NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome

This premeeting briefing presents:

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

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

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

Key issues for consideration

- The comparators listed in the final scope issued by NICE were: clopidogrel with aspirin or aspirin alone for people for whom clopidogrel is considered unsuitable. The ERG noted that other dual antiplatelet regimens such as aspirin in combination with ticagrelor or prasugrel are increasingly being used as treatment options in the acute and maintenance phases of acute coronary syndrome (ACS) in England and that these regimens are recommended by NICE. Should ticagrelor in combination with aspirin and prasugrel in combination with aspirin be considered as comparators for this appraisal?

- The ERG questioned the generalisibity of the results from ATLAS-ACS 2 TIMI 51 to the population seen in clinical practice in England.

    - The ERG noted that the mean age of all patients randomised to ATLAS-ACS 2 TIMI 51 was 61.8 years. The ERG commented that patients with ACS in England are usually older with a mean age of 65 years and 72 years for ST segment elevation myocardial infarction (STEMI) and non ST segment elevation myocardial infarction (NSTEMI) respectively.
    - The company stated that that the baseline patient characteristics of those enrolled into ATLAS-ACS 2 TIMI 51 were representative of a moderate-to-high risk population of patients with ACS. The ERG highlighted that the European Medicines Agency's (EMA) assessment report noted that patients in the trial were considered to be at low risk. Patients in the trial had little co-morbidity, lower than usual use of percutaneous coronary intervention (PCI), included a relatively small proportion of people aged over 75 years, or who had impaired renal impairment.
    - The ERG highlighted that the sensitivity of biomarker assays has increased since ATLAS-ACS 2 TIMI 51 was conducted, and therefore the use of more sensitive assays in the trial might have led to the reclassification of patients with unstable angina (UA) and therefore included in the licensed population.

Are the results from ATLAS-ACS 2 TIMI 51 generalisable to the population seen in clinical practice in England?

- The mean treatment duration with rivaroxaban in ATLAS-ACS 2 TIMI 51 was 13.1 months. As a result the efficacy and safety of rivaroxaban 2.5 mg twice daily beyond this time is limited. This is reflected in the summary of product characteristics, which recommends that extension of treatment beyond 12 months should be done on an individual patient basis because experience up to 24 months is limited. What is the duration of maintenance treatment for ACS in clinical practice in England?

- The company presented efficacy results from the individual doses of rivaroxaban (that is 2.5 mg twice daily and 5 mg twice daily) and from the combined rivaroxaban dose. The company focussed its submission (including the cost effectiveness analysis) on the efficacy results from the 2.5 mg rivaroxaban twice daily dose. The ERG considered the efficacy results from the combined rivaroxaban dose to be more plausible than those of the individual doses as there was no clear biological mechanism to explain why the 2.5 mg dose would be more efficacious than the 5 mg dose. Which dose of rivaroxaban (2.5 mg dose or combined dose) provides the most plausible efficacy data for decision making?

- The ERG questioned the validity of the results from ATLAS-ACS 2 TIMI 51 as a result of the high discontinuation rates. The ERG noted that 15.5% of the total randomised population (n=15,526) prematurely discontinued from the trial. The ERG highlighted that the rates of premature withdrawal in the trial were higher than other similar randomised trials in patients with ACS. Are the discontinuation rates in ATLAS-ACS 2 TIMI 51 similar to other studies carried out in a population of patients with ACS and of similar trial duration?

- The ERG commented that as a result of the missing data from those patients who discontinued from the trial (proportion of patients with unknown vital statistics 3.2% [495/15,526]), there was a potential risk that it may lead to informative censoring. The ERG highlighted that the EMA's assessment report did not discuss this issue in detail. The ERG also commented that the likely magnitude of any bias introduced by informative censoring on the clinical outcomes or in the cost effectiveness analysis were unknown. Is the proportion of patients with unknown vital statistics sufficiently large to cause concern?

- The licensed population (people with ACS with elevated cardiac biomarkers and who have not previously had a stroke or transient ischaemic attack [TIA]) was based on a post hoc subgroup analysis of ATLAS-ACS 2 TIMI 51 (80% of the total trial population). The EMA recognised the validity of this analysis. Is this analysis sufficiently robust to make a decision on the clinical-effectiveness of rivaroxaban?

- The ERG raised a number of concerns regarding the company's economic model.

- The ERG commented that all issues regarding the generalisability of the population in ATLAS-ACS 2 TIMI 51 to clinical practice in England and informative censoring applied to the economic model results.
- The ERG commented that the model could not appropriately track the event of patients with multiple events which could cause inaccuracy in the cost effectiveness results presented.
- The ERG stated that the approach used by the company to calculate the transition probabilities for the transient health states was inappropriate as cost and QALYs of the events which occurred in the second year were not appropriately discounted.
- The ERG stated that it was not clear as to how the patients who continued rivaroxaban treatment after 1 year were selected from the rest of the patient population.
- The ERG had concerns with the methodology used to calculate the utility values for patients with a stroke.
- The ERG considered the model submitted by the company to be relatively inflexible which meant that the ERG could not conduct all the exploratory analyses which it deemed potentially relevant to the decision problem. The ERG commented that there were a number of key parameters that could not be adjusted within the model that may have changed the incremental cost effectiveness ratio (ICER) to a greater extent. These included: amendments to the hazard ratio for fatal bleeds; using pooled efficacy data rather than the 2.5 mg rivaroxaban twice daily dose alone; and adjusting for the possibility of informative bias.

