NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

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

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- The AMPLIFY trials:
  - assessed the effectiveness of anticoagulation post 6-months (AMPLIFY-EXT) for people in whom there was uncertainty about whether continued anticoagulation was needed (clinical equipoise) and did not include people in whom continued anticoagulation was definitely indicated
  - did not include people who had a provoked VTE and were considered at no risk of having a recurrent event.

  Are the efficacy estimates from the AMPLIFY trials applicable to all people who would be indicated for apixaban according to its marketing authorisation?

- Are the characteristics of the populations in AMPLIFY and AMPLIFY-EXT generalisable to the population who would receive apixaban in clinical practice in England?
- To what extent are vitamin K antagonists and rivaroxaban used in clinical practice for the treatment and prevention of venous thromboembolism (VTE)? What is the main comparator for apixaban in this indication?
- Is dabigatran etexilate a relevant comparator for apixaban?
- In both network meta-analyses (NMA 1 combining trials assessing treatment and NMA 2 combining trials assessing secondary prevention) apixaban was similarly effective in preventing recurrent VTE and VTE-related deaths, but the estimated rates of major or clinically relevant non-major bleeding were lower with apixaban than its comparators. Can the combining of indirect evidence in these meta-analyses provide a robust estimate of the relative efficacy and safety of apixaban compared with its comparators?
- The prevention network meta-analysis (NMA 2) carried out by the company compared apixaban with a vitamin K antagonist (VKA), rivaroxaban, dabigatran, aspirin and placebo for preventing a recurrent VTE in people who had received between 6 weeks and 18 months treatment for their initial VTE. The studies included in NMA 2 varied in the length of time people received treatment for secondary prevention (6-37 months) and the length of follow up (10 to 37 months). The company asserted that the different treatment periods and follow up times would not significantly impact the size of the relative treatment effect, but the ERG considered that there are likely to be more events in studies with longer treatment follow up times and it was inappropriate to combine the studies included in NMA2 to estimate the relative efficacy of apixaban and its comparators. Are the efficacy estimates from NMA 2 robust?

Cost effectiveness

- The company presented base case results for a 6-month treatment duration and a lifelong treatment duration.
    - In the 6 month treatment duration base case the ICER for apixaban compared with LMWH/VKA was £2,406 per QALY gained and apixaban dominated (was more effective and less costly than) rivaroxaban and LMWH/dabigatran.

  - In the lifelong treatment duration base case the ICER for apixaban compared with LMWH/VKA was £16,676 per QALY gained. Rivaroxaban was dominated by LMWH/VKA and LMWH/dabigatran was extendedly dominated by LMWH/VKA and apixaban.
  - In all sensitivity analyses for the 6 month duration base case the ICER for apixaban compared with its comparators remained below £20,000 per QALY gained.
  - The sensitivity analyses that resulted in the largest impact in the ICER for lifelong treatment were those in which the bleeding risk was equivalent or nearly equivalent between apixaban and its comparators.
- The ERG noted that it could not test the plausibility or effect on the results of several assumptions because it did not have the data required to do so or the model structure did not allow it to. These included:
  - Testing the effect of assuming that the risks of further recurrent VTE events if a person has already had a recurrent VTE are higher than the risk of a first recurrent VTE. It is assumed in the base case that a person's risk of a recurrent VTE is independent of whether they have had a recurrent VTE previously.
  - Testing whether the company's assumption that the risks of events measured at the final data collection point in AMPLIFY-EXT would be expected to stay the same over lifelong treatment duration.

  Can the cost effectiveness results be considered a reliable basis for decision making?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of apixaban within its licensed indication for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism.

Table 1 Decision problem

	Final scope issued	Decision problem	Comments from the	Comments from the

	by NICE	addressed in the submission	company	ERG
Pop.	People with deep vein thrombosis and/or pulmonary embolism		none	No clinical data presented for people: • with distal DVT; • who had a definite need for continued anticoagulation post 6-months; • who had a provoked VTE but considered at no risk of having recurrent event.
Int.	Apixaban		none	none
Com.	• Initial treatment with a low molecular weight heparin or fondaparinux and continued vitamin K antagonist • Rivaroxaban For people for whom a vitamin K antagonist is unsuitable: • Low molecular weight heparin or fondaparinux alone • rivaroxaban	As stated in the final scope 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 was however considered a relevant comparator and is therefore included in this submission.	Fondaparinux not a relevant comparator because rarely used in the UK and the Committee accepted that it was not a comparator in technology appraisal 287 (rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism). There is no evidence identified through systematic review on relative effectiveness of LMWH monotherapy or rivaroxaban compared with apixaban in a population in whom warfarin [VKA] is unsuitable. The efficacy and safety	Agreed with company's exclusion of fondarparinux as a comparator because clinical advice to ERG was that fondaparinux is rarely used in clinical practice in England and Wales as treatment for VTE. The ERG agreed that the company had tried to find evidence for the clinical effectiveness of apixaban in people in whom a VKA is not suitable (e.g. people with allergy/intolerance of VKA, people with cancer, pregnant women, people with highly unstable INRs, intravenous drug users, people with HIV, people

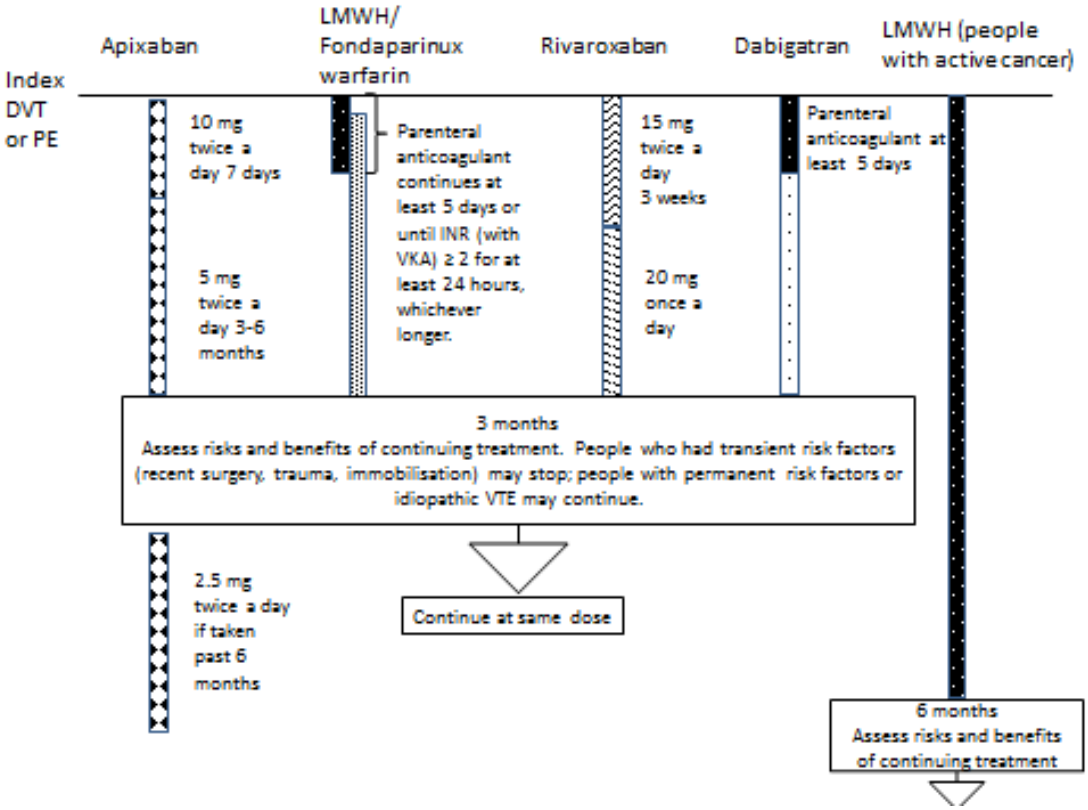
			of apixaban is not established in patients with active cancer. LMWH/dabigatran is now licensed for the treatment and prevention of recurrent DVT and/or PE, and is currently being appraised by NICE for this indication. LMWH/dabigatran was acknowledged at the scoping meeting for the apixaban appraisal by the NICE Chair and VTE clinical experts as being a relevant comparator, however it was not included in the final scope	with chronic alcoholism and people at high risk of non-compliance to VKA). ERG agreed no relevant evidence was available.
Out.	• Mortality • Venous thromboembolism recurrence • Complications following deep vein thrombosis or pulmonary embolism, including post thrombotic syndrome and chronic thromboembolic pulmonary hypertension • Adverse effects of treatment (particularly bleeding, including intracranial and gastrointestinal bleeding)	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.		The ERG commented that the lack of health related quality of life data [from a clinical trial] was disappointing.

