Response to questions from NICE and ERG in connection with STA submission

Rivaroxaban in the treatment of pulmonary embolism and prevention of recurrent venous thromboembolic events

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General request

1. Priority request: Please supply the Clinical Study Report for EINSTEIN PE

We are happy to provide individual tables from the CSR as need be, and our submission document contains relevant data from the CSR that is not otherwise published, but it is not Bayer policy to provide complete Clinical Study Report (CSR) documents.

2. Priority request: Please supply the CHMP assessment report for rivaroxaban in the treatment of pulmonary embolism.

No such document is available as the EMA have not yet published a European Public Assessment Report (EPAR) for rivaroxaban in the treatment of PE and prevention of recurrent DVT and PE. We will provide the EPAR to NICE once the EMA publishes it.

Literature searching

3. In section 7.1.1, the search strategy for cost effectiveness studies is described. On page 106 of the submission it states that "horizon scanning using key words" was performed. Please clarify how this was done (e.g. using the National Horizon Scanning Centre database).

This refers to additional searching through an internet search engine. Apologies but the description of the search was inadvertently omitted from section 10.10.5 of the submission.

The following `key words' or terms were used in the Google search engine to identify media or government reports: venous thromboembolism, VTE, deep vein thrombosis, DVT, pulmonary embolism, PE combined with cost-effective, cost-utility, model. There was no searching of the National Horizon Scanning Centre website / database. No articles in addition to those already captured by the review were identified through searching with these terms.

Section A: Clarification on effectiveness data

EINSTEIN-PE population

A1. The SmPC for rivaroxaban states that rivaroxaban can be used with caution in patients with severe renal impairment, defined as a creatinine clearance of 15-29 mL/min. Patients with a creatinine clearance of < 30 mL were excluded from the EINSTEIN-PE trial. Despite this exclusion criterion, 6 people with a creatinine clearance of <30 mL/min were included in EINSTEIN-PE.

For clarification, the full text on renal impairment from the SmPC is reproduced below.[191,192] The dosage recommendations for severe renal impairment (creatinine clearance 15-29 mL/min) also apply in patients with moderate renal impairment (creatinine clearance 30-49 mL/min).

No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) (see section 5.2).

In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment the following dosage recommendations apply:

- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15 mg once daily (see section 5.2).

- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE: Patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, the recommended dose is 20 mg once daily. A reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting (see sections 4.4, 5.1 and 5.2).

Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased, therefore, Xarelto is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).

- **Please clarify why patients with a creatinine clearance of <30 mL were excluded from the trial.**

It is correct that `creatinine clearance < 30 mL/min' was an exclusion criterion for EINSTEIN-PE (as noted on page 54 of the submission); also EINSTEIN-DVT and EINSTEIN-Ext. The inclusion/exclusion criteria of EINSTEIN-PE, and its study design more generally, were set with regard for EMA requirements and designs of other RCTs for novel treatments for the treatment of pulmonary embolism and deep vein thrombosis. For example, the MATISSE trials of fondaparinux in DVT and PE published in 2003-4 excluded patients with severe renal impairment, though this was defined through elevated creatinine levels rather low creatinine clearance.

- The MATISSE trial in patients with PE excluded patients with serum creatinine level above 2.0 mg/dL (177 µmol/L). Among the study population of 2213 patients, 54 patients (2.4%) had creatinine clearance < 30mL/min at baseline.[193]
- The MATISSE trial in patients with DVT also excluded patients with serum creatinine levels above 2.0 mg/dL (177 µmol/L). Among the study population of 2205 patients, 44 patients (2.0%) had creatinine clearance <30 mL/min at baseline.[194]

- **Please clarify what evidence there is for the efficacy of rivaroxaban for the treatment of PE and prevention of recurrent venous thromboembolism in a population with severe renal impairment?**

Limited clinical data for patients with severe renal impairment, as noted in the SmPC, not least because the trial was not designed to include such patients.[195] Despite the exclusion criterion, 6 patients with creatinine clearance less than 30 mL/min were included in the ITT population of EINSTEIN-PE (4 assigned to rivaroxaban, 2 assigned to enoxaparin/VKA, Table 9 on page 56 of the submission). [redacted]

Other anticoagulants, including UH, LMWHs and fondaparinux, are eliminated primarily via the kidneys. Decreased clearance and increased exposure to these anticoagulants may place patients with renal impairment at increased risk of major bleeding episodes, even at standard doses. In contrast, rivaroxaban has a dual mode of elimination, with two-thirds of the dose being metabolised in the liver through oxidative and hydrolytic pathways, half of which is excreted via the kidneys and half via the faecal route. One third of the dose is eliminated as unchanged drug in the urine. It is thought, therefore, that rivaroxaban may be easier to use in patients with renal impairment, because impaired renal function during the course of treatment is less likely to result in undesirable increases in exposure.

A study into the effects of renal impairment on the pharmacokinetics (PK), pharmacodynamics and safety of rivaroxaban was conducted which involved 32 subjects with varying renal function: 8 healthy control patients (creatinine clearance >80 mL/min), 8 with mild impairment (creatinine clearance 50-79 mL/min), 8 with moderate impairment (creatinine clearance 30-49 mL/min) and 8 with severe impairment (creatinine clearance < 30 mL/min). A single oral dose of 10 mg (2 x 5 mg tablets) was used in the morning under fasting conditions. This found that clearance of rivaroxaban was decreased in subjects with renal impairment, leading to a moderate increase in exposure, even in subjects with severe renal impairment.[195] Population analyses of phase II clinical trial data indicated that the pharmacokinetics and pharmacodynamics of all rivaroxaban doses was predictable and were affected by expected demographic factors in patients with acute DVT. The influence of renal function was moderate.[196]

In conclusion, rivaroxaban may be easier to use than other anticoagulants in patients with renal impairment, because impaired renal function during the course of treatment is less likely to result in undesirable increases in exposure, even in subjects with severe renal failure.[195] The influence of renal function on the clearance of rivaroxaban has been found to be moderate.[195,196] However, as recognised here and in the SmPC, there is limited data for rivaroxaban with severe renal impairment. The evidence above, in particular PK modelling, supports the dosage recommendations made in the SmPC.[191,192]

A2. On page 99 it states that 62.5% of people received just one day of pre-randomisation anticoagulation whereas in the NEJM article (Table 2) the corresponding percentages are slightly lower: (n=1389/2419 [57.4%] rivaroxaban; n=1400/2413 [58.0%] standard therapy).

