Rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome: A Single Technology Appraisal

Errata

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1 SUMMARY

1.1 Critique of the decision problem in the manufacturer's submission

The population considered within the manufacturer's submission (MS) is defined in accordance with the licensed indication as 'adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers' (i.e. ST segment elevation myocardial infarction [STEMI] and non-ST segment elevation myocardial infarction [NSTEMI]). The Evidence Review Group (ERG) notes that since completion of the ATLAS ACS 2-TIMI 51 trial in 2011 (the main evidence source), sensitivity of biomarker assays has increased. As a result, biomarker negative patients in the reported studies might now be biomarker positive using current more sensitive assays. In accordance with the scope the MS defines the intervention as rivaroxaban in combination with aspirin alone or with aspirin and a thienopyridine (clopidogrel). The MS considered clopidogrel with aspirin or aspirin alone for people for whom clopidogrel is considered unsuitable as the most relevant comparator, as reflected in the scope. Other dual antiplatelet regimens such as aspirin in combination with ticagrelor or prasugrel, which are recommended in NICE guidelines (Clinical Guideline 167 and 172 and Technology Appraisal Guidance 236 and 317) for the acute and maintenance phases of ACS, were absent from the scope. The outcome measures identified in the scope: death from any cause; non-fatal cardiovascular events; incidence of revascularisation procedures; adverse effects; and health related quality of life (HRQoL) were included. Additional relevant outcomes presented in the MS included rates of cardiovascular mortality and stent thrombosis. The results provided are presented in terms of cost per quality adjusted life years (QALY) with a lifetime horizon represented by a 40-year time horizon. Costs were considered from a NHS and Personal Social Services perspective.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The MS included a systematic review of the clinical effectiveness literature. The ATLAS ACS 2-TIMI 51 trial, which forms the basis of the submission, was a phase III, randomised, double blind, placebo controlled, event driven, multicentre (766 sites in 44 countries including the UK) study, which compared the efficacy and safety of oral rivaroxaban tablets (either 2.5 mg or 5 mg twice daily) with placebo in 15,526 adults with ACS (STEMI, NSTEMI and unstable angina). All patients received standard care (aspirin alone [stratum 1, n=1053] or aspirin and a thienopyridine [stratum 2, 14,473] either as clopidogrel [approx. 99%] or ticlopidine according to national or local guidelines). The higher dose of rivaroxaban (5 mg twice daily) was presented for completeness and is not part of the marketing authorisation (n=5176). The mean duration of treatment with the study drug was 13.1 months. All primary and secondary efficacy endpoint analyses were subject to a hierarchical testing strategy and were conducted according to a modified intention-to-treat (mITT) approach (the primary evaluation strategy) with sensitivity analyses using variations of the intention-to-treat analysis sets. A large number of patients discontinued from the study (15.5% (2402/15,526). Corresponding data for the licensed population were not provided by the manufacturer at the initial request. The manufacturer

offered to generate the data if the ERG confirmed they needed these data; however, given the timescales of the STA process, the ERG did not pursue these data. The main reasons for study discontinuation were withdrawal of consent and adverse events.

The ERG considered the hazard ratios (HR) of the efficacy results from the combined rivaroxaban dose to be more plausible than those of the individual doses as there is no clear biological mechanism that the 2.5 mg dose would be more efficacious than the 5 mg dose. This view was supported by US Food and Drug Administration briefing documents for the Cardiovascular and Renal Drugs Advisory Committee, which considered these findings to be likely spurious. Similarly, the European Medicines Agency assessment report concluded that these findings may partly have been due to chance. The manufacturer has also conceded that the two doses were likely to be 'more similar than they are different'. Hence, the combined efficacy results are presented in this summary.