	• Health-related quality of life.			

2 The technology and the treatment pathway

2.1 Apixaban (Eliquis, Bristol-Myers Squibb and Pfizer) is an anticoagulant which affects the blood coagulation cascade by directly inhibiting activated factor X (factor Xa), which inhibits thrombin formation and the development of thrombi (blood clots). It is administered orally. To treat deep vein thrombosis (DVT) or pulmonary embolism (PE) 10 mg apixaban should be taken twice a day for the first 7 days, followed by 5 mg twice a day for at least 3 months. For the prevention of recurrent DVT or PE people who have completed 6 months of treatment of their initial DVT or PE should take 2.5 mg twice a day. The Summary of Product Characteristics states that apixaban should be used with caution in people with severe renal impairment.

Figure 1: anticoagulant treatment regimens following a deep vein thrombosis or pulmonary embolism



2.2 NICE clinical guideline 144 recommends offering people with confirmed proximal deep vein thrombosis or pulmonary embolism a choice of low molecular weight heparin (LMWH) or fondaparinux to be started as soon as possible and a vitamin K antagonist such as warfarin should be started within 24 hours. Unfractionated heparin is recommended for some patient groups as an alternative option to LMWH or fondaparinux including people with severe renal failure, people with a pulmonary embolism with haemodynamic instability or people at increased risk of bleeding. Treatment with LMWH, fondaparinux or unfractionated heparin should continue for at least 5 days or until an international normalised ratio (INR) of greater than or equal to 2 is reached for at least 24 hours, whichever is longer. The guidance states that treatment with a vitamin K antagonist should continue for at least 3 months and may be continued depending on the person's risk of bleeding. Monitoring and possible adjustment of dose is needed with the use of vitamin K

antagonists. For people in whom a vitamin K antagonist is not considered an appropriate treatment, unfractionated heparin or LMWH may be continued instead. In particular, it is recommended that people with active cancer should receive LMWH monotherapy for at least 6 months. NICE technology appraisals 261 and 287 also recommend rivaroxaban as an option for treating deep vein thrombosis and pulmonary embolism respectively. NICE technology appraisal 327 recommends dabigatran etexilate for treating deep vein thrombosis and pulmonary embolism.

Table 2 Technology

	Apixaban	**Dabigatran etexilate**	**Rivaroxaban**	**Vitamin K antagonist (VKA) warfarin**	**Low molecular weight heparin**
Marketing authorisation‡	Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT, and PE in adults.			Prophylaxis and treatment of venous thrombosis and pulmonary embolism	The treatment of venous thrombotic disease presenting with deep vein thrombosis, pulmonary embolism or both
Administration method	Oral apixaban 10 mg twice daily for 7 days, 5 mg twice daily for at least 3 months. If needed past 6 months dose is 2.5 mg twice daily.	Oral dabigatran 150 mg twice daily preceded by acute parenteral treatment (LMWH) for at least 5 days	Oral rivaroxaban 15 mg twice daily for 3 weeks, then 20 mg once daily	Oral warfarin dosed to achieve a target INR of 2.0 to 3.0, preceded by acute parenteral treatment	Subcutaneous injection. Dose by body weight (dose varies by LMWH), once or twice daily
Setting	Inpatient or outpatient				
Acquisition cost/day	£4.40 first 7 days, £2.20 thereafter	£2.20*	£4.20 first 21 days £2.10 thereafter.	£0.009*	£9.02
Duration of treatment	At least 3 months				Around 5-8 days (if used with warfarin

		or dabigatran). At least 6 months for people with cancer with DVT and or PE.

‡ showing indications relating to DVT/PE only; *Does not include costs of initial parenteral treatment

3 Comments from consultees

3.1 Patient and professional groups stated that the available treatment options for people who have a PE or DVT are LMWH with warfarin or rivaroxaban (see section 2.2). The groups noted that apixaban can be used in both primary and secondary care and specialist clinics and the initiation of anticoagulation treatment is primarily in secondary care. The professional groups stated that apixaban (and rivaroxaban), unlike warfarin, does not need monitoring of anticoagulation and dose adjustments and as such is expected by professional groups to be simpler to use than LMWH with warfarin. However they noted that the dose of both apixaban and rivaroxaban needs to be reduced after 7 and 21 days of treatment respectively. A professional group stated that doctors should discuss the different treatment options with the patient when deciding which treatment is the best option but the differences between rivaroxaban and apixaban may be difficult to explain to patients. They noted that although the level of anticoagulation experienced does not need to be routinely monitored during treatment with apixaban, dose adjustments are needed for people with renal impairment, and renal function needs to be monitored while on apixaban.

3.2 The patient group explained the experience of having a DVT or PE and the impact of warfarin monitoring on patients' lives. It stated that a DVT can cause pain, swelling, a feeling of heaviness, warmth, redness and tenderness of the affected limb and a person's mobility may be affected. A

PE may cause breathlessness, chest pain or cause the person to collapse and in some cases it can be fatal. It stated that recovery from a PE may require intensive care and can take up to several months and the increased risk of having another venous thromboembolism (VTE) is of considerable concern to patients. Treatment with warfarin requires frequent monitoring, involving multiple blood tests to check that the person's INR is in the therapeutic range and they are taking the correct dose. This monitoring can impact on a person's work and lifestyle because they have to attend monitoring appointments and because warfarin can be affected by diet and is contraindicated to other drugs.

3.3 Professional groups highlighted that because apixaban (and rivaroxaban) do not need routine monitoring and dose adjustment, there are less opportunities to assess whether people are taking their treatment. They noted that if people miss dose(s) of apixaban, they may not be getting the anticoagulation they need, particularly as apixaban has a short half-life. The professional groups further noted that there is no routine blood test for the level of anticoagulation and there is no antidote to reverse the effect of apixaban if a person experienced a bleed whilst taking the drug.

3.4 One professional group highlighted that the AMPLIFY trial excluded: people with hospital acquired thrombosis following surgery or medical treatment and these people would typically need only 3 months of anticoagulant therapy; people with cancer and people with poor renal function. It therefore noted that AMPLIFY may not reflect all people who need anticoagulation for treating and preventing DVT and PE in current UK practice. One professional group noted that there may be people with extensive thrombosis (e.g. massive or sub-massive pulmonary embolism or ileofemoral deep vein thrombosis) who may not be eligible for apixaban.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company submission presented clinical effectiveness data from 2 trials: AMPLIFY and AMPLIFY-EXT. AMPLIFY was a randomised, active controlled, parallel-group, double blind, triple dummy study carried out in 28 countries including 14 in Europe. There were no study centres in the UK. The aim of AMPLIFY was to determine if apixaban was non-inferior to LMWH/warfarin 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. The criteria to demonstrate non-inferiority were a relative risk (RR) of less than 1.8 and a risk difference of less than 3%. Participants were randomised 1:1 to apixaban (n=2691) or LMWH/warfarin (n=2704). The dose of apixaban was 10 mg twice a day for 7 days followed by 5 mg twice a day. People in the LMWH/warfarin arm received 1 mg/kg subcutaneous enoxaparin (a LMWH) twice a day for at least 5 days and warfarin to achieve an INR of between 2 and 3. People stopped enoxaparin when they had met the target INR and the median duration of enoxaparin treatment was 6.5 days (interquartile range 5.0 to 8.0). Participants were treated for 6 months and were followed up for a further 30 days after they stopped treatment.