This question refers to the following taken from page 99: `A similar proportion of patients in both arms received pre-randomisation anticoagulation: 92.5% in the rivaroxaban arm vs. 92.1% in the LMWH/VKA arm (P=0.62, post hoc binomial test). The intensity of pre-randomisation anticoagulation was small. Among those receiving any pre-randomisation anticoagulation, the treatment was received for just one day in 62.5% of cases.'

- **The denominator in the NEJM article is the ITT population, whereas it appears that the denominator in the submission is the total number who received pre-randomisation treatment. Please clarify this apparent discrepancy.**

That is correct. The denominator in the NEJM figures is `all patients' (57.4% and 58.0%) whereas the denominator for the 62.5% cited in the submission is `patients receiving pre-randomisation anticoagulation'.

More specifically, the 62.5% figure refers to the number of patients receiving pre-randomisation anticoagulation for just one day as a proportion of the number of patients receiving any pre-randomisation anticoagulation. It is calculated from 2789/4460, derived from data presented in the NEJM publication as follows.

- Numerator: Number of patients receiving pre-randomisation anticoagulation for just one day, ie: 1389+1400 = 2789.
- Denominator: Number of patients receiving any pre-randomisation anticoagulation, ie: 1389+801+47+1400+777+46 = 4460. The denominator excludes patients who received no pre-randomisation anticoagulation.

The other figures refer to the proportion of all patients receiving one day of anticoagulation.

- Numerators: Number of patients receiving one day of pre-randomisation anticoagulation, ie: 1389 for rivaroxaban and 1400 for enoxaparin/VKA.
- Denominators: Study ITT population, ie: 2419 for rivaroxaban and 2413 for enoxaparin/VKA.

- **Please clarify whether all treatments used prior to randomisation were LMWH as implied by the denominator in Figure 7 (page 73 of the submission), or whether unfractionated heparin and fondaparinux was also used, as implied by Table 2 of the NEJM article?**

Table 2 of the NEJM article, Figure 7 on page 73 of the submission and Appendix Figure 1 of the NEJM article refer to pre-randomisation treatment with LMWH, heparin or fondaparinux. The data from both sources is summarised in Table 1 below.

The durations summarised in Table 2 of the NEJM article were calculated from the difference between stop date and time and start date and time (after onset of first index event) plus the assumed pharmacological effect after last dose. The assumed pharmacological effect is up to 12 hours for LMWH bid and for UH and up to 24 hours for

LMWH od and for fondaparinux. The duration was zero in cases where there was no pre-treatment.

The durations summarised in the graphical figures (Figure 7 on page 73 of the submission and Appendix Figure 1 of the NEJM article) were calculated from the difference between the stop date and time and the start date and time without any addition. The duration was zero in cases where there was no pre-treatment.

Table 1: Duration of pre-randomisation treatment with LMWH, heparin or fondaparinux, including and excluding assumed pharmacological effect after last dose, ITT population

Duration of pre-randomisation treatment (days)	Distribution of patients, including assumed pharmacological effect (Table 2 of NEJM article)		Distribution of patients, excluding assumed pharmacological effect (Appendix Figure 1 of NEJM article)	
	Rivaroxaban	Enoxaparin/VKA	Rivaroxaban	Enoxaparin/VKA
0	182	190	182	190
1	1389	1400	1754	1760
2	801	777	460	443
>2	47	46	23	20

A3. Pre-randomisation LMWH is listed as one of the pre-specified subgroups in Figure 7 (page 73 of the submission). However, a reference to this subgroup could not be found in the trial protocol. Please clarify whether use of pre-randomisation LMWH was a pre-specified subgroup.

The subgroups to be evaluated in analyses of the efficacy and safety outcomes were pre-specified in statistical analysis plan documentation rather than the protocol document. Pre-randomisation LMWH was indeed a pre-specified subgroup.

A4. The publication from the EINSTEIN-PE trial notes in its discussion (NEJM article page 1296, paragraph 3), that the study population was representative of the spectrum of patients who present with symptomatic pulmonary embolism, with the exception of those for whom fibrinolytic therapy was planned. Please explain how the exclusion of people for whom fibrinolytic therapy was planned in EINSTEIN PE would affect the generalisability of EINSTEIN PE to a UK population?

It is noted on page 55 of the submission and in the study protocol[63] that there was the following exclusion criterion in EINSTEIN-PE: `Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of DVT and/or PE'.

Related to this, the NEJM article states (as noted in this question): `We believe that our population is representative of the spectrum of patients who present with symptomatic pulmonary embolism, with the exception of those for whom fibrinolytic therapy is planned'.

The UK licensed population would exclude patients specifically contraindicated as well as those whom the SmPC indicates should not be recommended rivaroxaban. The SmPC states that rivaroxaban is not recommended in PE patients `who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy'[191,192] (as did the draft SmPCs provided with the submission[4]). Thrombolysis would be a fibronolytic therapy. Section 2.2 of the submission is relevant here (pages 24-27). We note in this section that the

proportion of patients who present with haemodynamically unstable PE was estimated to be 5-10% in NICE CG144.[8] In total, for the purposes of estimates required in this section of the submission template and elsewhere (eg section 8) we assume that 15% of PE patients would not be suitable for rivaroxaban.