As the main focus of this appraisal was based on the licensed indication, a post-hoc subgroup analysis of patients after an ACS with elevated cardiac biomarkers without prior stroke or transient ischaemic stroke i.e. the licensed population (all strata, n=12,353; 80% of total population) showed that treatment with rivaroxaban significantly reduced the primary composite efficacy endpoint of cardiovascular death, MI or stroke for the combined rivaroxaban group (2.5 mg and 5 mg twice daily) compared with the placebo group, with rates of 6.2% and 7.9%, respectively (HR 0.79, 95% confidence interval [CI]: 0.69 to 0.91, p=0.001). When the components of the primary efficacy endpoint were analysed individually, the combined rivaroxaban group (2.5 mg and 5 mg twice daily) significantly reduced the risk of death from cardiovascular causes (HR 0.72, 95% CI: 0.57 to 0.90, p=0.004) and MI (HR 0.81, 95% CI: 0.68 to 0.97, p=0.021) compared with placebo but increased (albeit non-significantly) the risk of stroke (HR 1.30, 95% CI: 0.85 to 2.01, p=0.225).

Results for secondary endpoint 1 (a composite efficacy endpoint of all-cause death, MI or stroke), mirrored those of the primary efficacy endpoint (HR 0.79, 95% CI: 0.69 to 0.91, p<0.001) as the majority of deaths [redacted] were cardiovascular in origin. [redacted]

Among patients who received at least one dose of a study drug, premature discontinuation of treatment occurred in 26.9% (1376/5115) of patients receiving the 2.5 mg dose of rivaroxaban, 29.4% (1504/5110) receiving the 5 mg dose of rivaroxaban and 26.4% (1351/5125) receiving placebo. No statistical comparisons were reported for these differences. As compared with placebo, rivaroxaban increased the rates of non-coronary artery bypass grafting (CABG) Thrombolysis in Myocardial

[redacted]

Whilst all study withdrawals were adequately described and all patients were accounted for (p70, MS), 15.5% (n=2402) of the total randomised population (n=15,526) prematurely discontinued from the study (2.5 mg twice daily, 15.0% [775/5174]; 5 mg twice daily, 16.3% [844/5176]; placebo, 15.1% [783/5176]). Corresponding data for the licensed population were not provided by the manufacturer at the initial request. The manufacturer offered to generate the data if the ERG confirmed they needed these data (manufacturer's response to clarification question A21); however, given the timescales of the STA process, the ERG did not pursue these data.

As noted by Krantz & Kaul,[35] rates of premature withdrawal in the ATLAS ACS 2-TIMI 51 trial were considerably higher than other similar randomised ACS trials: APPRAISE-2 (apixaban), 1.8% [131/7392][36]; TRACER (vorapaxar), 5.9% [761/12,944][37]; PLATO (ticagrelor), 3.0% [562/18,624][38] and TRITON (prasugrel), 5.9% [804/13,619].[39] Due to high discontinuation rates, the ERG consider the validity of the ATLAS ACS 2-TIMI 51 trial to be questionable.[40]

The main reason for premature discontinuation in the ATLAS ACS 2-TIMI 51 trial was 'consent withdrawn' (1294/15,526 [8.3%]; p70, MS). A greater percentage of the subjects who withdrew consent, were in the rivaroxaban treatment groups (889/10,350 [8.6%; p70, MS]) than in the placebo group (405/5176 [7.8%], p70, MS). At the end of the trial, vital status was unknown in 1117 patients of the 1294 patients who withdrew consent.[35] Following extensive efforts by the manufacturer to obtain vital status information on consent withdrawn patients (p102-103, MS and manufacturer's clarification response to question A21) the proportion of patients with unknown vital status was reduced to 495/15,526 patients (3.2%). [redacted] As noted by Krantz & Kaul,[35] missing vital status data in the ATLAS ACS 2-TIMI 51 trial was higher than other recent randomised ACS trials: TRACER, 1.9% [249/12,944][37]; PLATO, 0.01% [2/18,624][38] and TRITON, 0.12% [16/13,619][39]).

Due to the missing data, there is a potential risk that it may lead to informative censoring (i.e. patients who drop out [and are therefore censored] are more or less likely to experience the primary outcome of interest compared to those remaining in the study in a non-random manner), which may be compounded if the reasons for, or frequency of, dropout differs between treatment groups.[35] This issue was discussed in detail by the FDA,[32] albeit in the total population of the ATLAS ACS 2-TIMI 51 trial, rather than the licensed subgroup population being appraised here. In contrast, no detailed discussions were provided in the EMA assessment report.[2] Nevertheless, the ERG note that the FDA briefing document[32] states that 'informative censoring should be expected in the ATLAS ACS 2-TIMI 51 trial as rivaroxaban causes more bleeding, bleeding leads to dropouts, and ACS patients with

manufacturer's response to clarification question A11) using the ITT analysis set (which included all randomised subjects and endpoint events occurring at or after randomisation until the global treatment end date) and the ITT-total analysis set (which included all events from randomisation up to last contact for each subject were conducted as sensitivity efficacy analyses). [redacted]

