebo	1.80	0.46	13.17

INR=international normalised ratio; LMWH=low molecular weight heparin; VKA=vitamin K antagonist

Non-Bayesian analysis

A maximum likelihood mixed Poisson model with a fixed treatment effect and a random trial effect resulted in an estimated random effects variance of 0 (boundary estimate), suggesting no evidence of heterogeneity, e.g. slight under dispersion of counts. The resulting model is then a fixed treatment and trial effects Poisson Generalised Linear Model. Results are shown in Table 63.

Table 63 Major bleed results (non-Bayesian analysis)

Treatment	Rate ratio (MLE)	95% Confidence interval	
		Lower limit	Upper limit
Apixaban (2.5mg)	1	-	-
Rivaroxaban	3.87	0.71	21.12
Dabigatran	2.53	0.58	11.08
LMWH/VKA (INR 2-3)	4.64	1.12	19.14
Aspirin	2.24	0.48	10.39
No treatment/Placebo	1.43	0.33	6.21

INR=international normalised ratio; MLE=maximum likelihood estimator; LMWH=low molecular weight heparin; VKA=vitamin K antagonist

Discussion

The rate ratio of treatment with LMWH/VKA compared to treatment with apixaban is considerably lower than that generated by either of the company's prevention period NMAs (the original or that generated as part of the clarification process). This is unsurprising since the Poisson method assumes the total person-years follow-up for warfarin (INR 2-3) is 3894.6 years whereas the original risk based approach effective assumed 2173 years. The person-years follow-up for apixaban is unaffected (as the AMPLIFY-EXT[37] follow-up is assumed to be 12 months).

CRNM bleeding

Data for the number of events and patients are taken from Table 23 of the Appendix to the manufacturer's submission.

Bayesian analysis

Results generated using WinBUGS from 50000 samples following a burn-in of 50000. The model assumes fixed treatment effects and random trial effects. Results are shown in Table 64.

Table 64 CRNM bleed results (Bayesian analysis)

Treatment	Rate ratio (MLE)	95% Confidence interval	
		Lower limit	Upper limit
Apixaban (2.5mg)	1	-	-
Rivaroxaban	3.65	1.39	10.24
Dabigatran	2.29	0.96	5.75
LMWH/VKA (INR 2-3)	4.12	1.63	10.75
Aspirin	0.95	0.29	3.25
No treatment/Placebo	0.74	0.40	1.33

INR=international normalised ratio; MLE=maximum likelihood estimator; LMWH=low molecular weight heparin; VKA=vitamin K antagonist

Non-Bayesian analysis

Fitting a model with random trial effects indicated the presence of heterogeneity across trials (study random effects variance 0.537). The resulting model is therefore a fixed treatment, random trial effects model. The maximum likelihood estimates are similar to those of the Bayesian estimate. Results are shown in Table .

Table 4 CRNM bleed results (non- Bayesian analysis)

Treatment	Rate ratio (MLE)	95% Confidence interval	
		Lower limit	Upper limit
Apixaban (2.5mg)	1	-	-
Rivaroxaban	3.50	1.33	9.20
Dabigatran	2.25	0.96	5.26
LMWH/VKA (INR 2-3)	4.02	1.65	9.80
Aspirin	0.80	0.28	2.31
No treatment/Placebo	0.73	0.40	1.32

INR=international normalised ratio; MLE=maximum likelihood estimator; LMWH=low molecular weight heparin; VKA=vitamin K antagonist

Discussion

The impact of adjusting for trial length is less evident for the CRNM bleeding network compared to the network associated with major bleeding. This is primarily a consequence of the exclusion of several of the longer warfarin versus comparator trials from the network due to the absence of reporting of CRNM bleeds.

Appendix 8

Implementation of ERG decision model amendments

Model amendments implemented by the ERG are activated by a series of modification logic switches; these take the value 0 when the original model logic is active, and positive integer values (1, 2,…,n) when alternative values or assumptions are active. The logic switches are labelled Mod_1 to Mod_7.