Therefore, we believe that EINSTEIN-PE is generalisable to a UK population of PE patients potentially appropriate for treatment with rivaroxaban according to its licence.

Subgroups in EINSTEIN PE

A5. Priority question: The percentages for unprovoked/ provoked 'index event' for the ITT population (15.8% and 84.2% respectively) presented on page 72 of the submission are different to the proportions presented in Table 9 (approximately 64.5 unprovoked) and Table 10 (49.3% idiopathic DVT/PE) in the submission (pages 56 and 57 respectively) and Table 1 in the NEJM publication (where the proportion of unprovoked and provoked PE was 64.5% and 35.5%, respectively).

- **Please explain the reason (s) for these differences.**
- **Please provide the definition used to include people in the provoked or unprovoked index event subgroups.**

Several figures/sources are referred to here from the EINSTEIN-PE trial.

- Table 9 of the submission (pages 56-57) states that 1566 (64.7%) rivaroxaban patients and 1551 (64.3%) of enoxaparin/VKA patients had a cause of PE or DVT which was `unprovoked'. This is also as stated in Table 1 of the NEJM publication. Overall, this is equivalent to 64.5% of the ITT population, as given in this question.
- Table 10 of the submission (page 57) states that 49.3% of patients (ITT population) had idiopathic DVT or PE.
- Page 72 of the submission states: `The study distinguished between patients whose index event was considered idiopathic (spontaneous or unprovoked, 15.8% of ITT patients) from those which were not (secondary or provoked, 84.2% of ITT patients).'

The statement on page 72 referred to in bullet 3 is incorrect, for which we apologise. Trial data on three related baseline characteristics / risk factors is provided in Table 2 below, which supports the data referred to in bullets 1 and 2 above.

Table 2: Patients (%) in EINSTEIN-PE with certain baseline characteristics / risk factors

	Rivaroxaban		Enoxaparin/VKA		Total	
ITT population	2419		2413		4832	
Idiopathic DVT/PE	1196	(49.4)	1186	(49.2)	2382	(49.3)
Secondary DVT/PE	853	(35.3)	862	(35.7)	1715	(35.5)
Spontaneous DVT/PE	1566	(64.7)	1551	(64.3)	3117	(64.5)

Notes:

- Idiopathic DVT/PE was reported as per the assessment of the investigator.
- Secondary DVT/PE is defined as a patient who had experienced any of the following risk factors: (i) recent surgery or trauma, (ii) immobilisation, (iii) use of oestrogen containing drugs, (iv) puerperium, (v) active cancer.
- Spontaneous DVT/PE is defined as a patient who was not classed as secondary DVT/PE according to the definition above.

The paragraph on page 72 referred to in bullet 3 went on to state: [redacted] In the 64.5% of patients with spontaneous DVT/PE, the treatment effect was [redacted] in the 35.5% of patients with secondary DVT/PE, the treatment effect was [redacted] On reviewing this statement, the phrase `nature of the index event (idiopathic vs not)' should more accurately have read `nature/aetiology of the index event (spontaneous vs secondary)'.

A6. Priority question: Please clarify the rationale for the subgroups considered in the subgroup analysis of safety outcomes (Figure 10, page 77 of the submission) and those considered for efficacy outcomes (Figure 7, page 73 of the submission).

As noted in response to question A3, the subgroups to be evaluated in analyses of the efficacy and safety outcomes were separately pre-specified in statistical analysis plan documentation rather than the protocol document.

In general, the subgroups selected for the efficacy analyses were based around risk factors thought to be relevant for VTE recurrence; and the subgroups selected for the safety analyses were based around risk factors thought to be relevant for bleeding. There was a desire to avoid excessive numbers of subgroup analyses to minimise the hazards incumbent with multiple testing.

The subgroups pre-specified were those that focussed around factors thought to be potentially influential on drug concentration levels in patients receiving either rivaroxaban or the comparator: age, weight, gender and creatinine clearance might affect VTE recurrence or bleeding so were included as subgroups in the analyses of efficacy and safety endpoints. Similarly active cancer is a known risk factor for both recurrent VTE and bleeding events in patients on anticoagulation, and presence of active cancer at baseline is already specifically controlled for in any estimates of treatment effect (as described in the submission at section 6.3.6, paragraph 2).

Additionally, in the analysis of efficacy outcomes, risk factors known to impact on recurrent VTE risk but are not linked with bleeding were examined (extent and severity of VTE

disease, previous VTE event, idiopathic VTE and immobilization), as were presence of chronic cardiac disease or pulmonary disease. Studies of predictive variables for recurrent and bleeding events for VTE patients on anticoagulation from the RIETE registry confirm this.[197-199]

Statistical analysis in EINSTEIN PE

A7. Please provide a citation for the meta-analysis of historical trials used to inform the non-inferiority margin (page 62 of the submission).

Please see section 13.7 of the trial protocol[63], which describes a literature search and consequent data synthesis of 14 trials.

A8. It is noted that page 97 of the submission states that the non-inferiority margin was pre-specified as per EMA guidance. However, please provide further information about the pre-specified decision that for non-inferiority to be concluded, rivaroxaban had to retain at least 50% of the efficacy of enoxaparin/VKA (that is, the upper 95% CI needed to below the hazard ratio margin of 2.0)? Specifically, please clarify why this fraction of efficacy (i.e. at least 50%) was considered appropriate for this indication.