4.2.4 Summary and critique of results

This section presents the results, as reported by the manufacturer, for the licensed population i.e. adult patients after an ACS with elevated cardiac biomarkers without prior stroke or TIA (all strata, n=12,353; 80% of total population) of the ATLAS ACS 2-TIMI 51 trial. As noted in the MS (p74), this population was identified as the group of patients who derived the most favourable benefit from the addition of rivaroxaban to existing antiplatelet therapy, at the lowest risk. All primary and secondary efficacy endpoint analyses were subject to a hierarchical testing strategy and were conducted according to the mITT principle (the primary evaluation strategy) with sensitivity analyses using the ITT and ITT-total analysis sets (further details and definitions are provided in section 4.2.1). In addition, 184 (1.2%) participants from three sites were excluded from the efficacy population (equally distributed between treatment groups) due to potential trial misconduct (p61, MS). The exclusion of these data was considered to be acceptable by the EMA.[2] Additional information, not reported in the MS, was provided by the manufacturer in their response to the clarification questions raised by the ERG. Where applicable, data have been re-tabulated by the ERG to provide further clarity. For completeness, results based on the total population of the ATLAS ACS 2-TIMI 51 trial are provided in Appendix 1 and Appendix 2, respectively.

Moreover, although all event rates were reported as Kaplan-Meier estimates through 24 months in the primary published paper,[31] the MS presents data as crude rates. As noted in the manufacturer's clarification response to question A17, this method shows the proportion of patients that have experienced the respective endpoint in the study, is easy to understand and no assumptions have to be made. However, the limitation of this method is that the timing of an event as well as the length of the observation is ignored. For completeness the manufacturer presented Kaplan-Meier estimates over time in steps of 30 days and as Kaplan-Meir plots for the total (primary and secondary endpoints) and licenced populations (primary endpoints only) by dose, strata and analysis type (mITT and ITT). Unfortunately, secondary endpoint data for the licensed population were not available but the manufacturer states that it is currently working in collaboration with Janssen to provide the full dataset. For further details see manufacturer's clarification response to question A17.

- Secondary efficacy endpoints

A summary of the secondary outcome results is presented in Table 7. In all strata, secondary endpoint 1, a composite efficacy endpoint of all-cause death, MI or stroke was significantly reduced by the combined rivaroxaban group compared with the placebo group, with rates of 6.3% and 8.1%, respectively (HR 0.79, 95% CI: 0.69 to 0.91, p<0.001). These findings were very similar to the primary efficacy endpoint (composite of CV death, MI or stroke) [redacted]. In the analysis of the two individual doses of rivaroxaban, each significantly reduced the composite of all-cause death, MI or stroke compared with placebo (2.5 mg twice daily: HR 0.80, 95% CI: 0.68 to 0.94, p=0.007; and 5 mg twice daily: HR 0.79, 95% CI: 0.67 to 0.93, p=0.004, respectively). [redacted] When the survival component of the secondary efficacy endpoint was analysed individually, rivaroxaban 2.5 mg twice daily significantly reduced the risk of death from all causes compared with placebo (HR 0.58, 95% CI: 0.44 to 0.77, p<0.001). In contrast, rivaroxaban 5 mg twice daily did not reduce the risk of death from all causes (HR 0.89, 95% CI: 0.69 to 1.14, p=0.353). A similar pattern was also observed for the total population (Appendix 2).

For secondary endpoint 2, the net clinical outcome (a composite of CV death, MI, IS or TIMI major bleeding not associated with CABG), neither the combined rivaroxaban group (p=0.110) nor the individual 2.5 mg twice daily (p=0.166) or the 5 mg twice daily group (p=0.184) significantly decreased the net clinical endpoint compared with the placebo group. As a result, the hierarchical testing for secondary endpoints 3 and 4 was stopped in all strata. [redacted]. Although results of the remaining composite secondary efficacy endpoints are presented in Table 7 significance cannot be claimed (p64, 86, MS).