1. REBASING THE LONG-TERM PREVENTIVE TREATMENT MODEL TO COMMENCE AFTER 6 MONTHS VTE RECURRENCE EVENT-FREE (Mod_1)

Create range name Mod_1 (binary variable taking values 0 or 1)

On Sheet 'Parameters',

Modify formula in cell K34 as follows:

=IF(Settings!$F$13="Lifetime",516-6*Mod_1,Settings!$F$13)

On Sheet 'Markov Apixaban',

Modify formula in cell L32 as follows:

=IF(Extonly="Yes",IF(K32=1,2,3),(IF(AND(K32=1,B32<=1),1,IF(AND(K32=1,B32>=2),2,3))))*(Mod_1=0)+(Mod_1>0)*IF(Extonly="Yes",IF(K32=1,2,3),(IF(AND(K32=1,B32<0),1,IF(AND(K32=1,B32>=0),2,3))))

Copy formulae in cell L32 to range L33: L292

Modify formula in cell P32 as follows:

='RecVTE Curves'!AE9*(Mod_1=0)+(Mod_1>0)*'RecVTE Curves'!AE11

Modify formula in cell Q32 as follows:

='RecVTE Curves'!AF9*(Mod_1=0)+(Mod_1>0)*'RecVTE Curves'!AF11

Copy formulae in range P32:Q32 to range P33: Q292

Modify formula in cell R32 as follows:

=F10*(Mod_1=0)+(Mod_1>0)*MIN(1,CHOOSE($L32,$F$10,$G$10,$H$10)*MBriskadjustmentCycle^$C32)

Modify formula in cell S32 as follows:

=L10*(Mod_1=0)+(Mod_1>0)*MIN(1,CHOOSE($L32,$L$10,$M$10,$N$10)*MBriskadjustmentCycle^$C32)

Modify formula in cell T32 as follows:

=F14*(Mod_1=0)+(Mod_1>0)*MIN(1,CHOOSE($L32,$F$14,$G$14,$H$14)*CRNMBriskadjustmentCycle^$C32)

Modify formula in cell U32 as follows:

=L14*(Mod_1=0)+(Mod_1>0)*MIN(1,CHOOSE($L32,$L$14,$M$14,$N$14)*CRNMBriskadjustmentCycle^$C32)

Copy formulae in range R32:U32 to range R33: U33

Modify formula in cell L330 as follows:

=IF(Extonly="Yes",IF(K32=1,2,3),(IF(AND(K32=1,B32<=1),1,IF(AND(K32=1,B32>=2),2,3))))*(Mod_1=0)+(Mod_1>0)*IF(Extonly="Yes",IF(K32=1,2,3),(IF(AND(K32=1,B32<0),1,IF(AND(K32=1,B32>=0),2,3))))

Copy formulae in cell L330 to range L331: L590

Modify formula in cell P330 as follows:

='RecVTE Curves'!AE9*(Mod_1=0)+(Mod_1>0)*'RecVTE Curves'!AE11

Modify formula in cell Q330 as follows:

='RecVTE Curves'!AF9*(Mod_1=0)+(Mod_1>0)*'RecVTE Curves'!AF11

Copy formulae in range P330:Q330 to range P331: Q590

Modify formula in cell R330 as follows:

=F10*(Mod_1=0)+(Mod_1>0)*MIN(1,CHOOSE($L32,$F$10,$G$10,$H$10)*MBriskadjustmentCycle^$C32)

Modify formula in cell S330 as follows:

=L10*(Mod_1=0)+(Mod_1>0)*MIN(1,CHOOSE($L32,$L$10,$M$10,$N$10)*MBriskadjustmentCycle^$C32)

Modify formula in cell T330 as follows:
=F14*(Mod_1=0)+(Mod_1>0)*MIN(1,CHOOSE($L32,$F$14,$G$14,$H$14)*CRNMBriskadjustmentCycle^$C32)

Modify formula in cell U330 as follows:
=L14*(Mod_1=0)+(Mod_1>0)*MIN(1,CHOOSE($L32,$L$14,$M$14,$N$14)*CRNMBriskadjustmentCycle^$C32)

Copy formulae in range R330:U330 to range R331: U331

On Sheet 'Markov Comp2',
Repeat the above modifications as specified for Sheet 'Markov Apixaban'

2. USE ANNUAL DISCOUNTING INSTEAD OF CONTINUOUS DISCOUNTING (Mod_2)

Create range name Mod_2 (binary variable taking values 0 or 1)

On Sheet 'Markov Apixaban',

Modify formula in cell H33 as follows:
=1/(1+discC)^IF(Mod_2=0,E33,INT(E33))

Modify formula in cell I33 as follows:
=1/(1+discH)^IF(Mod_2=0,E33,INT(E33))