The pre-specified non-inferiority margin of 2.0 was derived on the basis of retaining approximately 66% rather than 50% of the effect.

Regulatory guidance for the statistical design of non-inferiority trials recommends, in general, maintaining at least 50% of the historical effect of a drug.[200,201] The derivation of the non-inferiority margin used an estimate of relative treatment effect from a meta-analysis of trials of heparins/VKA vs various `less effective' therapies. As a consequence of the comparators in this meta-analysis not only being placebo, it was decided to retain at least 66% rather than 50% of the effect, resulting in the more conservative (lower) non-inferiority margin of 2.0.

This margin is considered appropriate in the context of contemporary VTE trials, ie: trials that had not completed or published at the time the EINSTEIN-PE trial was designed. The margin is also considered appropriate given the low absolute event rates which were expected (and observed) for this outcome measure.

A9. On page 72 of the submission, results are reported for the primary efficacy outcome in the ITT population, the PP population, and also the 'ITT on-treatment' and 'PP on-treatment' populations. Please define the ITT on-treatment' and 'PP on-treatment' populations, and provide the numbers of patients in each, according to trial arm.

The `ITT on treatment' population is defined as randomized patients who received study treatment. This population may be regarded as a subgroup of the safety population as it excludes patients who received study medication other than randomized. The `ITT on treatment' analysis, which was reported on page 72, was conducted in the `ITT on treatment' population reflecting only those events which occurred during study treatment as randomised, and not later than 2 days after stop of study treatment.

The PP population is defined in the study disposition graphic (Figure 5, page 65). The `PP on treatment' analysis, which was reported on page 72, was conducted in the PP population reflecting only those events which occurred during study treatment as randomised, and not later than 2 days after stop of study treatment.

The numbers of patients in each study population, by treatment arm, is provided in Table 3. `PP on treatment' is not included in this table as the `PP on treatment' analysis was conducted in the PP study population.

Table 3: Study populations by treatment arm in EINSTEIN-PE

Study population	Rivaroxaban	Enoxaparin/VKA
ITT	2419	2413
Safety	2412	2405
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

EINSTEIN PE outcomes

A10. Priority question: The definition of bleeding events that are excluded from treatment-emergent adverse events on page 78 of the submission is unclear, as not all bleeds (e.g. epistaxis) are excluded. Please list the bleeding outcomes that were and were not included in the analysis of treatment-emergent adverse events described on table 18 and table 22 (on page 92 of the submission). For each bleeding outcome included in the treatment emergent adverse event please, provide numbers, proportions and P-values, risk ratios, absolute risk differences and associated 95% confidence intervals.

On page 78 is stated: `The incidence of treatment-emergent adverse events (excluding bleeding and recurrent VTE) was comparable between treatment groups, as shown in Table 18'.

The primary safety outcomes, clinically relevant bleeding and its constituent components (eg `major bleeding') were not included in this table; nor were the principle efficacy outcome, recurrence of VTE, or its components. Both clinically relevant bleeding and VTE recurrence may potentially have been considered by readers of this submission as adverse events, so the purpose of this sentence was to highlight that these outcomes were not considered in this table. Nothing further was meant by this statement. This table otherwise contains any adverse events whose incidence rate was at least 4% in any treatment group of treatment emergent adverse events coded by MedDRA Version 14.1 by system organ class and preferred term.

Tables 18 and 22 (on pages 79 and 92) includes presentation of all treatment-emergent adverse events experienced in at least 4% of patients in either arm of any type. It is appreciated that the table provided in the submission stated that these were `adverse events' rather than `treatment-emergent adverse events' as they had been correctly referred to in the earlier paragraph of the submission and in this question. A replacement set of tables is provided in the appendix. See also question A16.

A11. The footnote to table 15 (page 70 of the submission) states that 'some patients may have experienced more than one event'. Please provide the number of patients experiencing more than one event and, which events were experienced together.

Table 15 provides data on the constituents of the primary efficacy outcome, which was a composite outcome, by treatment arm and intended treatment duration. It provides more detail than the Final Scope / Decision Problem requires, as this lists venous thromboembolism as an outcome rather than each of five constituents of the composite outcome. The footnote is recognition that the sum of the number of patients experiencing each of the five constituents will be greater than or equal to the number of patients experiencing the composite outcome as `some patients may have experienced more than one [constituent] event'.

[redacted]

A12. Priority Question: It is not clear from the submission which outcomes were assessed by the blinded central independent adjudication committee (CIAC). For example Table 8 (page 52 of the submission) states that "all suspected outcome events were classified by a central independent adjudication committee (CIAC) who members were unaware of the treatment assignments", Appendix 3 (page 300) states that the blinded CIAC also assessed the "key safety outcomes according to pre-defined criteria" and the NEJM publication states "in the case of suspected venous thromboembolism, the protocol required objective testing" (page 1289). Please clarify precisely which outcomes were assessed by the CIAC.

Please see section 6.2.3 of the trial protocol, provided with the submission[63]. This states that the following events, if suspected, were to be assessed by the central blinded and independent adjudication committee: recurrent PE or DVT, bleeding and vascular events. Additionally, in case of death, the protocol required that an autopsy should be requested, a serious adverse event form completed and certain further documentation should be sent for adjudication. This procedure therefore ensured adjudication not only of `suspected venous thromboembolism' but also `key safety outcomes'.

A13. Please clarify the total the number of patients in each arm who were included in the adverse events analyses detailed in Table 18, page 79 of the submission.

There were 2412 rivaroxaban patients and 2405 enoxaparin/VKA patients (safety population). See also Table 3 in this response.

