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

BMS/Pfizer Response to Evidence Review Group (ERG) Clarification questions

Addendum: 8th December 2014

BMS/Pfizer welcomes the opportunity to respond to the ERG's clarification questions from the Liverpool Reviews and Implementation Group (LRiG) for the review of apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism [ID726]. As outlined in our initial response on the 20th November, we were unable to undertake analyses for questions A27-38 due to time constraints. However, we committed to submit data for the priority questions (A27 and A28) requested by the ERG. In this follow-up addendum we are presenting the requested data for the two priority questions as well as the implications for the cost-effectiveness analyses of exploring the outcomes concerned.

As previously noted, BMS/Pfizer is confident that the clinical evidence of apixaban demonstrates efficacy and an appropriate safety profile in both the treatment and the prevention of DVT and/or PE. Throughout the economic modelling we have selected conservative inputs and assumptions when data are limited or missing. Therefore we are confident that we have presented a robust and credible estimate of apixaban's cost-effectiveness relative to comparators in the appraisal. Apixaban is a cost-effective use of NHS resources for this indication with ICERs well within established thresholds.

BMS/Pfizer would also like to reiterate our willingness to provide further clarification regarding the clinical assumptions underlying our clinical data and the apixaban model, so as to avoid misinterpretation, which could lead to avoidable uncertainty for the NICE Appraisal Committee. Furthermore, we would welcome the opportunity to undertake any additional analyses required by the ERG.

BMS/Pfizer response to additional request for KM analyses: General

Overall, a number of the requests for Kaplan-Meier (KM) analyses received from the ERG for outcomes from both AMPLIFY and AMPLIFY-EXT are likely to provide a highly uncertain estimation of the relative effectiveness of apixaban compared to comparators. For some of these requests there are only few events and this can cause the KM curves to fluctuate with large steps, which implies a large degree of uncertainty. Tests between groups based on KM are sensitive to event counts and it is likely they will lack power to show any differences. This is especially relevant for the analyses conducted on the DVT and PE subgroups. Consequently, BMS Pfizer consider these analyses to have limited clinical relevance and unlikely to inform consideration of the evidence available for apixaban.

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

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

confirm the reliability of this assumption, or to compare the trial evidence with other sources of relevant information in the published literature.

BMS/Pfizer response to additional request for KM analyses: Priority Questions A27 and A28

We understand the need to test the modelling assumptions to ensure a transparent evaluation of apixaban. However, it is unclear to BMS/Pfizer from the ERG's questions A27-A38 the exact thinking that led to the request for data for each of these outcomes. Our principal concern relates to the extrapolation of data beyond the end of the AMPLIFY trial. BMS/Pfizer appreciates that the ERG may be testing assumptions within the model regarding the temporal distribution of events within the trial period of AMPLIFY. However, we would like to highlight that the extrapolation of data via survival analysis beyond the end of AMPLIFY is likely to have limited applicability for the interpretation of apixaban efficacy and safety profile. This is due to the differences in the licensed dose of apixaban recommended for the treatment and prevention periods. Only the 2.5 mg twice daily dose should be initiated following completion of 6 months of treatment with Eliquis 5 mg twice daily (the dose in AMPLIFY). Therefore extrapolation of Eliquis 5mg twice daily from the AMPLIFY study beyond the six months treatment would not be appropriate and outside the product labelling. BMS/Pfizer also notes that the data requested do not conform to either the cycle length or definition of outcomes included in the model.

Please see below the tables requested for the 2 priority questions, A27 and A28. We have also re-presented scenario analyses that tested these outcomes within the cost-effectiveness model and may address some of the ERG's concerns.

A27. Priority Question: AMPLIFY trial data. Time to death from any cause K-M analysis, stratified by treatment arm and by index event type (i.e. DVT only vs PE +/- DVT) [i.e. 2 x 2 analyses]. This analysis should include the 30 day observation period after treatment discontinuation.

The results for these analyses are presented in Tables 1 to 4.