4.2 AMPLIFY-EXT was a randomised, parallel-group, double-blind, placebo-controlled study carried out in 28 countries including 7 centres in the UK. The aim of AMPLIFY-EXT was to determine if 2.5 mg or 5 mg twice daily apixaban was superior to placebo for the composite endpoint of symptomatic, recurrent VTE (non-fatal DVT or non-fatal PE) or all cause death in people who had an objectively documented index event of a proximal symptomatic DVT or symptomatic PE, who had completed 6 to 12 months of anticoagulant therapy for the treatment of their index event. The study included people who were considered to be at ‘clinical equipoise’ meaning that there was uncertainty about whether continued anticoagulation was needed (people

who definitely needed further anticoagulation were excluded from the study). People were randomised 1:1:1 to apixaban 2.5 mg twice daily (n=840); apixaban 5 mg twice daily (n=813) or placebo (n=829). People were treated for 12 months and were followed for a further 20 days after they stopped treatment. The company presented the results for the 2.5 mg dose of apixaban compared with placebo because it is the licensed dose if anticoagulation with apixaban is continued post-6 months (see section 2.1).

4.3 The mean age of people in AMPLIFY was 57 years and 58% of the population were male. The majority of people in the study (65%) had been randomised following a DVT, 25% had a PE and 9% had both a DVT and PE (the qualifying diagnosis for entry into the study could not be evaluated in the remaining people). The majority of people (90%) had a VTE which was considered unprovoked. Sixty six people (2.5%) in the apixaban arm and 77 people (2.9%) in the LMWH/warfarin arm had active cancer. Please see table 9 on page 48 of the company's submission for the full list of baseline characteristics in AMPLIFY. The mean age in AMPLIFY-EXT was also 57 years and 57% of the population were male. The qualifying diagnosis for inclusion in the study was DVT in 65% of the population and PE in 35% and 92% had a VTE considered unprovoked. Fifteen people (1.8%) in the apixaban 2.5 mg arm and 18 people (2.2%) in the placebo arm had active cancer. Please see table 10 on page 49 of the company's submission for the full list of baseline characteristics in AMPLIFY-EXT.

ERG comments

4.4 The ERG noted that the participants in both AMPLIFY and AMPLIFY-EXT were younger than the patients seen in clinical practice and that relatively few people were aged 75 years or over (14.3% in AMPLIFY and 13.3% in AMPLIFY- EXT). The ERG stated that a UK cohort study had found that the mean age of people having an unprovoked PE was 64 years and that 47% of these people were male. The ERG further commented that the proportion of males in the UK cohort study was smaller than the proportion of males in AMPLIFY and AMPLIFY-EXT (58% and 56% respectively).

4.5 The ERG discussed whether the population in AMPLIFY and AMPLIFY-EXT was representative of people who would receive apixaban for treating and preventing recurrent VTE. The ERG noted that both trials recruited patients who had a proximal DVT or PE and excluded people who had distal DVT. The ERG considered that the exclusion of patients with distal DVT may be appropriate because clinical advice to the ERG was that the duration of treatment for patients with distal DVT was likely to be 6 weeks, whereas for a proximal DVT people would be treated for at least 3 months. The ERG commented that AMPLIFY-EXT included people considered to be at clinical equipoise meaning that the risks and benefits of having continued anticoagulation were unclear. People who definitely needed extended anticoagulation were not included in this trial and the ERG noted that the extent to which the results of the AMPLIFY-EXT trial are directly applicable to patients who definitely require anticoagulation past 6 months was not discussed by the company in its submission. The ERG further commented that the clinical equipoise population in AMPLIFY-EXT was not clearly defined and open to subjectivity, noting that similar concerns had been raised about trials of extended treatment with rivaroxaban and dabigatran etexilate in populations described as being in clinical equipoise in previous NICE appraisals. The ERG lastly noted that there were no clinical data for people who had a provoked index event but were not considered to be at risk of a recurrent event because these people were not included in the trial.

4.6 The ERG commented that the company had stated that apixaban is not licensed for people with active cancer. It further noted that people with active cancer for whom treatment with LMWH was planned were excluded from AMPLIFY and these people were unlikely to meet the clinical equipoise criteria for AMPLIFY–EXT because patients with active cancer are treated with LMWH for extended periods of time. However, it noted that there were a small number of people with active cancer in AMPLIFY and it was unclear how these people had been recruited to the study given the study's inclusion and exclusion criteria.

4.7 The ERG noted that company reported the results from the trials for the majority of outcomes listed in the final scope issued by NICE. The exceptions were that trial data on post-thrombotic syndrome (PTS), chronic thromboembolic pulmonary hypertension and health related quality of life was not collected in the AMPLIFY trials.

Clinical trial results

4.8 In AMPLIFY, the efficacy population was the 'efficacy evaluable patients for primary endpoint' defined as the intention-to-treat population for whom the outcome status at 6 months was documented (2609 people in the apixaban arm and 2635 people in the LMWH/warfarin arm). In the apixaban arm 59 people (2.3%) and 71 people (2.7%) in the LMWH/warfarin arm had a recurrent VTE or died because of a VTE (relative risk RR 0.84, 95% CI 0.60 to 1.18, p<0.01 for non-inferiority). Secondary outcomes from AMPLIFY are reported in table 19 on page 65 of the company's submission.

4.9 In AMPLIFY-EXT, all efficacy outcomes were analysed in the ITT population. Results for the primary outcome were imputed so that patients who were lost to follow-up were counted as having had a primary outcome event. There were 13 people in the apixaban arm (1.5%) and 19 people in the placebo arm (2.3%) who were lost to follow up. In this ITT analysis 33 people (3.8%) in the apixaban 2.5 mg arm and 96 people (11.6%) in the placebo arm had recurrent VTE or died by 12 months (RR 0.33, 95% CI 0.22 to 0.48, [redacted]). The company carried out sensitivity analyses in which it used different approaches to input missing data from people who were lost to follow up. The results of the sensitivity analyses were reported in the clinical study report for AMPLIFY-EXT and were consistent with the findings of the primary efficacy analysis, demonstrating a statistically significantly lower number of recurrent VTE events or VTE related deaths with apixaban in comparison to placebo. Secondary outcomes from AMPLIFY-EXT are reported in table 26 on page 72 of the company submission.

ERG comments

4.10 The ERG commented that the dose of the LMWH enoxaparin used in AMPLIFY (1 mg/kg twice daily) was different from the dose administered to patients in clinical practice in England and Wales (1.5mg/kg once daily). The ERG noted that the company stated that published evidence suggested that once or twice daily doses of enoxaparin are as effective as unfractionated heparin for the treatment of VTE and that the 1 mg/kg twice daily dose of enoxaparin had been used in the trials that provided the key evidence in NICE technology appraisal 261. The ERG further commented that advice from its clinical experts was that the difference in the doses of enoxaparin used in the AMPLIFY trial and in clinical practice in England and Wales was unlikely to have any impact on the outcomes of the AMPLIFY trial.

Adverse effects of treatment

4.11 In AMPLIFY the proportion of people who discontinued treatment in the apixaban and LMWH/warfarin groups was comparable (14.0% vs. 15.3% respectively). The most frequent reason for discontinuation was having an adverse event (5.6% of people in the apixaban arm and 6.7% of people in the LMWH/warfarin arm). In AMPLIFY-EXT fewer people discontinued treatment before 12 months in the apixaban arm (13.6%) than the placebo arm (22.7%). The proportion of people who discontinued due to adverse events (which included recurrent VTE) was 7.7% in the apixaban arm and 15.2% in the placebo arm.

4.12 In AMPLIFY, fewer people (15 [0.6%]) in the apixaban arm had a major bleed than the LMWH/warfarin arm (49 [1.8%]) (RR 0.31, 95% CI 0.17 to 0.55; $p<0.001$). Three people (0.1%) in the apixaban arm and 6 people (0.2%) in the LMWH/warfarin arm had an intracranial bleed. Seven people (0.3%) in the apixaban arm and 18 people (0.7%) in the LMWH/warfarin arm had a major gastrointestinal bleed. One person in the apixaban arm and 2 people in the LMWH/ warfarin arm died because of their bleed. The company noted that the rates of major bleeds across the pre-specified subgroups were

consistent with the full population. Fewer people had a clinically relevant non-major bleed with apixaban (103, 3.8%) than LMWH/warfarin (215, 8.0%) (RR 0.48, 95% CI 0.38 to 0.60). In AMPLIFY 67.1% of people in the apixaban arm and 71.5% of people in the LMWH/warfarin arm had an adverse event; 15.6% of people in the apixaban arm and 15.2% of people in the LMWH/warfarin arm had a serious adverse event.