A14. Page 96 of the submission reports percentages of patients with 'confirmed events' (VTE recurrence – 10.2% in the rivaroxaban group vs. 9.7% in the dual enoxaparin/VKA arm). These percentages do not appear to be consistent with those reported on page 69 of the submission, which states for the primary efficacy outcome "the outcome was confirmed in 50 (2.1%) patients in the rivaroxaban group and 44 (1.8%) patients in the dual enoxaparin/ VKA arm". Please clarify which of the figures are correct.

Both sets of figures are correct. The statement cited from page 69 of the submission (and elsewhere) refers to the number of patients with confirmed VTE events as a proportion of the ITT study population. The statement cited from page 96 of the submission, which is in the context of a discussion of internal validity, refers to the proportion of patients with suspected events which were then confirmed. Further explanatory data is provided in Table 4.

Table 4: Patients with suspected and confirmed VTE events in EINSTEIN-PE

	Rivaroxaban	**Enoxaparin/VKA**
ITT patients	2419	2413
[redacted]	[redacted]	[redacted]
Patients with confirmed VTE (ITT analysis)	50	44
Patients with confirmed VTE as a proportion of all patients	2.1%	1.8%
Patients with confirmed VTE as a proportion of patients with suspected events	10.2%	9.7%

Discontinuations in EINSTEIN PE

A15. Priority question Page 62 of the submission states "when enrolment was discontinued, patients completed their assigned treatment except for those in the 12 month duration group who completed at least 6 months".

- **Please clarify whether it was specified in the protocol for EINSTEIN-PE that people in the 3- and 6-month treatment groups must finish their treatment if they have not completed by the time of enrolment discontinuation, whilst people in the 12-month treatment group should continue until 6 months or whether all people in the 3- and**

6-month treatment groups in EINSTEIN PE, but not the 12-month treatment group had completed their treatment at the time enrolment was discontinued.

The study was terminated by the sponsor after the planned number of events was reached.

The NEJM publication states: `When enrolment was discontinued, patients completed their assigned treatment except for those in the 12-month stratum who completed at least 6 months of treatment.' To clarify further, and in line with the study protocol[63], this means:

- Further recruitment of patients into the study stopped.
- Patients in the 3 months group who had not completed their 3 months intended treatment duration remained on treatment until the end of the 3 months intended treatment duration.
- Patients in the 6 months group who had not completed their 6 months intended treatment duration remained on treatment until the end of the 6 months intended treatment duration.
- Patients in the 12 months group who had not completed their 12 months intended treatment duration, either:
  - continued treatment until they had completed 6 months of treatment, if they had not already completed 6 months of treatment; or
  - ceased treatment immediately, if they had already completed at least 6 months of treatment.
- **Please provide the number and proportion of patients overall and by each trial arm did not complete the full 12 months of treatment?**

The proportion of patients who did not complete 12 months of treatment or who discontinued due to the study's termination varied according to treatment arm and intended treatment duration. None of the patients in the 3 or 6 months intended treatment duration completed 12 months of treatment; [redacted] of 1809 patients in the 12 months intended treatment duration group did not complete 12 months of treatment. Further data is shown in Table 5, including the impact of sponsor termination in each treatment duration group.

Table 5: Continuation with treatment to intended treatment duration or 12 months in EINSTEIN-PE, by treatment arm and patient group (intended treatment duration)

Patient group	Rivaroxaban		Enoxaparin/VKA	
	N	(%)	N	(%)
3 months intended treatment duration				
Randomised subjects	127		122	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 months intended treatment duration				
Randomised subjects	1388		1387	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months intended treatment duration				
Randomised subjects	905		904	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A16. Priority question: Please clarify why the number of patients stated to have discontinued the study drug as a result of an adverse event in Table 18 page 79 of the submission differs to the number stated in Table 13 page 64 and Figure 5 page 65 of the submisson. Please clarify which data are correct.

Table 18 on page 79 contains an error in the section headed `treatment-emergent adverse events', which should be headed simply `adverse events'. A replacement of this table and Table 22 from pages 91-92 are provided in an appendix to this response.

Several figures/sources are referred to in this question, from the EINSTEIN-PE trial.

- Table 13 on page 64 states that 111 (4.6%) rivaroxaban patients and 92 (3.8%) enoxaparin/VKA patients prematurely discontinued from study drug primarily due to having experienced an adverse event. This was taken from Table 2 of the NEJM study publication. The proportions refer to randomised subjects.
- Figure 5 on page 65 states that [redacted] patients prematurely discontinued from study drug primarily due to having experienced an adverse event. This corresponds with Table 2 of the NEJM study publication mentioned above.

- Table 18 on page 79 contains an error as noted above. This table states that 123 (5.1%) rivaroxaban patients and 99 (4.1%) enoxaparin/VKA patients experienced a treatment-emergent adverse event that led to permanent discontinuation of study drug. It should state that these numbers and proportions of patients received an adverse event that led to permanent discontinuation of study drug. This was taken from Table 3 of the NEJM study publication.

There remain small differences between the numbers and proportions of patients discontinuing treatment due to experiencing an adverse event between Tables 2 and 3 of the NEJM study publication. The reason for these differences relates to the source of data used in either table, and the relevant denominator study population.

- Data in Table 2 of the NEJM study publication is sourced from information recorded in the end of treatment case report form, and is based on the judgement of investigators. It is recognised that because of investigators judgement of primary reason for premature termination, the number of termination due to adverse events may be unequal to the number of subjects with adverse events and `drug discontinued permanently' documented as action. The denominator study population is randomised subjects.
- Data in Table 3 of the NEJM study publication is sourced from information recorded in the adverse event case report form. The denominator study population is the safety population.

Einstein-PE patient treatment satisfaction

Since making the submission to NICE, the treatment satisfaction data has been published.[15] We include with this response a copy of the conference poster publication, which may go some way towards answering the questions raised.