- Other analyses

Stent thrombosis was evaluated as a pre-specified standalone efficacy endpoint (p57, MS) and the results are summarised in Table 7. [redacted]. The ERG note that the EMA assessment report[2] states that 'Regarding the analyses of the occurrence of stent thrombosis the comparisons between rivaroxaban and placebo were post-hoc… These analyses were no part of the hierarchical testing procedure and hence, nor the initially planned confirmatory strategy. Formally

this may be a false positive finding, and, strictly, no claims should be made as a part of the indication'.

In the MS (p98-100) a range of subgroup analyses were presented for the total population; however, no subgroup analyses based on the licensed population were undertaken by the manufacturer. The MS (p100) states that 'such analyses are not statistically sound as the trial was not powered to draw conclusions about (non-specified) subgroups of subgroups.' The ERG notes that whether the trial was powered for the licensed population was not stated. Nevertheless, following an ERG request (manufacturer's clarification response to question A20), the manufacturer provided subgroup analysis data for the following groups (as per the final scope issued by NICE)[8]: people with NSTEMI, people with STEMI, people with diabetes mellitus, people who received prior primary PCI; and people who did not receive prior primary PCI in the acute phase of management. Whilst caution is urged in interpreting these data, rivaroxaban treatment (combined and individual doses) was generally associated with improved outcomes on the primary efficacy endpoint for type of index event (STEMI, NSTEMI, UA or NSTEMI plus UA), PCI for index event and for people with diabetes. The manufacturer states that 'In general, the rivaroxaban treatment was consistently associated with improved outcomes on the primary efficacy endpoint across all major subgroups. A favourable HR for rivaroxaban compared with placebo was observed across the majority of subgroups, both for the combined rivaroxaban groups, as well as for the 2.5 mg b.i.d. and 5 mg b.i.d. doses individually compared with placebo. For the majority of analyses, interaction p values were >0.05.' For detailed results, see the manufacturer's clarification response to question A20. [redacted]

4.2.4.2 Safety and tolerability

This section presents the main safety evidence, as reported by the manufacturer, of the licensed population from all participants who received at least one dose of study drug within the ATLAS ACS 2-TIMI 51 trial (i.e. primary safety analysis population). Where applicable, data have been re-tabulated by the ERG to provide further clarity.

The MS (including the manufacturer's clarification response to question A21 and A23, which suggest that data are not currently available) did not report any data in relation to treatment compliance or premature discontinuation of study treatments for the licenced population. Available data from the published ATLAS ACS 2-TIMI 51 trial[31] (including data from the MS [p102] and the manufacturer's clarification response to question A23) suggest that compliance with study treatment was high for the total population. During treatment, the proportion of patients who were at least 85% compliant with the study drug was 93.9%, 94.0% and 94.6% for the rivaroxaban 2.5 mg dose, 5 mg dose and placebo respectively. However, compliance with aspirin and thienopyridines was not reported. As a result, it

is not known if patients stopped using these drugs or were poorly compliant with them. Among

[redacted] In the MS (p116-122), the reporting of treatment-emergent adverse events data was not well reported or transparent for the licensed (post-hoc analysis) and total population of the ATLAS ACS 2-TIMI 51 trial. A summary of the treatment-emergent adverse events (defined as those events starting on or after the first dose of study drug up to 2 days after the last dose of study medication) occurring in at least 1% of patients in any treatment group, as reported by the manufacturer, is reproduced (with minor changes) in Table 9.

[redacted]

5.1.3 What studies were included in the cost-effectiveness review and what were excluded? Where appropriate, provide a table of identified studies. Please identify the most important cost-effectiveness studies

The systematic review identified a total of 59 records, 46 of which were unique mathematical models. Of the 46 identified mathematical models, 8 were presented in conference abstract form. The manufacturer identified no studies which had evaluated the cost-effectiveness of rivaroxaban plus aspirin with or without clopidogrel compared to aspirin with or without clopidogrel for the secondary prevention of ACS.