4.13 In AMPLIFY-EXT similar proportions of people in the 2.5 mg apixaban arm (71.0%) and the placebo arm (73.4%) had an adverse event and a higher proportion of people in the placebo group (19.1%) had a serious adverse event than the 2.5 mg apixaban group (13.3%). DVT was classed as an adverse event. In AMPLIFY-EXT similar proportions of people in the 2.5 mg apixaban arm (3.2%) and placebo arm (2.7%) had major or clinically relevant non-major bleeding RR 1.20, 95% CI 0.69 to 2.10.

ERG comments

4.14 The ERG noted that in the LMWH/warfarin arm of AMPLIFY a greater proportion of people whose index event was a PE (with or without DVT) had a major bleed (25/902, 2.8%) than people whose index event was a DVT (24/1772, 1.4%).

Meta-analyses

4.15 The company did not identify any head-to-head trials comparing apixaban with rivaroxaban or dabigatran etexilate for treating DVT or PE or the secondary prevention of recurrent VTE. It therefore carried out 2 network meta-analyses; the first (NMA 1) included trials which assessed anticoagulant therapy for the treatment of an initial VTE event and the second (NMA2) included trials which assessed extended anticoagulant therapy in people who had already received treatment for a VTE event and were receiving continued treatment with an anticoagulant for secondary prevention of a recurrent event.

4.16 NMA 1 was carried out to estimate the relative treatment effect and safety of apixaban compared with rivaroxaban and dabigatran etexilate for the treatment of an initial VTE event and included the following trials:

- AMPLIFY- comparing apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily) with LMWH/warfarin. The ITT data set was used for efficacy analyses and the on-treatment population was used for safety analyses.
- RE-COVER and RE-COVER II. These were 2 trials, identical in design, comparing unfractionated heparin (UFH) or LMWH/ dabigatran etexilate with UFH or LMWH/warfarin. A modified ITT data set was used for efficacy analyses in which people who did not receive any study drug were excluded. The on-treatment population was used for safety analyses.
- EINSTEIN DVT and EINSTEIN PE. These 2 trials differed by the index event a person had (DVT or PE). Both trials compared rivaroxaban (15 mg twice daily for 21 days followed by 20 mg once daily). The company used a pooled data set from these trials. The ITT data set was used for efficacy analyses, the on-treatment population was used for safety analyses.

The company noted that the majority of trials in the network used a modified ITT analysis that is, people from the ITT population who had no outcome data were excluded from the analysis. The company presented results using a fixed effects model, because there were a small number of studies in the network.

4.17 The results for the treatment period network meta-analysis (NMA1) are presented in table 3. There were no differences in the number of recurrent VTE or VTE- related deaths with apixaban compared with LMWH/VKA, LMWH/dabigatran or rivaroxaban. There were statistically significantly lower rates of bleeding (the composite outcome of major or clinically relevant non major bleeding, major bleeding assessed separately and clinically relevant non-major bleeding) with apixaban compared with LMWH/VKA, LMWH/dabigatran and rivaroxaban. In response to clarification, the company re-ran the meta-analysis different statistical modelling assumptions requested

by the ERG (these included using an alternative vague prior for the trial effect and treating the trial effect as random rather than fixed). These results, shown in table 3 and labelled 'analysis requested by ERG', resulted in marginal differences to the company's base case results. The company carried out 3 further sensitivity analyses in which it used a modified ITT population rather than the ITT population, used published pooled results from RE-COVER and RE-COVER II rather than using the results from each trial separately and in which it excluded the dabigatran trials from the meta-analysis. The impact of these sensitivity analyses were marginal (for the results please see table 35 on pages 90 to 91 of the company's submission).

Table 3: Base case analysis for treatment period network (NMA 1) results – 6 month timepoint – fixed-effect model (statistically significant results are shown in bold) (Company submission table 34 page 90, clarification response table 4 page 25, ERG report table 26 page 76).

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*			
Base case	[redacted]	0.76 (0.46, 1.27)	0.93 (0.59, 1.46)
Analysis requested by ERG	[redacted]	[redacted]	[redacted]
Major or CRNM bleeding			
Base case	[redacted]	**0.69 (0.51, 0.94)**	**0.47 (0.36, 0.61)**
Analysis requested by ERG	[redacted]	[redacted]	[redacted]
Major bleeding			
Base case	[redacted]	**0.40 (0.19, 0.81)**	0.55 (0.27, 1.09)
Analysis requested by ERG	[redacted]	[redacted]	[redacted]
CRNM bleeding			
Base case	[redacted]	0.80 (0.57, 1.12)	**0.47 (0.36, 0.62)**

Analysis requested by ERG	[redacted]	[redacted]	[redacted]
Overall treatment discontinuation			
Base case	[redacted]	[redacted]	[redacted]
Analysis requested by ERG	[redacted]	[redacted]	[redacted]
All-cause mortality			
Base case	[redacted]	0.79 (0.44, 1.41)	0.82 (0.50, 1.34)
Analysis requested by ERG	[redacted]	[redacted]	[redacted]

CrI: Credible interval; CRNM: Clinically relevant non-major; DVT: Deep vein thrombosis; LMWH: Low molecular weight heparin; PE: Pulmonary embolism; RR: Relative risk; UFH: Unfractionated heparin; 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

4.18 No head-to-head trials comparing apixaban with rivaroxaban or dabigatran etexilate for secondary prevention were identified through systematic review. NMA 2 included the trials listed in table 4. The Company noted that the network of studies included a mixture of open label and double-blind studies and differences in the proportions of people who had an unprovoked VTE rather than a VTE which could be attributed to a specific cause. Other differences between the studies were the proportion of people with active cancer, treatment duration with anticoagulants prior to entering the secondary prevention trials and the study follow up. The company also noted that there may have been differences with respect to clinical judgement regarding the need for continuation of anticoagulation across the trials and the participants in the trials may have had different baseline characteristics. The company tested statistically for heterogeneity of the studies included in the network meta-analysis using the I^2 statistic and found little evidence for heterogeneity. The network meta-analysis was performed using a random effects model.

Table 4: RCTs included in NMA 2 (Prevention Period) (table 31 page 81 of company's submission and table 24 page 72 ERG report).

Trial	Treatment (as described in the trial)	Comparator (as described in the trial)	Treatment and follow up period
AMPLIFY-EXT	Apixaban 2.5 mg bd/ 5 mg bd	Placebo	Initial 6 to 12 months treatment Trial: 12 months preventative period 30 day observation period
EINSTEIN-EXT	Rivaroxaban 20 mg od	Placebo	Initial 6 to 12 months treatment Trial: 6 to 12 months treatment. One month observation period
WARFASA	Aspirin 100 mg od	Placebo	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
RE-SONATE	Dabigatran 150 mg bd	Placebo	6 to 18 months initial treatment Trial: 6 months treatment
RE-MEDY	Dabigatran 150 mg bd	Warfarin (INR 2.0–3.0)	3 to 12 months initial treatment Trial: 6 to 36 months
ASPIRE	Aspirin 100 mg od	Placebo	Initial treatment 6 to 24 weeks Trial: 2 to 4 years Mean: 37.2 months
LAFIT	Warfarin (INR 2.0–3.0)	Placebo	3 months initial treatment. Trial: 24 months treatment. Mean: 10 months
ELATE	Warfarin (INR 1.5–1.9)	Warfarin (INR 2.0–3.0)	3 months initial treatment Duration of trial period not specified.