A17. Please clarify how many patients from each trial arm were included in the analyses of patient treatment satisfaction and how the patients included in these analyses were selected.

A subset of all the patients enrolled in EINSTEIN-PE from seven countries, based on translations available at the start of the trial (Canada, France, Germany, Italy, The Netherlands, UK, and US), was used to evaluate patient satisfaction. A total of 2397 patients in EINSTEIN-PE were eligible to participate in this substudy (rivaroxaban: 1200, enoxaparin/VKA: 1197). Characteristics of patients involved in this substudy appeared representative of the overall EINSTEIN PE population in terms of age, gender, prior history of VTE, and nature of index PE.

A18. Please provide the rate of missing data across each trial arm in the patient satisfaction analyses (for the ACTS measure), and the strategy for dealing with missing data.

ACTS data were collected and calculated via questionnaire responses at multiple timepoints, so data completeness varies according to whether an individual questionnaire response is considered or whether it is instead the ability to calculate a ACTS subscale score (Benefit or Burden). Response varies between timepoint, and not all patients were eligible to complete

the questionnaire at 6 or 12 months, depending on their intended study duration. The questionnaire providing the basis of ACTS scoring was provided in section 13.5 of the study protocol.[63]

Taking account of the proportion eligible to complete a questionnaire at any point, completion of all 17 items of the ACTS questionnaire varied between [redacted] of patients depending on treatment arm and timepoint (as shown in Table 6).

Table 6: Completion of all 17 ACTS items in treatment satisfaction substudy of EINSTEIN-PE[15], before imputation

Timepoint	Rivaroxaban			Enoxaparin/VKA		
	Number of subjects at visit	Subjects with complete data	% complete	Number of subjects at visit	Subjects with complete data	% complete
Day 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The ACTS scoring mechanism involved imputation of scores in certain circumstances.

- If fewer than 7 items relevant to the Burden scale were incomplete for a given patient and timepoint, then the Burden scale was calculated as equal to the mean of the completed item score x 12. No imputation of Burden score was permitted if 7 or more items were incomplete.
- If fewer than 2 items relevant to the Benefit scale were incomplete for a given patient and timepoint, then the Benefit scale was calculated as equal to the mean of the completed item score x 3. No imputation of Benefit score was permitted if 2 or more items were incomplete.

Taking into account this imputation led to the completion of ACTS scoring for between [redacted] of patients depending on treatment arm and timepoint (data tables analogous to Table 6 are available to support this).

ACTS scoring data were analysed using a repeated measures model, stratified by planned treatment duration, and including a term for treatment group. Visit was a repeated measures factor, with an unstructured variance/covariance matrix. This mixed modelling method employed uses all patient visit data collected, including data from patients where data from certain timepoints are missing (`unbalanced' dataset), without any further imputation required for missing data.

A further category of missing data is where no questionnaire responses are available for any time period for an eligible patient. Given the high and balanced rates of completion in this study, this category of missing data was judged not to be able to influence the overall results under reasonable assumptions.

A19. Please clarify whether the TSQM analyses were performed for the ITT population, and if so, please provide the rate of missing data and the strategy for dealing with missing data as above.

A20. Please clarify the methods used to analyse the TSQM data. Please also provide the underlying data to support the final sentence in the third paragraph on page 38.

We answer both questions together (A19 and A20). Version 2 of the TSQM instrument was used, whose scoring mechanism and construct validity was discussed in Atkinson et al, 2005[202], and also the third paragraph on page 38 of the submission.

TSQM data were collected and calculated via questionnaire responses at multiple timepoints so, as with ACTS data, completeness varies according to whether an individual questionnaire response is considered or whether it is instead the ability to calculate the overall or one of the four TSQM subscale scores. Response varies between timepoint, and not all patients were eligible to complete the questionnaire at 6 or 12 months, depending on their intended study duration. The questionnaire providing the basis of TSQM scoring was provided in section 13.6 of the study protocol[63] and Atkinson et al[202].

Taking account of the proportion eligible to complete a questionnaire at any point, completion of all 11 items of the TSQM questionnaire varied between [redacted] of patients depending on treatment arm and timepoint (as shown in Table 7).

Table 7: Completion of all 11 TSQM items in treatment satisfaction substudy of EINSTEIN-PE[15], before imputation

Timepoint	Rivaroxaban			Enoxaparin/VKA		
	Number of subjects at visit	Subjects with complete data	% complete	Number of subjects at visit	Subjects with complete data	% complete
Month 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The TSQM scoring mechanism involved imputation of scores in certain circumstances.

- If fewer than 2 items relevant to the Side Effects scale were incomplete for a given patient and timepoint, then this score was calculated as equal to the mean of the completed item score x 2. No imputation of this score was permitted if 2 or more items were incomplete.
- If fewer than 2 items relevant to the Convenience scale were incomplete for a given patient and timepoint, then this score was calculated as equal to the mean of the completed item score x 2. No imputation of this score was permitted if 2 or more items were incomplete.
- There was no imputation of the Effectiveness or Global Satisfaction subscales.

Taking into account this imputation led to the completion of TSQM scoring for between [redacted] of patients depending on treatment arm and timepoint (data tables analogous to Table 7 are available to support this).

As with ACTS scoring, TSQM scoring data were analysed using a repeated measures model, stratified by planned treatment duration, and including a term for treatment group. Visit was a repeated measures factor, with an unstructured variance/covariance matrix. This mixed modelling method employed uses all patient visit data collected, including data from patients where data from certain timepoints are missing (`unbalanced' dataset), without any further imputation required for missing data.

A further category of missing data is where no questionnaire responses are available for any time period for an eligible patient. Given the high and balanced rates of completion in this study, this category of missing data was judged not to be able to influence the overall results under reasonable assumptions.