5.1.4 What does the review conclude from the data available? Does the ERG agree with the conclusions of the cost-effectiveness review? If not, provide details

As no cost-effectiveness studies comparing rivaroxaban plus aspirin with or without clopidogrel to aspirin with or without clopidogrel in the secondary prevention of ACS were identified by the manufacturer, a *de novo* model was constructed.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

5.2.1 Objective of the model, intervention and comparator

Several errors and limitations were identified with the initial model. In response to the clarification questions, the manufacturer provided a version of the model with additional analyses/functionality, as follows:

- An option to age adjust the general population utilities (manufacturer's clarification response to question B22)
- An option to alter the treatment duration of rivaroxaban (manufacturer's clarification response to question B28)
- An option to estimate the transition probabilities using the ATLAS ACS 2-TIMI 51 trial data (manufacturer's clarification response to question B26)

Several errors which were not fixed include:

- Ignoring the published uncertainty in the PSA (manufacturer's clarification response to question B1)
- Inappropriately ignoring the correlation between model parameters (manufacturer's clarification response to question B3)

Further to these errors the manufacturer partially fixed time cycle in the first 96 weeks of the model in clarification question B4. In the manufacturer's response, the health state costs were appropriately adjusted; however, the life years gained matrix and the times used for discounting costs and QALYs was not.

The ERG will consider the model sent following the clarification process for most of this critique. The ERG did ask the manufacturer to change their approach to the probabilistic sensitivity analyses (PSA) in clarification questions B1, B2 and B3. In the manufacturer's response to these clarification questions, some additional PSAs were conducted. However, a full set of PSA results was not presented in the manufacturer's response to these questions. Therefore the ERG will focus on critiquing the original PSA.

The objective of the model was to estimate the costs incurred and QALYs accrued by two competing strategies: providing aspirin with or without clopidogrel (the comparator); or providing rivaroxaban plus aspirin with or without clopidogrel. For patients who could not take clopidogrel the model compared rivaroxaban with aspirin to aspirin alone.

It was assumed that patients aspirin treatment would continue indefinitely, their clopidogrel treatment would continue for one year and their rivaroxaban treatment would continue for between one and two years. The summary of product characteristics[17] states that 'among patients receiving dual anti-platelet therapy 98.8% received clopidogrel, 0.9% received ticlopidine and 0.3% received prasugrel' (the primary published paper[31] and the MS [p45-48] suggest that thienopyridine use was limited to clopidogrel or ticlopidine) with a mean treatment duration of 13.3 months.[31] The MS (p132) notes that prasugrel and ticagrelor were not approved or part of standard care protocols at the time the ATLAS ACS 2-TIMI 51 trial was initiated; however, the ERGs clinical advisors believe that ticlopidine is not standard practice in the UK and is excluded from the scope of this appraisal.

5.2.2 The population modelled

The population modelled was the patient subgroup from the ATLAS ACS 2-TIMI 51 trial who were biomarker positive and had not experienced a previous stroke/TIA. The data in the rivaroxaban model arm was not pooled from both rivaroxaban trial arms. As such, the population for rivaroxaban is limited to those patients who received 2.5 mg rivaroxaban twice daily. Therefore all issues with the generalisability of the population identified in section 4.6.3 apply to the mathematical model results.

5.2.3 The model structure

The manufacturer submitted a state transition cohort model written in Microsoft Excel (Microsoft Corporation, Redmond, Washington). The model used a time horizon of 40-years that was divided into two periods: an observation period which was intended to replicate the duration of the trial data and an extrapolation period. The extrapolation period started after 96 weeks and had a cycle length of 6 months. In the observation period the initial two cycles had a cycle length of 4 and 8 weeks

5.2.4 The health states within the model

The model consisted of a number of health states corresponding to whether no further ACS event occurred or whether the patient suffered an ACS event. The ACS events considered in the model were: MI, IS, haemorrhagic stroke or intracranial haemorrhage (HS/ICH); a bleeding event measured on the TIMI scale; and revascularisation. These ACS events fell into two broad categories: those with longer term implications for the relative risks of developing further conditions, utility and costs; and those deemed to be transient events where the impacts were limited to one model cycle.

Patients could die at any time in the model and there were multiple causes of death simulated in the model. Patients could die from an MI, IS or HS/ICH or other CV death, which included deaths relating to bleeding. Patients could also die from non-CV causes, at any time point in the model.