Trial	Treatment (as described in the trial)	Comparator (as described in the trial)	Treatment and follow up period
			Mean: 2.4 years
WODIT DVT	VKA continuation	VKA discontinuation/ observation	3 months initial treatment Trial: 9 months treatment Observation period not specified Mean: 37.8 months in patients with recurrent VTE
WODIT PE	VKA continuation	VKA discontinuation/ observation	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
PREVENT	Warfarin (INR 1.5–1.9)	Placebo	At least 3 months initial treatment. Duration of trial period not specified. Mean: 2.1 years

Bd: Twice daily; INR: International normalised ratio; od: Once daily; VKA: Vitamin K antagonist

4.19 The results of the company's network meta-analysis for secondary prevention (NMA2) are presented in table 5. There were no statistically significant differences between apixaban, LMWH/dabigatran, rivaroxaban or LMWH/VKA in the rates of recurrent VTE or VTE-related death. Apixaban was associated with fewer recurrent VTE or VTE-related deaths than aspirin or placebo. Apixaban was associated with statistically significantly fewer major or clinically relevant non major bleeding events (assessed as a composite outcome) than LMWH/VKA; LMWH/dabigatran and rivaroxaban. When major bleeding and clinically relevant non-major bleeding were assessed as separate outcomes, people receiving apixaban had statistically

significantly fewer bleeds of either severity than people receiving LMWH/VKA or rivaroxaban, but the rates of bleeds were not statistically significantly different between apixaban and LMWH/dabigatran. In response to clarification, the company re-ran the meta-analysis using different statistical modelling assumptions requested by the ERG (these included using an alternative vague prior for the trial effect and treating the trial effect as random rather than fixed). The results of these analyses are presented in table 5. The results of these analyses were broadly consistent with the company's base case but the likelihood of a major bleed was no longer statistically significantly lower with apixaban than with rivaroxaban. The company carried out 3 further sensitivity analyses: using ITT population from the trials, excluding the WODIT trials and excluding the dabigatran trials. These sensitivity analyses gave similar results to the company's base case. In the ITT sensitivity analysis apixaban was associated with statistically significantly fewer recurrent VTE events or VTE-related deaths than LMWH/VKA [redacted].

Table 5: Base case analysis for the prevention period NMA (NMA 2) – fixed-effect model (statistically significant results are shown in bold) (Company submission table 37 page 94, clarification responses table 10 page 29 and ERG report table 30 page 80).

Outcome	Apixaban 2.5 mg bd vs. dabigatran 150 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. rivaroxaban 20 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. VKA (INR 2.0–3.0), RR (95% CrI)	Apixaban 2.5 mg bd vs. aspirin 100 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. placebo, RR (95% CrI)
Recurrent VTE or VTE-related death*					
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analyses requested by ERG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrent VTE-related death					
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Outcome	Apixaban 2.5 mg bd vs. dabigatran 150 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. rivaroxaban 20 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. VKA (INR 2.0–3.0), RR (95% CrI)	Apixaban 2.5 mg bd vs. aspirin 100 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. placebo, RR (95% CrI)
Analyses requested by ERG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major or clinically relevant non-major bleeding					
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analyses requested by ERG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding					
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analyses requested by ERG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinically relevant non-major bleeding					
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analyses requested by ERG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall treatment discontinuation					
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analyses requested by ERG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All-cause mortality					
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analyses requested by ERG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Bd: twice daily; CrI: Credible interval; CRNM: Clinically relevant non-major; DVT: Deep vein thrombosis; INR: International normalised ratio; PE: Pulmonary embolism; od: once daily; RR: Relative risk; VTE: Venous thromboembolism; VKA: Vitamin K antagonist

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

ERG comments

4.20 The ERG considered that the key characteristics of the trials included in the initial treatment period NMA 1 were similar enough to allow appropriate combination of the results from these trials. It noted however that the trials of rivaroxaban compared with LMWH/VKA included a higher proportion of people with PE (58%) than the other trials in the network of evidence (the percentage of patients with PE across the other trials ranged from 21.2% to 25.2%).

4.21 The ERG were concerned that there were substantial differences between the time spent on treatment (from 6 months in RE-SONATE to 37.2 months in ASPIRE) and the follow-up periods of trials (from 10 months in LAFIT to 37.2 months in ASPIRE) in the prevention network meta-analysis (NMA2) which included trials that had assessed anticoagulants for secondary prevention. The ERG did not consider it appropriate to combine data from these trials and did not agree with the company's assertion that the different treatment periods and follow-up times would not significantly impact the size of the relative treatment effects. The ERG stated that there are likely to be more events in studies with longer treatment periods and follow-up times. It concluded that because of this, the prevention network meta-analysis was not appropriate and only direct clinical evidence for apixaban from AMPLIFY–EXT was appropriate to assess the clinical effectiveness of apixaban for secondary prevention of recurrent VTE.

4.22 The ERG noted that the company had provided continuity correction factors for outcomes in which there were no events in one of the study arms in the trials and that this had resulted in high estimates of relative risk for some outcomes presenting the example that the relative risk for major bleeding for apixaban compared with rivaroxaban was [redacted]. The ERG were satisfied however that the company's analyses provided in response to clarification resulted in less extreme estimates of the underlying treatment effect (were less likely to overestimate or under-estimate the treatment effect). Using the ERG's preferred meta-analysis model assumptions the

relative risk for major bleeding for apixaban compared with rivaroxaban was [redacted].

4.23 The ERG commented that in the prevention network meta-analysis (NMA2) the company had included some trials in which people receiving warfarin had an INR which was in the range 1.5 to 1.9 which is lower than the standard target range of 2.0 to 3.0 and included data from the 5 mg apixaban arm from AMPLIFY–EXT (noting the 5 mg dose is not licensed for secondary prevention). The ERG accepted that the company had included these trials to include an additional indirect evidence loop which it used to assess inconsistency between direct and indirect evidence from the treatment loops as a validity check of the model.

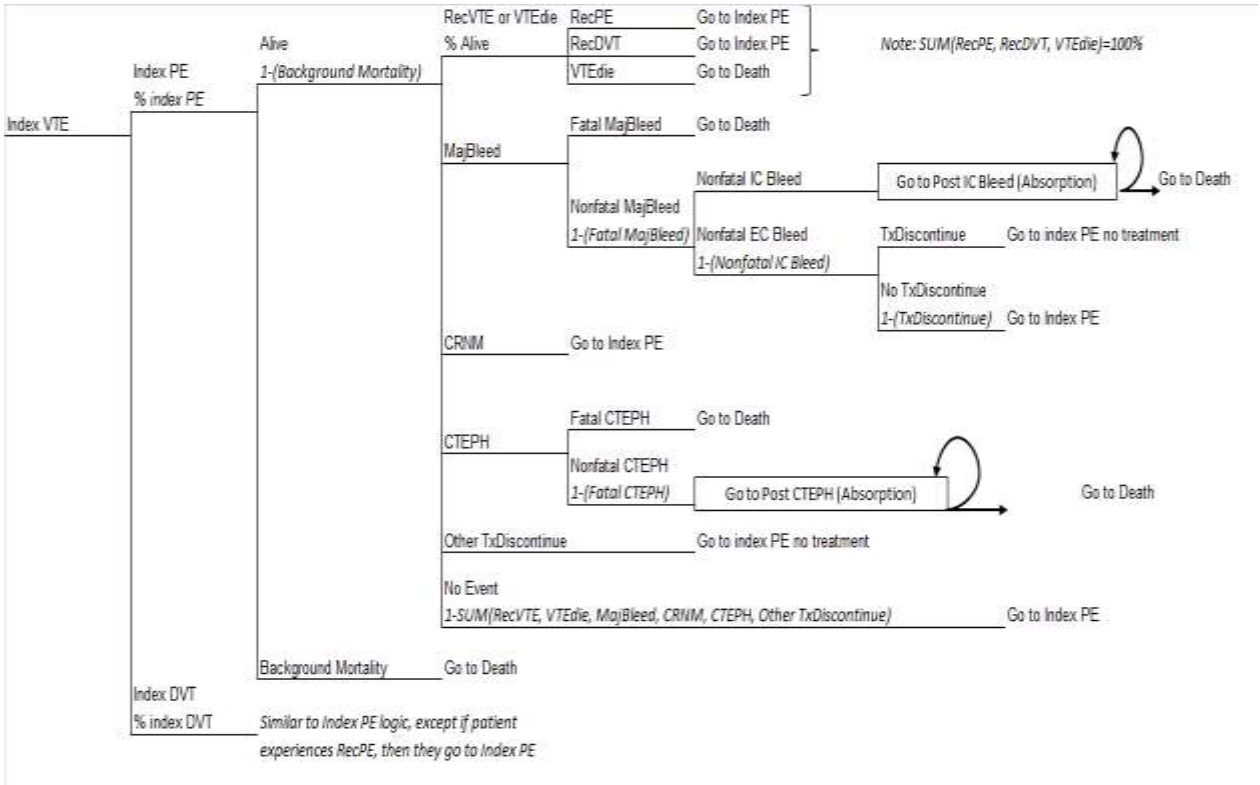
5 Cost-effectiveness evidence

Model structure

5.1 The company developed a new Markov model, with a 3 month cycle length and lifelong time horizon (people were assumed to live to a maximum age of 100 years). People entered the model following a PE or a DVT. It was assumed that [redacted] of people had a PE and [redacted] of people had a DVT. The company modelled two treatment regimens: 'treatment' in which people received 6 months treatment and 'prevention' in which people received initial treatment for 6 months with continued treatment for secondary prevention for the remainder of their lives. In the model it was assumed people could have a recurrent DVT/PE, have a bleed (an intracranial bleed, a non-intracranial major bleed or a clinically relevant non major bleed), discontinue treatment or die (either because of a recurrent DVT/PE, bleed or other reasons). People who had an intracranial bleed were assumed to discontinue treatment permanently. The company assumed that [redacted] of people who survived a non-intracranial major bleed would discontinue treatment permanently and the remaining people would have a 2 week treatment break and resume treatment. People who had a clinically relevant non-major bleed were