Section B: Clarification on cost-effectiveness data

B1. Priority Question: Table 28 on page 120 of the submission reports the probabilities of a VTE in patients on LMWH/VKA by patient treatment duration and period. Please provide the probabilities by period for rivaroxaban equivalent to the data in table 28, for LMWH/VKA.

The requested data, analogous to that provided in Table 28 of the submission, is provided here in Table 8.

Table 8: Probabilities of a VTE by treatment duration and period, rivaroxaban arm

Patient group (treatment duration) and period	Patients with event	ITT population	Risk	Lower 95% CL	Upper 95% CL
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CL – confidence limit.

Notes:

- The column labelled `base case' in the submission is equivalent to the column labelled `risk' here.
- The column labelled `alpha' in the submission is equivalent to the column `patients with event' here.
- The column labelled `beta' in the submission is equivalent to the difference between the columns `patients with event' and `ITT population' here.

B2. Priority Question: The treatment effect is applied in the model using a hazard ratio assuming a proportional hazard (page 120 of the submission).

- **Please clarify whether a test was performed to support the assumption of proportional hazard? If so, please describe which test was used and provide the result of the test.**

The proportional hazards assumption was checked with plots of scaled Schoenfeld residuals according to the protocol and SAP. Plots were produced by treatment group and by presence of baseline cancer for the following stratified proportional hazards models: primary efficacy outcome, primary efficacy outcome excluding events confirmed by an important change in antithrombotic therapy only, net clinical benefit 1, net clinical benefit 2, secondary efficacy outcome, symptomatic recurrent PE, symptomatic recurrent DVT, deaths, and vascular events up to the end of intended treatment period. There was no evidence for a clear deviation from the proportional hazards assumption for any of the above outcomes.

In addition to these plots, the proportional hazards assumption in the primary efficacy analysis was tested by including the time-dependent covariate treatment group x log(time) in the model. There was no evidence for a non-proportional hazard ratio (p-value for time-dependent variable: [redacted]).

- **Please clarify whether consideration was given to using separate probabilities or relative risk ratios for the rivaroxaban and the comparator arm, rather than a proportional hazard?**

Proportionality of hazards

Firstly, we would highlight both relative risks and hazard ratios require an implicit assumption of proportional hazards over which they are assumed to continuously apply (eg: in an economic model). In the absence of censoring, relative risks and hazard ratios are equivalent approaches to deriving comparative risks. Extending the equations provided in the submission on pages 120,123, 125:

$$r_2 = 1 - (1 - r_1)^{HR} = RR \times r_1$$

where r_1, r_2 are risks, HR is a hazard ratio and RR the equivalent relative risk.

In the presence of censoring, as in EINSTEIN-PE and other trials where discontinuation is not impossible, the hazard ratio is considered a superior measure of treatment effect to relative risk for a time to event outcome, such as the efficacy and safety outcomes in EINSTEIN-PE.

Consideration of applying observed rates specific to each treatment arm

The NICE Methods Guide requires that the economic evaluations `include the quantification of the effect of the technologies under comparison on the course of the relevant disease' (paragraph 3.3.2)[65].

It is of course feasible to model event rates in the rivaroxaban arm according to observed trial rates, rather than through estimates of treatment effect measured in the trial according to its statistical analysis plan. Such an approach may appear to help assure that the model reflects the outcomes observed in a trial, to the extent that this may not be clear from model validity checks (eg: sections 7.7.1-2 of the submission).

However, it is important that an evaluation of the relative cost-effectiveness of a pair of interventions is reflective of a robust and unbiased evaluation of the relative clinical effectiveness of the interventions. Where the relative effectiveness derives from primary outcomes measured and evaluated according to a statistical analysis plan from a clinical trial using best practice statistical methods, the economic model should adopt assumptions as to relative treatment effects consistent with this. In EINSTEIN-PE, the primary efficacy and safety outcomes, around which the model is largely based, were analysed using methods which properly account for exposure time, discontinuation, the nature of the outcome type (time to event) and presence of active cancer. It is therefore appropriate that the resulting hazard ratios were employed directly in the economic model in both deterministic and probabilistic forms.

The approach described above for the PE economic model was consistent not only with the economic model developed for the previous DVT appraisal[19], but also the economic model developed for NICE CG144 in the evaluation of the relative cost-effectiveness of alternative durations of anticoagulation treatment for VTE[8]. Probabilities were assumed in relation to VTE recurrence in untreated patients and a treatment effect (relative risk) applied to derive recurrence in treated patients. Similarly, probabilities were assumed in relation to incidence of major bleeding in treated patients and a treatment effect (relative risk) applied to derive incidence in untreated patients.

Consideration of further stratification by patient group (intended treatment duration)

The EINSTEIN-PE trial was, as EINSTEIN-DVT, a trial evaluating rivaroxaban vs dual enoxaparin/VKA in three patient groups: patients requiring 3, 6 or 12 months of anticoagulation. The consideration described of applying observed rates to each treatment arm of the economic model extends to whether these observed rates should also be specific to each intended treatment duration patient group (as per the data provided in response to question B1). The economic model submitted incorporates event rates which are specific to each patient group, and measures of treatment effect evaluated using the full trial data.

During the NICE STA of rivaroxaban for DVT treatment in 2011 (TA261), ScHARR (as the ERG) requested that Bayer conduct cost-effectiveness analyses based on treatment effects specific to each intended duration patient group. Bayer complied with this request and produced the required additional analysis.[19] This is similar, in effect, to one that might be based around using observed trial event rates specific to each treatment arm and intended treatment duration patient group. We would question the methodological desirability of such an approach for reasons given previously. In particular, such an approach might lead to an economic model that incorporated quantification of the effect of the technologies inconsistent with conclusions made in the clinical effectiveness aspect of this technology assessment. Also a probabilistic analysis might no longer reflect true parametric uncertainty or respect trial randomisation, if treatment arms were to be modelled entirely independently.