The long term ACS events included the MI, IS and HS/ICH conditions. The long term ACS events had two subsequent tunnel states to allow for the patients utility to improve over time, and for the cost of treatment of the event and the relative risk of suffering from a subsequent event to fall over time. Patients could suffer from up to three ACS events; the specific types of ACS event were recorded when patients suffered from two or fewer events. When three events occur, it is assumed that one event of each type (i.e. an MI, an IS and a HS/ICH) has occurred to the patients in this health state.

The submitted model structure leads to the potential for systematic errors to occur, as the time between multiple events is not tracked. This causes the potential for systematic errors in three ways; firstly, the patients who suffer from two events in one time cycle are not distinguished from those patients who suffer multiple events in separate time cycles. Secondly, for the patients who suffer from multiple events in separate time cycles any improvement over time that they may have experienced becomes irrelevant. Finally, for those patients who transition into the multiple event states from the single event states, the first event is not tracked. The exact errors relating to the structure will be addressed in sections 5.2.6.2 and 5.2.7.1. There are two solutions to this problem; firstly, a more complicated state transition cohort model could be developed so that cost and utilities for each multiple event state can vary by the preceding health state and the time between the events. Secondly, a patient level simulation approach could be taken.

The health states corresponding to the bleeding and revascularisations were assumed to be transient health states, when a patient enters these states a one off cost and utility decrement was applied. These transient health states were applied to only the patients in the observation period of the model, implicitly assuming that the bleeding and revascularisation rates for the two interventions are

Table 15: Annual age specific increased risk estimated for ACS events obtained from literature and predicted by the model (p210, Table 46, MS)

Event	% Increase with age from literature	% Increase with age predicted by the model	Literature source
MI	1.075	1.074	Smolina et al 2012[50]
IS	1.093	1.093	Hippisley-Cox et al 2004[48]
HS/ICH	1.093	1.094	Assumption based on Hippisley-Cox et al 2004[48]
OCD	1.103	1.087	Smolina et al 2012[50]
NCD	1.097	1.089	ONS 2012[49]
Case fatality MI	1.045	1.046	Smolina et al 2012[50]
Case fatality IS	1.056	1.048	Factor of 1.67 based on relative difference in fatal and non-fatal MI presented in Smolina et al 2012[50]
Case fatality HS/ICH	1.056	1.048	Assumption based on case fatality IS

MI, myocardial infarction; IS, ischaemic stroke; HS/ICH, haemorrhagic stroke or intracranial haemorrhage; OCD, other cardiovascular death; NCD, non-cardiovascular death

The ERG is uncertain as to how the '% increase with age' predicted by the model in Table 15 is calculated, as these figures appear to contradict the growth rates used in the model which are presented in Table 14.

The conversion of the trial event rates from 12 weeks to 26 weeks was conducted appropriately.

The formulae used to extrapolate the transition probabilities over time are given in Appendix 14 of the MS (p449 – 451). An error was identified in the growth rate of surviving and dying from an ACS event given that one occurred, in the manufacturer's response to clarification question B26 it was established that the correct formulae should apply $(1+r_{change})^t$ instead of $1/(1+r_{change})^t$. In the model these formulae were correctly applied.

For example the probability that a MI is fatal should read:

$$P_{MI}^{D}(t) = Exp\left(Ln\left(1 - \frac{\lambda_{MI}^{S}}{\lambda_{MI}^{S} + \lambda_{MI}^{D}}\right) * \left(1 + r_{MI}^{change}\right)^{t}\right) * P_{MI}(t)$$

And the probability that a MI is non-fatal should read:

$$P_{MI}^{S}(t) = 1 - [Exp\left(Ln\left(1 - \frac{\lambda_{MI}^{S}}{\lambda_{MI}^{S} + \lambda_{MI}^{D}}\right) * \left(1 + r_{MI}^{change}\right)^{t}\right) * P_{MI}(t)]$$

The ERG could not verify all of the 19,968 transition probabilities were correctly specified due to time constraints. However these formulae were generally appropriate.

how the patients who continue rivaroxaban treatment after one year are selected from the rest of the patient population. It is unknown whether the data presented in Table 18 would be applicable to the UK population if rivaroxaban were to be recommended by NICE.