Copy formulae in range H33:I33 to range H34: I292

Modify formula in cell H331 as follows:
=1/(1+discC)^IF(Mod_2=0,E331,INT(E331))

Modify formula in cell I331 as follows:
=1/(1+discH)^IF(Mod_2=0,E331,INT(E331))

Copy formulae in range H331:I331 to range H332: H590

On Sheet 'Markov Comp2',

Modify formula in cell H33 as follows:
=1/(1+discC)^IF(Mod_2=0,E33,INT(E33))

Modify formula in cell I33 as follows:
=1/(1+discH)^IF(Mod_2=0,E33,INT(E33))

Copy formulae in range H33:I33 to range H34: H292

Modify formula in cell H331 as follows:
=1/(1+discC)^IF(Mod_2=0,E331,INT(E331))

Modify formula in cell I331 as follows:
=1/(1+discH)^IF(Mod_2=0,E331,INT(E331))

Copy formulae in range H331:I331 to range H332: H590

3. REVISED TIMING OF TREATMENT COSTS (Mod_3)

Create range name Mod_3 (binary variable taking values 0 or 1)

On Sheet 'Markov Apixaban',

Modify formula in cell CH33 as follows:
=(IF(Mod_3=0,AVERAGE($AL32:$AL33),$AL32)*CHOOSE($CG33,CH$27,CH$28,CH$29,$CH$30))*$H32

Copy formula in cell CH33 to range CH34:CH292

Modify formula in cell CH331 as follows:
=(IF(Mod_3=0,AVERAGE($AL330:$AL331),$AL330)*CHOOSE($CG331,CH$325,CH$326,CH$327,$CH$328))*$H330

Copy formula in cell CH33 to range CH332:CH590

On Sheet 'Markov Comp2',

Modify formula in cell CH33 as follows:
=(IF(OR(Mod_3=0,comp2=5),AVERAGE($AL32:$AL33),$AL32)*CHOOSE($CG33,CH$27,CH$28,CH$29,$CH$30))*$H32

Copy formula in cell CH33 to range CH34:CH292

Modify formula in cell CH331 as follows:

=(IF(OR(Mod_3=0,comp2=5),AVERAGE($AL330:$AL331),$AL330)*CHOOSE($CG331,CH$325,CH$326,CH$327,$CH$328))*$H330

Copy formula in cell CH33 to range CH332:CH590

4. Use English mean body weight in place of trial mean weight (Mod_4)

Create range name Mod_4 (binary variable taking values 0 or 1)

On Sheet 'Parameters',

Modify formula in cell K44 as follows:

=IF(Mod_4=0,Population!$F$24,77.4)

5. Alternative hazard ratios for long-term Major Bleeding, CRNM, and VTE events/deaths (Mod_5)

Create range name Mod_5 (binary variable taking values 0 or 1)

Modify various cell formulae as follows:

Sheet	Cell	Revised formula
Recurrent VTE	F29	=IF(Mod_5=0,1.08,0.9901)
	F30	=IF(Mod_5=0,1.31,1.1236)
	F31	=IF(Mod_5=0,1.2,1.1111)
	G29	=IF(Mod_5=0,0.69,0.6803)
	G30	=IF(Mod_5=0,0.79,0.7576)
	G31	=IF(Mod_5=0,0.85,0.8264)
	H29	=IF(Mod_5=0,1.69,1.4706)
	H30	=IF(Mod_5=0,2.16,1.7241)
	H31	=IF(Mod_5=0,1.7,1.5385)
	M29	=IF(Mod_8=0,CHOOSE(s_apixExt,X29,AA29),1)
	M30	=IF(Mod_8=0,IF(Mod_5=0,CHOOSE(s_apixExt,X30,AA30),0.5882),1)
	M31	=IF(Mod_5=0,CHOOSE(s_apixExt,X31,AA31),0.4098)
	M33	=IF(Mod_5=0,CHOOSE(s_apixExt,X33,AA33),3.7037)
	M34	=IF(Mod_5=0,CHOOSE(s_apixExt,X34,AA34),5.2632)
	N29	=IF(Mod_5=0,CHOOSE(s_apixExt,Y29,AB29),0.369)
	N30	=IF(Mod_5=0,CHOOSE(s_apixExt,Y30,AB30),0.2222)
	N31	=IF(Mod_5=0,CHOOSE(s_apixExt,Y31,AB31),0.1587)
	N33	=IF(Mod_5=0,CHOOSE(s_apixExt,Y33,AB33),2.0408)
	N34	=IF(Mod_5=0,CHOOSE(s_apixExt,Y34,AB34),3.125)
	O29	=IF(Mod_5=0,CHOOSE(s_apixExt,Z29,AC29),2.5)
	O30	=IF(Mod_5=0,CHOOSE(s_apixExt,Z30,AC30),1.4925)
	O31	=IF(Mod_5=0,CHOOSE(s_apixExt,Z31,AC31),1.0309)
	O33	=IF(Mod_5=0,CHOOSE(s_apixExt,Z33,AC33),7.1429)
	O34	=IF(Mod_5=0,CHOOSE(s_apixExt,Z34,AC34),10)
Bleeding	G24	=IF(Mod_5=0,1.83,1.7857)
	G25	=IF(Mod_5=0,2.51,2.5)
	G26	=IF(Mod_5=0,3.33,3.2258)
	H24	=IF(Mod_5=0,0.92,0.9615)
	H25	=IF(Mod_5=0,1.23,1.3333)
	H26	=IF(Mod_5=0,1.89,1.9608)
	I24	=IF(Mod_5=0,3.76,3.4483)
	I25	=IF(Mod_5=0,5.34,4.7619)
	I26	=IF(Mod_5=0,6.25,5.8824)
	G77	=IF(Mod_5=0,2.12,2.1277)
	G78	=IF(Mod_5=0,1.25,1.1364)
	G79	=IF(Mod_5=0,2.08,2.0408)
	H77	=IF(Mod_5=0,1.62,1.6667)

	H78	=IF(Mod_5=0,0.89,0.8264)
	H79	=IF(Mod_5=0,1.67,1.6393)
	I77	=IF(Mod_5=0,2.8,2.7778)
	I78	=IF(Mod_5=0,1.75,1.5873)
	I79	=IF(Mod_5=0,2.63,2.5641)
	N24	=IF(Mod_8=0,CHOOSE(Mod_5+1,CHOOSE(s_apixExt,X24,AA24), 7.14,5.04,3.87),1)
	N25	=IF(Mod_8=0,CHOOSE(Mod_5+1,CHOOSE(s_apixExt,X25,AA25), 4.17,3.1,2.53),1)
	N26	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,X26,AA26),9.09,5.79,2.53)
	N28	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,X28,AA28),3.7,2.61,2.24)
	N29	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,X29,AA29),2.5,1.8,1.43)
	O24	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,Y24,AB24),0.75,0.8,0.71)
	O25	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,Y25,AB25),0.68,0.71,0.58)
	O26	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,Y26,AB26),1.54,1.48,0.58)
	O28	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,Y28,AB28),0.57,0.54,0.48)
	O29	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,Y29,AB29),0.53,0.46,0.33)
	P24	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,Z24,AC24),100,48.38,21.12)
	P25	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,Z25,AC25),33.33,24.32,11.08)
	P26	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,Z26,AC26),100,43.91,11.08)
	P28	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,Z28,AC28),33.33,20.49,10.39)
	P29	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,Z29,AC29),20,13.17,6.21)
	N77	=IF(Mod_8=0,CHOOSE(Mod_5+1,CHOOSE(s_apixExt,X77,AA77), 3.03,3.65,3.5),1)
	N78	=IF(Mod_8=0,CHOOSE(Mod_5+1,CHOOSE(s_apixExt,X78,AA78), 2.04,2.29,2.25),1)
	N79	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,X79,AA79),3.85,4.12,4.02)
	N81	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,X81,AA81),0.91,0.95,0.8)
	N82	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,X82,AA82),0.75,0.74,0.73)
	O77	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,Y77,AB77),1.25,1.39,1.33)
	O78	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,Y78,AB78),0.91,0.96,0.96)
	O79	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,Y79,AB79),1.64,1.63,1.65)
	O81	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,Y81,AB81),0.3,0.29,0.28)
	O82	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,Y82,AB82),0.41,0.4,0.4)
	P77	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,Z77,AC77),100,10.24,9.2)
	P78	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,Z78,AC78),4.76,5.75,5.26)
	P79	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,Z79,AC79),9.09,10.75,9.8)
	P81	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,Z81,AC81),2.86,3.25,2.31)
	P82	=CHOOSE(Mod_5+1,CHOOSE(s_apixExt,Z82,AC82),1.33,1.33,1.32)