In considering the additional analysis and further information provided by Bayer in the DVT appraisal (TA261), the NICE Appraisal Committee `concluded that evidence of treatment effect should be based on the whole trial population of EINSTEIN-DVT' (paragraph 4.7 of the FAD).[19] There are other similarities between the evidence base relevant to this appraisal and with the previous appraisal of rivaroxaban in DVT treatment:

- EINSTEIN-PE and EINSTEIN-DVT have the same study protocol document, describing similar study designs, including procedures, outcomes and analyses.
- There were no clinical criteria or algorithms mandated for use in the EINSTEIN-PE trial in relation to the intended duration of treatment. Treatment periods were at trial investigator's discretion, on consideration of individual patient risk-profile and local guidelines.
- Resulting populations, described below, were similar in their risk profiles. A greater prevalence of risk factors tended to exist in the longer duration groups. This is consistent with application of UK guidelines, such as NICE CG144[8].

- There was no evidence of differences in the relative efficacy or safety of rivaroxaban between duration groups in EINSTEIN-PE. There was no significant statistical interaction between treatment and intended treatment duration in relation to the primary efficacy outcome ([redacted]), clinically relevant bleeding ([redacted]) or major bleeding ([redacted]).
- In any case, differences in treatment effects by intended treatment duration or other patient group characteristic should be considered in light of: the small numbers of patients and/or events in certain subgroups, variation in mean length of follow-up between patient groups, and the multiplicity of quantitative interaction tests across outcomes.

Conclusion

We conclude that the approach adopted in the economic model submitted was appropriate, given the considerations outlined above. This approach involved adopting event rates in the rivaroxaban arm consistent with event rates in the comparator arm and trial measurements of relative treatment effect, rather than observed trial event rates in the rivaroxaban arm. The approach adopted is methodologically appropriate, and consistent with previous Appraisal Committee decision-making (TA261)[19] and related de novo economic models developed for NICE[8] on the basis of systematic reviews of previous economic evaluations.

B3. The technology acquisition costs for rivaroxaban provided in Table 1 and subsequent tables for the base case cost-effectiveness analysis (£216.74, £392.52; £727.71 for 3, 6, 12 months, respectively) are slightly lower than those presented in Table 2 (£235.86, £427.61 or £811.13). Please clarify the discrepancy in these costs.

Table 1 reports costs and outcomes from the cost-effectiveness analysis. The technology acquisition costs included in this table therefore reflect the impact of VTE events, bleeding events or other discontinuation from treatment over time.

In contrast, Table 2 reports acquisition costs for a full 3, 6 or 12 months duration of treatment without adjustment. The figures in Table 2 are therefore slightly greater than those given in Table 1.

B4. Priority question: Please provide the mean (SD) number of INR monitoring visits for both arms of the EINSTEIN-PE trial for the first three months, and 3 month cycles thereafter.

Please see Table 9, which we trust should suffice. [redacted]

Table 9: Mean (SD) frequency of INR measurements after randomisation per patient, enoxaparin/VKA arm of EINSTEIN-PE, irrespective of intended treatment duration, and the corresponding number of patients

Period (months)	Number of patients	Mean	SD
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Appendix

Tables 18 and 22 of the submission (page 79 and pages 91-92 respectively) should be considered to be replaced by Table 10 and Table 11 below. The corrections are that the first box refers to adverse events rather than treatment-emergent adverse events; the second box refers to treatment-emergent adverse events rather than adverse events. The numbers and events are unchanged.

Table 10: Summary of adverse events in EINSTEIN-PE

	Rivaroxaban		Enoxaparin/VKA		P-value
Adverse events (AEs)					
Any	1941	(80.5)	1903	(79.1)	0.29
Serious event	476	(19.7)	470	(19.5)	0.86
Resulting in permanent discontinuation of study drug	123	(5.1)	99	(4.1)	0.10
Leading to or prolonging hospitalisation	475	(19.7)	430	(17.9)	0.82
Treatment-emergent AEs experienced in at least 4% of patients in either arm					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Other AEs of interest					
Acute coronary event	15	(0.6)	21	(0.9)	
Cerebrovascular event	12	(0.5)	13	(0.5)	
Systemic embolism	5	(0.2)	3	(0.1)	
Alanine aminotransferase level of more than three times the upper limit of the normal range and a bilirubin level of more than twice the upper limit of the normal range	5	(0.2)	4	(0.2)	

Table 11: Relative and absolute risk differences (ARD, %) for the adverse events in EINSTEIN-PE listed previously (95% CI)

	Risk ratio (95% CI)	ARD (%, 95% CI)
Adverse events (AEs)		
Any	[redacted]	[redacted]
Serious event	[redacted]	[redacted]
Resulting in permanent discontinuation of study drug	[redacted]	[redacted]
Leading to prolonged hospitalisation	[redacted]	[redacted]
Treatment emergent AEs experienced in at least 4% of patients in either arm		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	Risk ratio (95% CI)	ARD (%, 95% CI)
Other AEs of interest		
Acute coronary event	[redacted]	[redacted]
Cerebrovascular event	[redacted]	[redacted]
Systemic embolism	[redacted]	[redacted]
Alanine aminotransferase level of more than three times the upper limit of the normal range and a bilirubin level of more than twice the upper limit of the normal range	[redacted]	[redacted]

Note: See Table 10 in this NICE/ERG response for underlying data

References

The numbering of references continues from the original submission.

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