Table 1: All-cause death Kaplan-Meier analysis: apixaban (PE) from AMPLIFY

Days	Survival	Failure	Survival Standard Error	Number Failed	Number Left
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Table 2: All-cause death Kaplan-Meier analysis: enoxaparin/warfarin (PE) from AMPLIFY

Days	Survival	Failure	Survival Standard Error	Number Failed	Number Left
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 3: All-cause death Kaplan-Meier analysis: apixaban (DVT) from AMPLIFY

Days	Survival	Failure	Survival Standard Error	Number Failed	Number Left
[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]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4: All-cause death Kaplan-Meier analysis: enoxaparin/warfarin (DVT) from AMPLIFY

Days	Survival	Failure	Survival Standard Error	Number Failed	Number Left

[redacted]

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

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

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

These rates were adjusted by a HR of mortality for patients with VTE (excluding excess mortality due to the events modelled) versus the general population as obtained from a large cohort study following up patients for 8 years (Flinterman et al. 2012). This study found that even 8 years after the index event, VTE-associated mortality persists even when no other co-morbidities were present (Flinterman et al. 2012).

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

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

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

	Rivaroxaban	LMWH/Dabigatran	LMWH/VKA
Base case	**Dominant**	**Dominant**	**£2,406**

	Rivaroxaban	LMWH/Dabigatran	LMWH/VKA
Background mortality set to equal general population	**Dominant**	**Dominant**	**£1,485**

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

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

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

A28. Priority Question: AMPLIFY trial data. Time to treatment discontinuation K-M analysis, stratified by treatment arm and by index event type (i.e. DVT only vs PE +/- DVT) [i.e. 2 x 2 analyses], censoring patients at time to death from any cause.

The results for these analyses are presented in Tables 5 to 8. Note the KM estimations were performed using the all-randomised dataset for AMPLIFY to minimise missing data. This dataset includes patients who interrupted treatment during the trial. Consequently, for this analysis, discontinuations were observed beyond AMPLIFY's pre-specified treatment period.

Table 5: Treatment discontinuation Kaplan-Meier analysis: apixaban (PE)

Days	Survival	Failure	Survival Standard Error	Number Failed	Number Left
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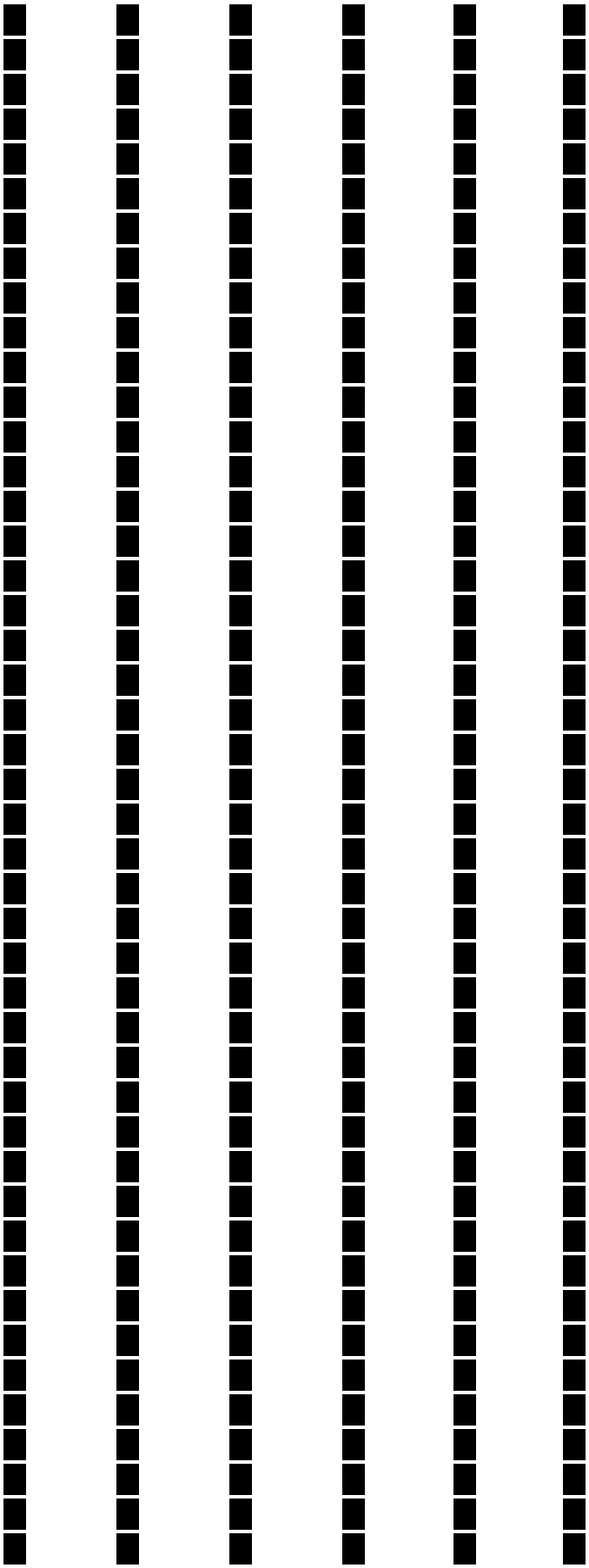