6. Correct formula error for LMWH monotherapy administration (Mod_6)

NB this amendment is not used in the ERG report as it is not normally relevant to the main assessment scenarios

Create range name Mod_6 (binary variable taking values 0 or 1)

On Sheet 'per cycle calculations',

Modify formula in cell F102 as follows:

=IF(Mod_6=0,(c_training)+((1-c_pSuccessEduc)*c_admin*timeDaysinCycle)*(1-pPEInpatient),((c_training)+((1-c_pSuccessEduc)*c_admin*timeDaysinCycle))*(1-pPEInpatient))

Modify formula in cell G102 as follows:

=IF(Mod_6=0,(c_training)+((1-c_pSuccessEduc)*c_admin*timeDaysinCycle)*(1-pDVTInpatient),((c_training)+((1-c_pSuccessEduc)*c_admin*timeDaysinCycle))*(1-pDVTInpatient))

7. ALTERNATIVE MEAN POPULATION UTILITY VALUES (Mod_7)

Create range name Mod_7 (variable taking values 0, 1, 2 or 3)

On Sheet 'Utility',

Modify formula in cell H11 as follows:
=IF(Mod_7=0,0.825,0.823)

Modify formula in cell I11 as follows:
=IF(Mod_7=0,0.17,0.004)

Create new ERG utility table in range K12:M18, and define its range name as 'ERG_utils'

Enter table values as follows:

18	0.94	0.0069
25	0.93	0.0055
35	0.91	0.0068
45	0.85	0.0113
55	0.80	0.0118
65	0.78	0.0118
75	0.73	0.0152

On Sheet 'Markov Apixaban',

Modify formula in cell G32 as follows:
=CHOOSE(Mod_7+1,Baselineutility,Baselineutility,INDEX(UtilityByAge,MATCH(F32,UtilityByAgeCat,1)),VLOOKUP(F32,ERG_utils,2))*timeDaysinCycle/timeDaysInYear

Copy formula in cell G32 to range G33:G292

On Sheet 'Markov Comp2',

Modify formula in cell G32 as follows:
=CHOOSE(Mod_7+1,Baselineutility,Baselineutility,INDEX(UtilityByAge,MATCH(F32,UtilityByAgeCat,1)),VLOOKUP(F32,ERG_utils,2))*timeDaysinCycle/timeDaysInYear

Copy formula in cell G32 to range G33:G292

8. SCENARIO ANALYSIS: EQUAL EFFICACY & BLEEDING RISKS FOR ALL NOACs (Mod_8)

Create range name Mod_8 (binary variable taking values 0 or 1)
This is implemented by the formula changes shown above for Mod_5.

9. AGE/SEX/EVENT POPULATION WEIGHTED AVERAGE RESULTS

This modification to the company model requires use of a new VBA macro **GetICER** (activated by pressing **Ctrl+Shift+I**). The calculations are carried out in a new worksheet (ByAge) which is included in the ERG modified version of the model, together with the new macro code.

On Sheet 'Population',

Set the value of cell F4 = 0 (default value when macro is not active)

Modify formula in cell F7 as follows:
=IF(F4=1,ByAge!C2,0.342)

Modify formula in cell F13 as follows:
=IF(F4=1,ByAge!B2,0.5871)

Modify formula in cell F19 as follows:
=IF(F4=1,ByAge!A2,56.9)

On Sheet 'Markov Apixaban',

Modify formula in cell BY33 as follows:
=(AVERAGE(CD32:CD33)*timeDaysinCycle/timeDaysInYear)

Copy formula in cell BY33 to range BY34:BY292

Modify formula in cell BY295 as follows:
=SUMIFS(BY32:BY292,$E$32:$E$292,"<="&timeHorizon,$E$32:$E$292,">"&0)

Modify formula in cell BY331 as follows:

=(AVERAGE(CD330:CD331)*timeDaysinCycle/timeDaysInYear)

Copy formula in cell BY331 to range BY332:BY590

Modify formula in cell BY592 as follows:

=SUMIFS(BY330:BY590,$E$32:$E$292,"<="&timeHorizon,$E$32:$E$292,">"&0)

On Sheet 'Markov Comp2',

Repeat the same amendments as shown above for