Given the ERG's concerns about the company's economic model, how robust are the ICERs presented?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of rivaroxaban within its

licensed indication for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome.

Table 1: Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	People with ACS with elevated cardiac biomarkers (STEMI and NSTEMI)	Adult patients after an ACS with elevated cardiac biomarkers	Essentially the same but wording as per the summary of product characteristics	The terminology 'elevated cardiac biomarkers' is less sensitive than if a patient exhibits a rise or fall in their cardiac markers (preferably troponins) as many patients have persistently raised markers outside the context of ACS and in clinical practice, the diagnosis of NSTEMI requires evidence of myocardial ischaemia combined with a rise or fall in the blood level of a cardiac biomarker (troponin)
Int.	Rivaroxaban (in combination with aspirin or with aspirin and a thienopyridine [clopidogrel])	Same as NICE scope	-	-
Com.	• clopidogrel with aspirin • aspirin alone for people for whom clopidogrel is considered unsuitable	Same as NICE scope	-	The ERG agreed that the comparators were appropriate. The ERG noted that other dual antiplatelet regimens such as aspirin in combination with

				ticagrelor or prasugrel are increasingly being used as treatment options in the acute and maintenance phases of ACS in the UK. In addition these regimens are recommended by NICE and the European Society of Cardiology. However, these treatment options were absent in the final scope issued by NICE.
Out.	• death from any cause • non-fatal cardiovascular events • incidence of revascularisation procedures • adverse effects of treatment (including bleeding events) • health-related quality of life.	• death from any cause • non-fatal cardiovascular events • incidence of revascularisation procedures • adverse effects of treatment (including bleeding events) • health-related quality of life subject to availability of data • cardiovascular mortality • stent thrombosis	Cardiovascular mortality and stent thrombosis are considered to be important outcomes in acute coronary syndrome	The ERG considered the additional outcomes (cardiovascular mortality and stent thrombosis) included by the company to be appropriate and clinically meaningful

2 The technology and the treatment pathway

2.1 The term ACS is used to refer to a group of conditions including STEMI, NSTEM and UA, arising from thrombus formation on an atheromatous

plaque (fat accumulation within heart vessel). The presence of ST segment elevation on an electrocardiogram usually indicates total occlusion of the affected artery, resulting in necrosis of the tissue supplied by that artery (acute myocardial infarction [MI]). ACS without STEMI is classified as either UA or NSTEMI. NSTEMI differs from UA primarily in the severity of myocardial ischaemia. In NSTEMI, the ischaemia is severe enough to result in the release of biochemical markers of myocardial injury into the blood.

2.2 Immediate treatment for these conditions aims to prevent progression to total occlusion of the artery and, for people at high risk of myocardial infarction, may include coronary revascularisation, either by means of PCI or coronary artery bypass graft (CABG). Long term management of ACS includes the use of aspirin and another antiplatelet agent (clopidogrel, prasugrel or ticagrelor). NICE has produced guidance on the use of aspirin, clopidogrel, prasugrel and ticagrelor for treating people with ACS. A summary of the NICE related recommendations is provided in table 2 and a diagram of the current treatment pathway in figure 1.

2.3 Rivaroxaban has a marketing authorisation in the UK in combination with antiplatelet therapy (that is, aspirin alone or aspirin plus a thienopyridine, usually clopidogrel). The company stated that rivaroxaban is complementary to currently available antiplatelets as it targets the dual pathway to thrombus formation. Rivaroxaban should be started as soon as possible after stabilisation of the ACS event (including revascularisation procedures); at the earliest 24 hours after admission to hospital and at the time when parenteral anticoagulation therapy would normally be discontinued.