assumed to have a 2-day treatment break then resume treatment. People who had a PE could develop chronic thromboembolic pulmonary hypertension (CTEPH). People who had a DVT could develop PTS. The company only modelled the cost and effect on quality of life of severe PTS because it stated that mild or moderate PTS had little effect on a person's utility or resource use.

Figure 2: diagram of company's model. (Company's submission figure 26 page 143)



CRNMbleed; 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 thromboembolism

5.2 The risks of having a recurrent DVT/PE or bleeding for people treated with LMWH/VKA or apixaban in the first 6 months were derived from the absolute risks of these events in AMPLIFY, and for patients treated with apixaban or no treatment after this period from AMPLIFY-EXT. The company used the estimates from the two network meta-analyses of the risks of DVT/PE or bleeding relative to apixaban for rivaroxaban, dabigatran etexilate (and aspirin) which it applied in its model. The company noted that the clinical trial evidence showed that the risk of recurrent DVT/PE decreased over time. The company ran the model for two treatment durations: a 6-month treatment followed by no treatment for the remainder of a person's life and lifelong treatment duration. In the 6 month treatment duration analysis, the risks of recurrent DVT/PE for people receiving no treatment after 6 months were derived from the rates in a prospective cohort of 1,626 patients over 10 years. In the lifelong treatment duration analysis, the risks of recurrent VTE for people receiving no treatment were derived from AMPLIFY-EXT (for the period 6 to 18 months post index event) and from the prospective cohort study (for the period 18 months to 10 years post index event). In the model the risks of major bleeding were derived from the AMPLIFY trials and the network meta-analyses. In the base case the risks of bleeding were unadjusted for aging. The company said that this was a conservative assumption because bleeding risks were lower for apixaban compared with the other comparators and the risk of bleeding would be expected to increase as the age of the modelled cohort increased. In the base case it was also assumed that 13.46% major bleeds would be fatal and of the remaining non-fatal bleeds, 13.97% would be intracranial bleeds. These proportions were based on a published pooled analysis of randomised trials in which people who had received anticoagulant treatment for at least 6 months and were assumed to be consistent across different types of anticoagulant. The model assumed a constant risk of CTEPH and PTS

over time and that the risk of these complications would be the same irrespective of the treatment a person had. People who had an intracranial bleed or CTEPH were assumed to have a higher mortality rate (hazard ratios [HR] 2.6, 95% CI 2.2 to 3.0 and HR 1.3, 95% CI 0.98 to 1.73 respectively).

ERG comments

5.3 The ERG commented that for the lifelong model the efficacy estimates of apixaban over the first 6 months were based on AMPLIFY and past this time data from AMPLIFY-EXT were used. The ERG noted the characteristics of the populations included in these 2 trials differed and only a third of people from AMPLIFY had gone on to participate in AMPLIFY-EXT. The ERG noted that AMPLIFY-EXT excluded people who had a recurrent VTE event during earlier treatment of their index VTE event and so at 6 months the characteristics of the modelled cohort effectively changes. The ERG suggested that 2 distinct decision models should have been developed, each based exclusively on a single trial; short-term use of apixaban compared with comparators using AMPLIFY data and long-term use of apixaban compared with no-treatment using AMPLIFY-EXT data.

5.4 The ERG noted that the model used age-specific mortality rates for all-cause death but did not adjust the model parameters (such as the risk of VTE event or bleeding) by age or sex. The ERG further commented that the age-specific mortality rates did not take into account that the ratio of men to women in the model cohort would be expected to change over time as women tend to live longer than men. The ERG stated that the company's approach would be expected to over-estimate the mortality rates of the modelled cohort by up to 4% per year.

5.5 The ERG noted that the model structure (in which people who have a non-fatal VTE without a permanent adverse event return to the index DVT or PE health state after 3 months) means that the model implicitly assumed that the risk of a second or third recurrent VTE was the same as the risk of having a first recurrent VTE. The ERG stated that there was no evidence to support this assumption and that a published study had suggested that the risk of a second recurrent VTE relative to a first recurrence of VTE was about 2-fold (RR 2.1, p=0.02). The ERG stated that as a consequence the long-term estimates of future VTE events (including deaths) were likely to be underestimated and this would mean that the costs and disutility value of events would be underestimated. The ERG noted that it was unable to test the effect of progressively increasing VTE recurrence rates in sensitivity analyses because the model structure did not allow this.

5.6 The ERG stated that there were differences in the proportion of people who had discontinued treatment in the model compared with the AMPLIFY trial results at a 90 days. At this time, [redacted] of people randomised to apixaban, and [redacted] of people randomised to LMWH/VKA in AMPLIFY had discontinued but the model indicated 7.7% and 13.0% of people randomised to apixaban and LMWH/VKA respectively had discontinued. The ERG further commented that it was unable to validate other model parameters against the trial data to determine whether a similar error had been made across the whole range of time-to-event model variables because the Kaplan Meier data it requested during the clarification process had not been provided.

Model details

5.7 No quality of life data were collected in the AMPLIFY or AMPLIFY-EXT trials and the company used utility values from published studies identified through systematic review in its model. The utility values used in the model are summarised in table 6.

Table 6: Summary of quality of life values for the cost-effectiveness analysis (table 67 company's submission page 170)

Utility scores for baseline, IC bleed, and CTEPH	Utility score	Utility measurement	Source	Duration	Source
Baseline Utility	0.825	EQ-5D	Kind et al. 1998 (NICE TA261; NICE TA287)	-	-
IC Bleed					
Acute care period	0.33	Time trade off	Locadia et al. 2004 (NICE TA261; NICE TA287)	91 days	Locadia et al. 2004
Post-acute care	0.61	EQ-5D	Pickard et al. 2004 (NICE TA287)	Beyond 91 days	
CTEPH					
Acute care period	0.65	EQ-5D	Ghofrani et al. 2013	30 days	Ghofrani et al. 2013
Post-acute care	0.65			Beyond 30 days	
Utility decrements associated with clinical events and use of anticoagulants	Utility decrement	Utility measurement	Source	Duration	Source
PE	-0.32	Time trade off	Locadia et al. 2004 (NICE TA261; NICE TA287)	30 days	Hogg et al. 2013
DVT	-0.11				
Bleeding					
Major non-IC bleed	-0.30	Time trade off	Locadia et al. 2004 (NICE TA261; NICE TA287)	30 days	Expert opinion
CRNM bleed	-0.0054	EQ-5D	Sullivan et al. 2011	2 days	Dorian et al. 2014
Severe PTS	-0.07	Standard gamble	Lenert et al. 1997 (NICE TA261; NICE TA287)	Throughout	Lenert et al. 1997
Anticoagulation					
Apixaban	-0.002	Time trade off	Gage et al. 1996	Whilst on treatment	Gage et al. 1996
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,					

5.8 The company used the NHS list prices for apixaban, rivaroxaban, dabigatran and enoxaparin. The costs and dosing regimen for each drug is summarised in table 7. The company modelled the cost of enoxaparin and noted that the recommended dose for enoxaparin in the UK is 1.5 mg/kg, but the dose of enoxaparin in AMPLIFY was 1.0 mg/kg. The company used the cost of the lower UK dose in its model, but the efficacy estimates were based on the higher dose. For people receiving LMWH it was assumed that 92% people would self-inject following a one-off training cost of £17. It was assumed that 8% of patients would have their LMWH administered by a nurse at a cost of £8.78.