Table 18: Base case parameters for the change in efficacy and costs to represent patient discontinuation in the second year of treatment. Table adapted from that on p199, Table 38, MS

	ATLAS 2 treatment continuation (2.5 mg bd, combined strata) [1-discontinuation rate]	Assumed proportion of patients who continue in the trial that would continue treatment in a real-world setting	Model treatment continuation rate
0-4 weeks	1-6.90%=93.10%	100 %	93.10%
4-12 weeks	1-10.46%=89.54%	100 %	89.54%
12-24 weeks	1-13.06%=86.94%	100 %	86.94%
24-36 weeks	1-17.77%= 82.23%	100 %	82.23%
36-48 weeks	1-21.55%=78.45%	100 %	78.45%
48-60 weeks	1-23.94%= 76.06%	25 %	19.02%
60-72 weeks	1-26.51%= 73.49%	18 %	13.23%
72-84 weeks	1-27.94%= 72.06%	12 %	8.65%
84-96 weeks	1-29.73%= 71.27%	6%	4.28%

bd, bis die (twice daily)

The change in efficacy and costs reflect the proportion of the costs and efficacy that are assumed to remain in the rivaroxaban arm, for those patients who have continued rivaroxaban treatment. No treatment effect or cost associated with rivaroxaban was assumed from the point of discontinuation. Patients still incurred the cost and transitions associated with aspirin for the remainder of the model, and incurred costs and benefits associated with rivaroxaban up until the point of discontinuation.

For example, in the 48-60 week of the ATLAS ACS 2-TIMI 51, 23.94% of patients had discontinued rivaroxaban treatment. For these patients the efficacy of rivaroxaban is zero and no costs are applied. The remaining 76.06% of patients continued rivaroxaban treatment in the 48-60 week period. However, the manufacturer does not believe that this many patients will continue rivaroxaban outside of a trial setting. It was assumed that the proportion continuing rivaroxaban would be only 25% of the trial value in a real-world setting. In the manufacturer's response to clarification question B7 they stated that the adjustment to the proportion of patients continuing on rivaroxaban was made on the basis of discussion with key opinion leaders. No further details were provided.

Table 26: Summary of quality of life values for cost-effectiveness analysis used in the manufacturer's base case (Greenhalgh *et al.*[53] and p269, Table 57, MS)

State	Utility Value	Standard Error	Reference in submission
No event	0.842	0.002	PLATO HECON sub-study (AstraZeneca STA submission[55], Section 6.4.3)
Non-fatal MI	0.779	0.010	As above
Post MI*	0.821	0.038	As above + Lacey[56]
Non-fatal stroke	0.703	0.010	As above
Post stroke**	0.703	0.038	As above + assumption
Dead	0.000	N/A	N/A

The meaning of the symbols * and ** was not provided in Greenhalgh *et al.*[53]

5.2.7.2 Utilities associated with the transient health states

The utilities associated with the transient states are given in Table 27. In the manufacturer's base case the utility values from the literature are used. To calculate the quality of life decrement associated with bleeding the utility value associated with the transient event state was subtracted from the no event health state and was then multiplied by the proportion of days in a 12 week period a patient would spend in the transient health state.

Table 27: The utilities of the transient states (p268, Table 56 and p273, Table 57, MS)

Health State / Event	**Value from the trial**	**Values from the literature (which were used in the model).**	**Assumed length of utility decrement (days) (p275, Table 58, MS)**	**Literature reference**
Major bleed	0.77	0.75	30	Crespin *et al.* 2011[57]
Minor bleed	0.84	0.80	2	Kazi *et al.* 2014[58]
Bleeding requiring medical attention	0.87	0.80	2	Sullivan *et al.* 2006[59]
PTCA / PCI	N/A	0.792	30	Latour-Perez 2008[60]
CABG	N/A	0.742	84	Latour-Perez 2008[60]

PTCA/PCI, Percutaneous transluminal coronary angioplasty/ Percutaneous coronary intervention; CABG, coronary artery bypass graft

Table 32: The results of the scenario analyses presented in the MS (p341, Table 80, MS)