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Table 6: Treatment discontinuation Kaplan-Meier analysis: enoxaparin/warfarin (PE)

Days	Survival	Failure	Survival Standard Error	Number Failed	Number Left
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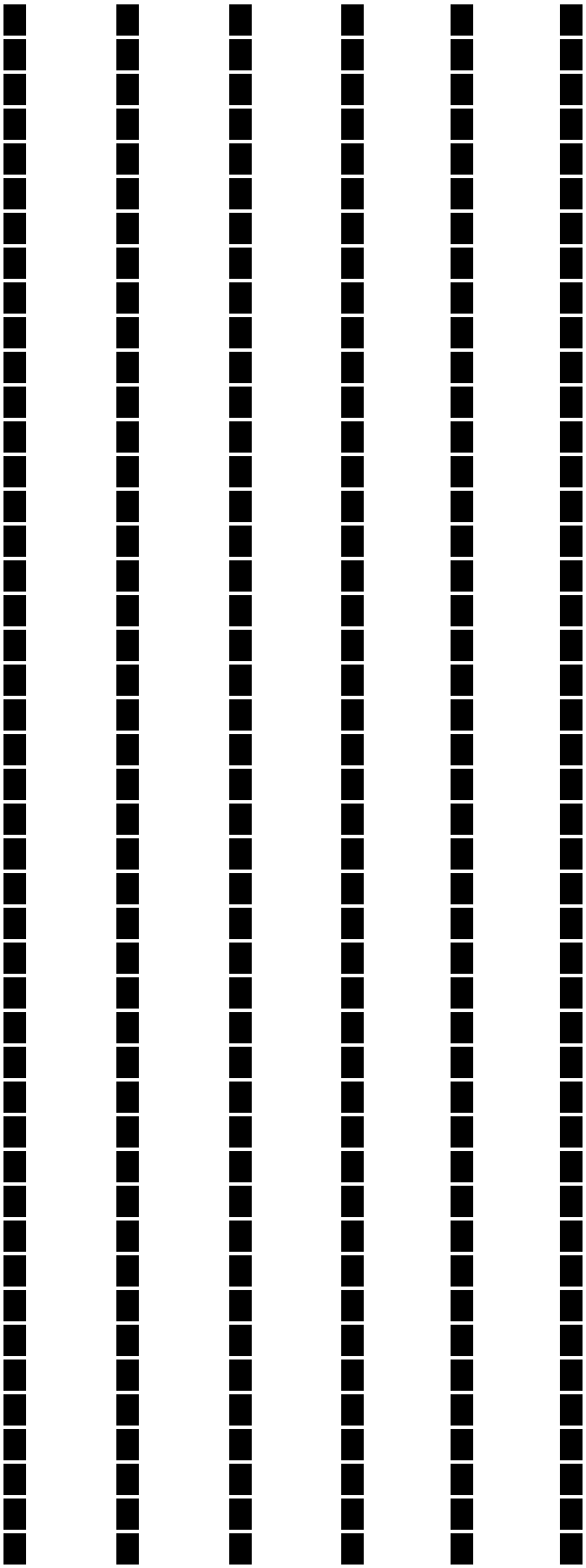
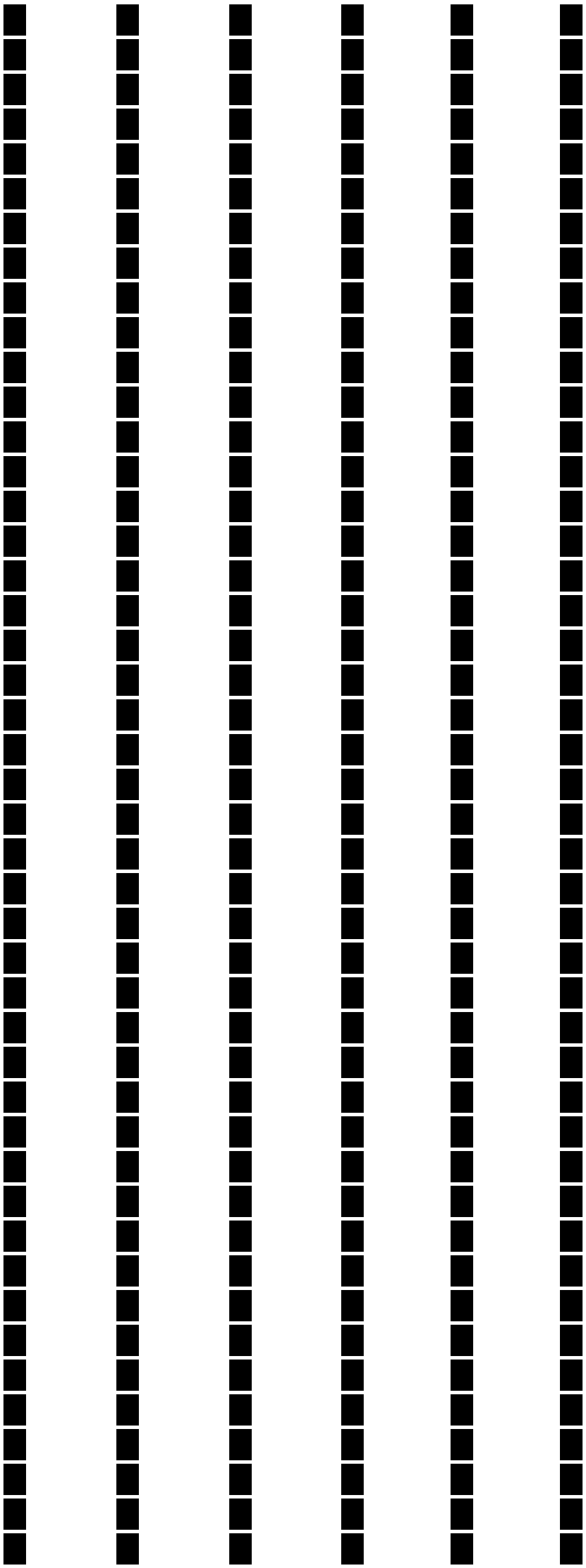