Table 7: Drug costs used in model

Treatment	Detail	Daily Price Induction (duration in model)	Daily Price Maintenance	Daily Price Prevention
LMWH/VKA	1 x 1 mg and 1 x 5 mg VKA Enoxaparin sodium 300 mg/1 ml solution for injection pre-filled syringes (7.64 days induction)	LMWH: £9.02 (7.64 days) VKA: £0.009 (5 days)	VKA: £0.009	VKA: £0.009
Apixaban	4 x 5 mg (induction) 2 x 5 mg (maintenance) 2 x 2.5 mg (maintenance and prevention)	£4.40 (7 days)	£2.20	£2.20
Rivaroxaban	2 x 15 mg (induction) 1 x 20 mg (maintenance and prevention)	£4.20 (21 days)	£2.10	£2.10
LMWH/dabigatran	22 x 150 mg dabigatran (maintenance and prevention) Enoxaparin sodium 300 mg/1 ml solution for injection pre-filled syringes (5 days)	LMWH: £9.02 (5 days)	Dabigatran: £2.20	Dabigatran: £2.20
Aspirin	1.33 x 75 mg	-	-	£0.005
LMWH: Low Molecular Weight Heparin; VKA: Vitamin K Antagonist				

5.9 For people receiving a VKA it was assumed that 6 monitoring visits would be needed in the first 3 months followed by 3 visits every 3 months thereafter. It was assumed that 66.45% of INR monitoring visits would be carried out in primary care and 33.55% would be undertaken in secondary care. It was further assumed that half the first INR monitoring visits conducted in primary care would be delivered by a GP with the remainder delivered by a nurse. The resulting annual cost of monitoring in the first year of the model was £319.19 and £252.52 in subsequent years.

5.10 It was assumed in the model that 67% of people who had a DVT and 17% of people who had a PE would be treated as an outpatient. Longer term monitoring and post-acute care was assumed to be carried out in primary care. Treatment of bleeds or CTEPH were assumed to be carried out in secondary care. Hospital costs were calculated using 2012/13 NHS reference costs where HRG codes were available. Unit costs associated with primary care were calculated from the Personal Social Services Research Unit (PSSRU) 2013. Where costs could not be identified from these sources unit costs were obtained from the published literature. The inpatient and outpatient treatment costs are summarised in tables 74 and 75 of the company submission pages 181 and 182. The costs of treating adverse events are summarised in table 76 and 77 on pages 183 and 184 of the company's submission.

ERG comments

5.11 The ERG commented on the baseline utility value assumed in the model which the company stated came from Kind et al. 1999. The ERG stated that the utility values referred to in Kind et al were published in the Centre for Health Economics (CHE) discussion paper 172 reporting data from the Measurement and Valuation of Health Survey. It further noted that the mean values in the company's model did not match utility values in this publication which were presented grouped by age and sex and the standard errors around the utility values in the

company's model were standard deviations. As a consequence the ERG stated that the utility values had been attributed to people of the wrong age in the model and the uncertainty surrounding the estimates were overstated by the company. The ERG further considered that the company's assumption surrounding baseline utility was flawed because the model did not account for the mean utility value in the modelled cohort decreasing as the age of the cohort increased over time.

5.12 The ERG commented that in the model the cost of anti-thromboembolic therapies for each 3 month cycle was based on the average number of patients alive and on treatment over the course of the cycle. The ERG considered that this may underestimate the true costs because oral medications prescribed at the start of a 3 month treatment cycle would not be able to be returned if they are not used.

5.13 The ERG commented that the cost of LMWH treatment in the model was based on a daily dose of 1.5 mg/kg assuming a mean body weight of 84.6kg (based on the mean weight of participants in AMPLIFY). However the ERG considered this to be considerably higher than the mean adult weight of 77.4 kg reported in the Health Survey for England 2012.

5.14 The ERG commented on the company's approach to discounting. It noted that the company had assumed a 3.5% discount rate which is consistent with the NICE reference case. However, the ERG noted that the company applied discounting at a different rate for every 3-month model cycle based on the time elapsed rather than using a more conventional approach of applying the discount every 4 cycles (that is, yearly) after the first year. The ERG noted that using the yearly discount method had a minimal impact on the company's base case results.

Company's base-case results and sensitivity analysis

5.15 The company presented deterministic pairwise and fully incremental results for a 6 month treatment duration and a lifelong treatment duration. If taken for 6 months the incremental cost effectiveness ratio (ICER) for apixaban compared with LMWH/VKA was £2,406 per quality adjusted life year (QALY) gained. Apixaban dominated (was less costly and more effective than) rivaroxaban and LMWH/dabigatran. If taken lifelong, the ICER for apixaban compared with LMWH/VKA was £16,676 per QALY gained; rivaroxaban was dominated by LMWH/VKA and LMWH/dabigatran was extendedly dominated by LMWH/VKA and apixaban. The company did not present probabilistic ICERs.

Table 8: Company's base case results (tables 81 and 84 company's submission pages 193 and 194).

6- month treatment duration						
Technology	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£) vs. LMWH/VKA	Incremental
LMWH/VKA	£4,955	8.389	-	-	-	-
Apixaban	£5,035	8.422	£80	0.033	£2,406	£2,406
Rivaroxaban	£5,069	8.412	£114	0.023	£5,017	Dominated
LMWH/dabigatran	£5,100	8.396	£145	0.007	£19,782	Dominated
Lifelong treatment duration						
Technology	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£) vs. LMWH/VKA	Incremental
LMWH/VKA	£6,136	8.472	-	-	-	-
Rivaroxaban	£9,013	8.075	£2,877	-0.397	Dominated	Dominated
LMWH/dabigatran	£9,083	8.591	£2,947	0.120	£24,622	Extendedly dominated
Apixaban	£9,497	8.673	£3,361	0.202	£16,676	£16,676
ICER: incremental cost effectiveness ratio; LMWH: Low Molecular Weight Heparin; QALY: quality adjusted life year; VKA: Vitamin K Antagonist						

Company scenarios

5.16 The company carried out one-way sensitivity analyses and scenario analyses. For the 6 month time period, in the one-way sensitivity analyses, the ICER for the comparison of apixaban compared with

LMWH/VKA varied between £1,628 and £5,330 per QALY gained. The highest ICER per QALY gained (£5,330) resulted from decreasing the baseline utility value to 0.385. For the lifelong treatment period, the ICER for the comparison of apixaban compared with LMWH/VKA varied from £2,157 to £41,394 per QALY gained. The three analyses resulting in an ICER above £30,000 per QALY gained were: reducing the relative risk of major bleeding for LMWH/VKA compared with apixaban to [redacted] (from [redacted] in the base case), setting the risk of bleeding to 0 and reducing the baseline utility to 0.385. The company tested the effect of over 30 scenarios. These are listed in section 7.6.1 pages 185 to 186 of the company's submission. The results of these scenario analyses were presented for a 6 month treatment duration in table 87 page 212, and for a lifelong treatment duration in table 89 page 215 of the company's submission. For a 6 month treatment duration apixaban dominated rivaroxaban and LMWH/dabigatran in all scenarios. The ICER for apixaban compared with LMWH/VKA was under £5,000 per QALY gained in all scenarios. The scenarios that resulted in the greatest impact were assuming fewer warfarin monitoring costs and excluding the costs of LMWH. For a lifelong treatment duration, assuming fewer warfarin monitoring visits (4 visits on initiation, 1 visit subsequent) increased the ICER for apixaban compared with LMWH/VKA from £16,676 per QALY gained in the base case to £21,301 per QALY gained. The only other scenarios that increased the ICER for apixaban compared with LMWH/VKA over £20,000 per QALY gained were: assuming that the utility decrements for all treatments were the same as that assumed for VKA (that is a utility decrement of -0.0013) resulting in an ICER of £25,999 per QALY gained, and assuming an alternative distribution of fatal major bleeds and non-fatal intracranial bleeds for people who had a major bleed resulting in an ICER of £24,038 per QALY gained. The sensitivity and scenario analyses that resulted in an ICER for apixaban compared with LMWH/VKA of over £20,000 per QALY gained are summarised in table 9.