Parameters tested	Rivaroxaban		"standard of care"		Incremental		ICER
	Costs	QALYs	Costs	QALYs	Costs	QALYs	
Manufacturer's base case							
None	£14,767.63	9.56	£14,004.05	9.44	£763.58	0.12	£6,202.84
Strata and transition probabilities (proportional hazards)							
Stratum 2	£15,362.74	9.52	£14,479.67	9.40	£883.07	0.12	£7,404.53
Transition probabilities							
Non-parametric	£16,290.40	9.75	£15,431.41	9.62	£858.99	0.13	£6,468.00
Clopidogrel efficacy							
Clopidogrel RRR=1	£13,794.17	10.09	£13,044.73	9.96	£749.44	0.13	£5,824.01
Utilities							
Utility values from trial	£14,767.63	9.83	£14,004.06	9.71	£763.58	0.13	£5,935.11
Utility values return to the baseline utility value in the post event cycles	£14,767.63	9.61	£14,004.05	9.49	£763.58	0.12	£6,195.36
Utility values applied to fatal events	£14,767.63	13.39	£14,004.05	13.28	£763.58	0.10	£7,147.39
Cost of events							
Cost of death = £0.00	£13,522.08	9.56	£12,707.38	9.44	£814.70	0.12	£6,618.13
Increased risk of events due to age and subsequent events							
RR = 1 for all subsequent events following a MI, IS or HS	£15,960.00	9.81	£15,169.14	9.68	£790.86	0.12	£6,439.04
Increased risk due to age = 0	£31,093.77	14.09	£30,194.98	13.91	£898.79	0.18	£4,927.81
RR = 1 and increased risk due to age = 0	£29,633.17	14.34	£28,704.75	14.16	£928.42	0.18	£6,745.04

The additional scenario analyses presented in Table 33 were conducted in the manufacturer's response to the clarification questions B4, B22, B25 and B28. The first set of additional scenario analyses involved adapting the model to have age adjusted utilities.

To age adjust all utilities in the model, the manufacturer used the formulae presented in Table 33 to age adjust the event free utility. To age adjust the ACS event health states, the manufacturer calculated the relative difference between the utility of each ACS event and the event free health state

Table 37: The relative risk of a subsequent event applied by the ERG in the exploratory analysis

Relative risks for subsequent events	**After MI**		
	1st 6 months	2nd 6 months	Post 12 months (later)
MI	4.9	2.1	1.5
IS	3.2	1.8	1.5
HS/ICH	1.0	1.0	1.0
Fatal MI	4.9	2.1	1.5
Fatal IS	3.2	1.8	1.5
Fatal HS/ICH	1.0	1.0	1.0
OCD	3.0	1.6	1.5
Relative risks for subsequent events	**After IS**		
	1st 6 months	2nd 6 months	Post 12 months (later)
MI	4.9	2.1	1.5
IS	3.2	1.8	1.5
HS/ICH	1.0	1.0	1.0
Fatal MI	4.9	2.1	1.5
Fatal IS	3.2	1.8	1.5
Fatal HS/ICH	1.0	1.0	1.0
OCD	3.0	1.6	1.5
Relative risks for subsequent events	**After HS**		
	1st 6 months	2nd 6 months	Post 12 months (later)
MI	1.0	1.0	1.0
IS	1.0	1.0	1.0
HS/ICH	4.9	2.1	1.5
Fatal MI	1.0	1.0	1.0
Fatal IS	1.0	1.0	1.0
Fatal HS/ICH	4.9	2.1	1.5
OCD	1.0	1.0	1.0
Relative risks for subsequent events	**3 events**		
	1st 6 months	2nd 6 months	Post 12 months (later)
MI			
IS	1.5	1.5	1.5
HS/ICH			
Fatal MI	1.5	1.5	1.5
Fatal IS	1.5	1.5	1.5
Fatal HS/ICH	1.5	1.5	1.5
OCD	1.5	1.5	1.5

MI, myocardial infarction; IS, ischaemic stroke; HS/ICH, haemorrhagic stroke or intracranial haemorrhage; OCD, other cardiovascular death; NCD, non cardiovascular death

These analyses will be conducted individually, and then an analysis will be conducted with all of the changes made simultaneously. Table 38 presents the ERGs results for scenarios 5 - 10 individually and for when scenarios 1 to 7 are applied simultaneously. The manufacturer had already conducted scenarios 1 to 4, for clarity the results for these scenarios will also be presented in Table 38 even though they are presented elsewhere in the report.