Table 7: Treatment discontinuation Kaplan-Meier analysis: apixaban (DVT)

Days	Survival	Failure	Survival Standard Error	Number Failed	Number Left



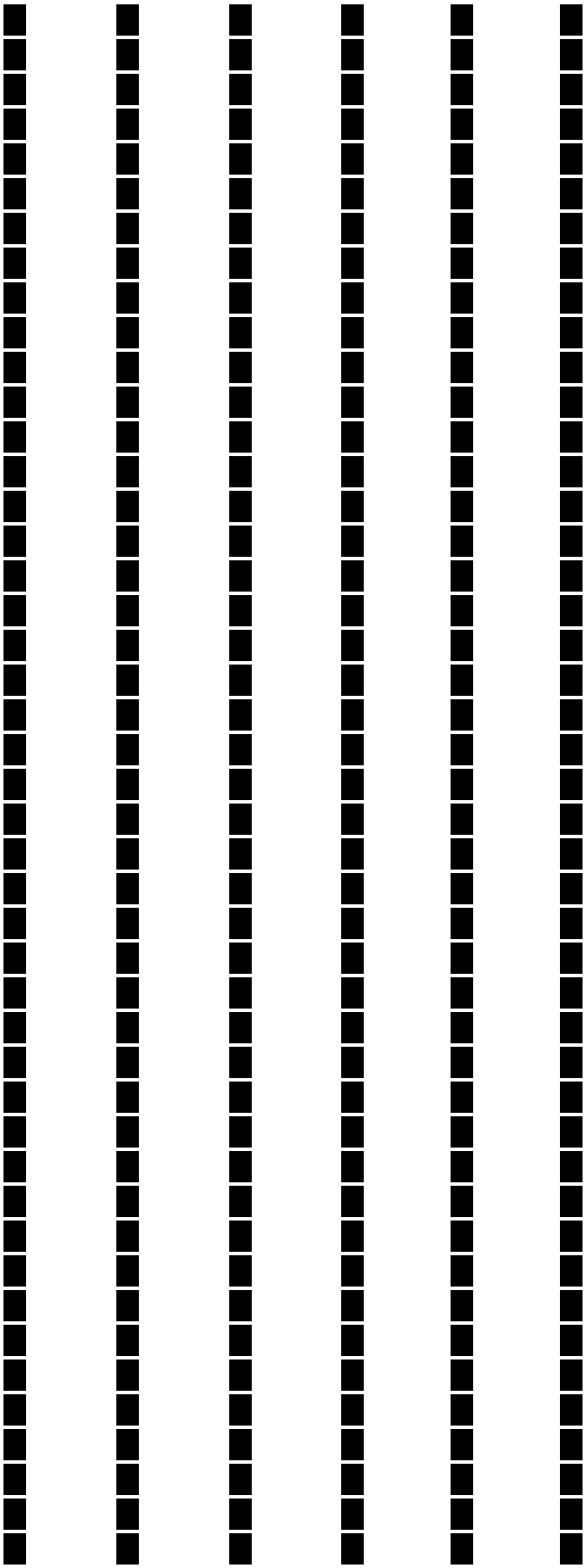
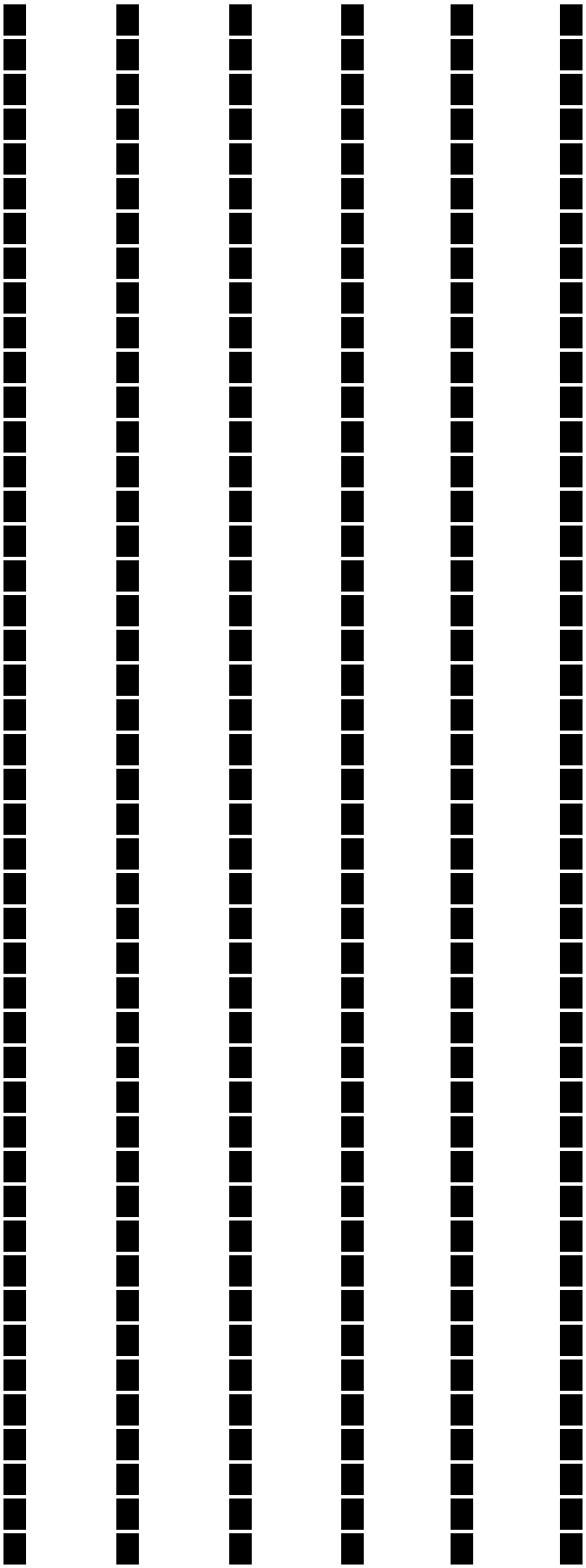
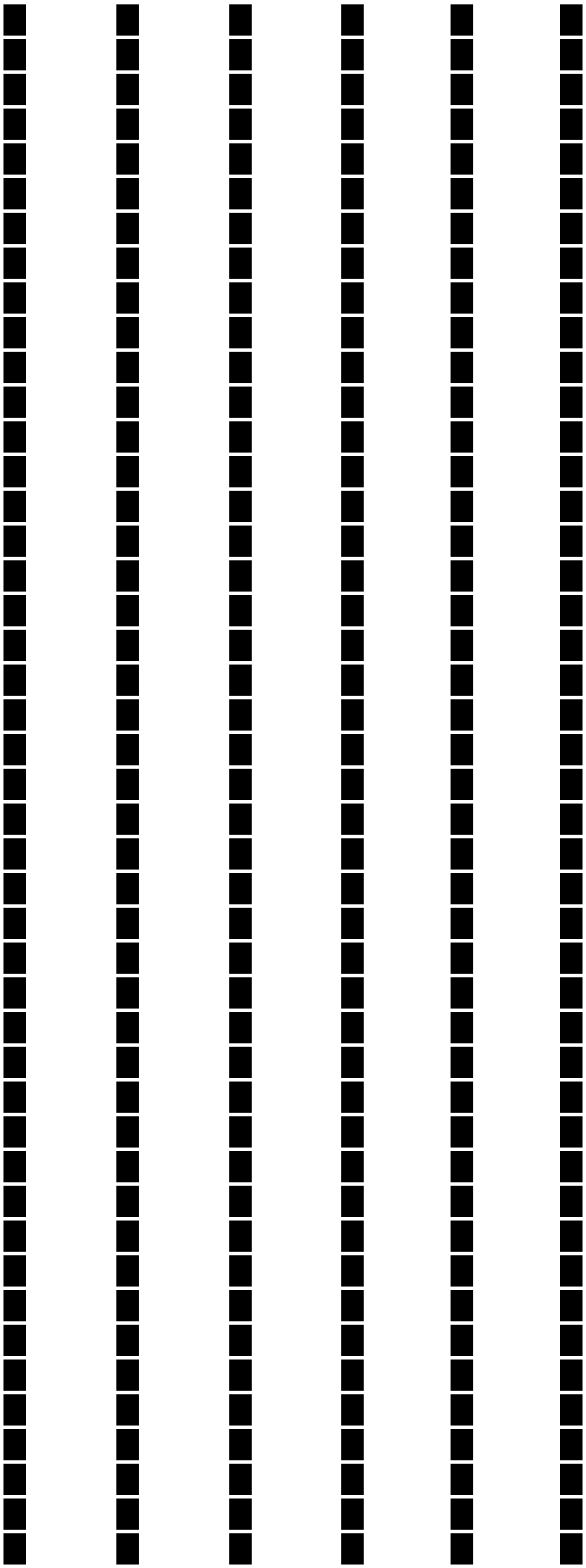


Table 8: Treatment discontinuation Kaplan-Meier analysis: enoxaparin/warfarin (DVT)

Days	Survival	Failure	Survival Standard Error	Number Failed	Number Left





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

In the apixaban model, the first 6 months risks were obtained from AMPLIFY and subsequently a constant risk of discontinuation was assumed based on AMPLIFY-EXT. Treatment discontinuation was modelled as a result of bleeding or that unrelated to bleeding. We therefore examined in the submission two extreme scenarios in the submission, setting the risks of other treatment discontinuation to 0 for all treatments and setting the risks of other treatment discontinuation to be equal between treatments.

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

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

We provide an additional scenario in the submission in the lifetime duration setting the risks of discontinuation to 0 beyond the first 18 months. The scenarios for the lifelong treatment suggest higher ICERs in comparison to

LMWH/VKA, LMWH/VKA followed by aspirin and placebo; however apixaban remains cost-effective below thresholds of £20,000 and £30,000 per QALY respectively. It should be noted that the latter scenario is also conservative as it is unlikely that discontinuation is zero beyond the first 18 months.

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

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