Table 9: Company's sensitivity analyses having the largest impact on the ICER for apixaban compared with LMWH/VKA lifelong treatment duration.

Assumption/parameter	Company base case	Sensitivity analysis	ICER apixaban vs. LMWH/VKA
Company's univariate sensitivity analyses			
Relative risk of major bleed LMWH/VKA vs. apixaban during the prevention period	[redacted] (estimate from NMA 2)	[redacted] (lower 95% CI surrounding estimate)	£41,394
Risk of bleeding	Rates for apixaban from AMPLIFY-EXT, relative risk of bleeding from NMA2 applied for comparators	Assuming no bleeding on any treatment in the prevention period	£41,285
Baseline utility value of modelled population	0.825	0.385	£31,822
Starting age of modelled cohort	[redacted]	70	£22,055
Discounting QALYs	3.5%	6%	£20,718
Discounting costs	3.5%	0%	£20,987
Company's scenario analyses			
Frequency of VKA monitoring visits	6 visits in first 3 months, 3 visits every 3 months thereafter	4 visits in first 3 months, 1 visit every subsequent 3 months	£21,301
Utility decrement associated with treatment	LMWH/VKA: -0.013 All other treatments: -0.002	All treatments: -0.013	£25,999
Proportion of major bleeds that are fatal	13.46% fatal	8.75% fatal	£24,038
ICER: incremental cost effectiveness ratio; LMWH: Low Molecular Weight Heparin; VKA: Vitamin K Antagonist			

ERG comments

5.17 The ERG commented that 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). The ERG considered that starting age should be a parameter for which there is general agreement. The ERG considered that there was uncertainty around the most plausible baseline utility as no HRQOL data were collected during the trials.

ERG exploratory analyses

5.18 The ERG stated that its ability to fully critique the company's economic model was limited by a lack of data. In particular it stated that without all 12 Kaplan Meier analyses it requested during the clarification process, it was unable to:

- verify key model parameters against the original data,
- Look at how the risks of events varied over time to determine whether it was reasonable to assume that the risks of events would remain constant past the time of the last measures taken in AMPLIFY-EXT
- Test how applying different hazard functions past the time of the last measures taken in AMPLIFY-EXT would impact on the results.

5.19 The ERG carried out a number of exploratory analyses including:

- Age/sex modelling: To assess the effect of the changing age and sex distribution of the modelled cohort over time on survival the ERG carried out multiple runs of the model for separate age/ sex/VTE subgroups from AMPLIFY from which it produced an overall weighted survival estimate stratified by type of index VTE event.
- Treatment costs: the treatment costs were calculated using the full number of patients who began treatment at the start of each 3 month cycle rather than assuming that people who discontinue treatment at any time during a cycle incur drug costs for only half the days in a cycle.
- Age-varying MVH: incorporating the baseline utility values by 10 year age band (under 25, 25-34 up to 65-74, and 75+) from the MVH (Measurement and Valuation of Health Survey, which is the source data in Kind et al 1999) in the model rather than the fixed mean value of 0.825 used by the company in its base case.
- Discounting method: using annual discounting rather than discounting at a different rate for every 3-month cycle based on the time elapsed.

- Body weight: assuming a mean adult body weight of 77.4 kg rather than 84.6 kg when calculating amount of LMWH administered to achieve a 1.5 mg/kg dose.
- Rebase prevention model (lifelong treatment duration): To address its concerns that the modelled assumption in the first 6-months of a lifelong treatment duration (based on the AMPLIFY population) did not reflect the experience of people on whom life-long treatment estimates were based (the population from AMPLIFY-EXT), the ERG excluded the first 2 cycles from the model to determine the lifelong treatment duration results. The ERG noted that this would reflect the third of patients who received 6 month treatment in the AMPLIFY trial before joining AMPLIFY-EXT.
- HRs requested by ERG: using the results from network meta-analysis 2 which incorporated the changes to the meta-analysis modelling approach requested by the ERG during clarification (these included using an alternative vague prior for the trial effect and treating the trial effect as random rather than fixed). See table 30 ERG report page 79.
- HRs Poisson (Bayesian and non-Bayesian): Using Poisson distributions in the model used for NMA 2 with and without Bayesian assumptions. The ERG carried out these analyses because the trials in NMA2 have different follow up lengths. Using a Poisson assumption in the model relates the incidence of events to the length of time that people are exposed to the risk of event and so it limits the potential bias of different follow up times in the meta-analysis.

5.20 The results of the ERG's exploratory analyses are presented in tables 10 and 11. Overall, the exploratory analyses had a small impact on the company's base case ICERs in the 6-month treatment duration analyses. The ICER for apixaban compared with LMWH/VKA remained under £3000 per QALY gained and apixaban dominated rivaroxaban and LMWH/dabigatran in all analyses. In the lifelong treatment duration analyses the majority of the ERG's exploratory analyses had a small impact on the company's base case ICERs. Only using data from the network meta-analyses incorporating Poisson assumptions increased

the ICER for apixaban compared with LMWH/VKA to over £20,000 per QALY gained.

Table 10: ERG exploratory analyses

6-month treatment duration			
Scenario	**ICER apixaban vs. LMWH/VKA**	**ICER apixaban vs. rivaroxaban**	**ICER Apixaban vs. LMWH/dabigatran**
Company's base case	£2,406	Apixaban dominant	Apixaban dominant
ERG R1: age sex modelling	£2,454	Apixaban dominant	Apixaban dominant
ERG R2: Treatment costs	£2,538	Apixaban dominant	Apixaban dominant
ERG R3: Age-varying MVH utility	£2,412	Apixaban dominant	Apixaban dominant
ERG R4: Discounting method	£2,397	Apixaban dominant	Apixaban dominant
ERG R5: Body weight	£2,577	Apixaban dominant	Apixaban dominant
R1-R5	£2,850	Apixaban dominant	Apixaban dominant
ICER: incremental cost effectiveness ratio; LMWH: Low Molecular Weight Heparin; VKA: Vitamin K Antagonist			

Table 11: ERG exploratory analyses lifelong treatment duration.

Lifelong treatment duration				
Scenario	**ICER apixaban vs. LMWH/VKA**	**ICER apixaban vs. rivaroxaban**	**ICER Apixaban vs. LMWH/dabigatran**	**ICER apixaban vs. LMWH/VKA followed by no treatment**
Company's base case	£16,676	£809	£5,058	£17,917
ERG R1: age sex modelling	£15,137	£627	£4,441	£15,353
ERG R2: treatment costs	£17,043	£800	£5,009	£18,207
ERG R3: age varying MVH utility	£17,516	£867	£5,425	£17,965
ERG R4: discounting method	£16,671	£810	£5,064	£17,920
ERG R5: body	£16,704	£810	£5,104	£17,944

weight				
ERG R6: Rebase prevention model	£19,283	£885	£7,758	£19,876
ERG S1: HRs requested by ERG	£14,837	£5,025	£5,617	£17,936
ERG s2: HRs-ERG Poisson (Bayesian)	£20,227	£6,938	£7,624	£17,936
ERG S3: HRs-ERG Poisson (non-Bayesian)	£31,501	£8,981	£9,532	£17, 936
B. R1-R6 + S1	£15,837	£4,869	£6,801	£17,700
C. R1-R6 + S2	£23,224	£6,801	£10,573	£17,700
D. R1-R6 + S3	£42,918	£8,875	£15,149	£17,700
ICER: incremental cost effectiveness ratio; LMWH: Low Molecular Weight Heparin; VKA: Vitamin K Antagonist				

5.21 The ERG carried out a further scenario analysis in which it assumed that the efficacy and bleeding risks of apixaban, rivaroxaban and dabigatran were the same over the secondary prevention period. In this scenario the ERG also applied its preferred assumptions R1-5 (see tables 9 and 10). In this scenario the ICER for apixaban compared with rivaroxaban increased from £809 per QALY gained to £21,798 per QALY gained. The ICER for apixaban compared with LMWH/dabigatran increased from £5,058 to £9,139 per QALY gained.

6 Equality issues

6.1 No equalities issues were raised by the company, patient or professional groups or the ERG.

7 Authors

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Appendix A: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002148/WC500173870.pdf