Table 2: Summary of NICE guidance

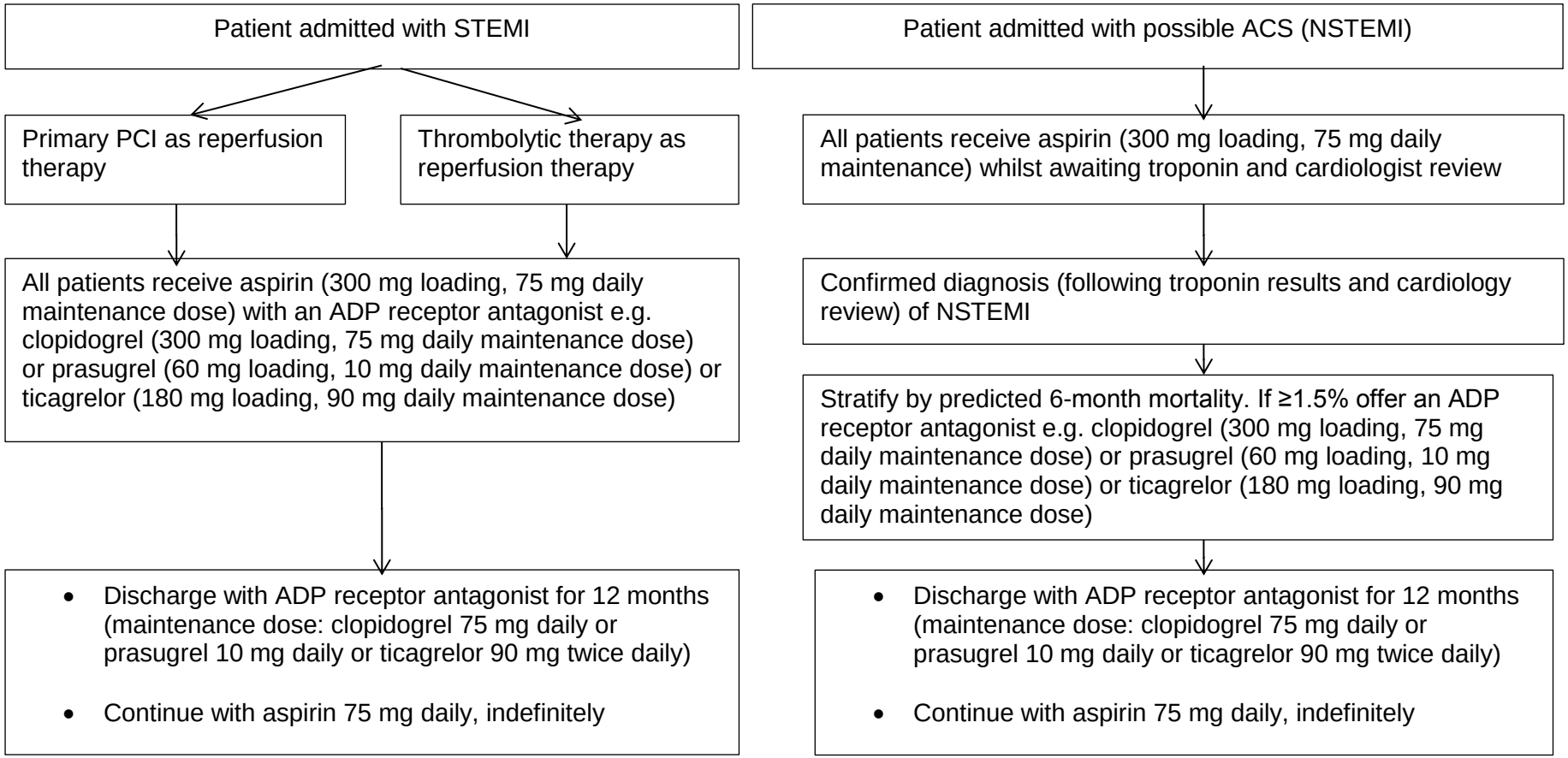
Guidance	Date	Drugs	Recommendation
NICE Technology Appraisals			
Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (review of technology appraisal guidance 182) Technology appraisal No. 317	2014	Prasugrel plus aspirin	Prasugrel 10 mg in combination with aspirin is recommended as an option within its marketing authorisation, that is, for preventing atherothrombotic events in adults with ACS (UA/NSTEMI or STEMI) having primary or delayed PCI.
Ticagrelor for the treatment of acute coronary syndromes[a] Technology appraisal No. 236	2011	Ticagrelor plus aspirin	Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults with ACS that is, people with: • STEMI – defined as ST elevation or new left bundle branch block on electrocardiogram – that cardiologists intend to treat with primary PCI or • NSTEMI or • Admitted to hospital with UA. Before ticagrelor is continued beyond the initial treatment, the diagnosis of UA should first be confirmed, ideally by a cardiologist.
NICE Clinical Guidelines			

Secondary prevention in primary and secondary care for patients following a myocardial infarction
 	
Clinical guideline No. 172
 	
(Clinical Guideline No. 172 is an update of Clinical Guideline No. 48)
	2013	Clopidogrel or ticagrelor plus aspirin	This guideline recommends:
			• Aspirin should be offered to all people after an MI and continue it indefinitely, unless they are aspirin intolerant or have an indication for anticoagulation.
			• For patients with aspirin hypersensitivity, clopidogrel monotherapy should be considered as an alternative treatment.
			• Clopidogrel should be considered as a treatment option for up to 12 months for:
			  ○ People who have had an NSTEMI, regardless of treatment
			  ○ People who have had a STEMI and received a bare-metal or drug-eluting stent.
			• Ticagrelor is also recommended as per Technology Appraisal No. 236 noted

			above • There are special recommendations for antiplatelet therapy in people with an indication for anticoagulation.
Myocardial infarction with ST-segment elevation: The acute management of myocardial infarction with ST-segment elevation Clinical guideline No. 167	2013	Ticagrelor plus aspirin	Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in people with STEMI – defined as ST elevation or new left bundle branch block on electrocardiogram – that cardiologists intend to treat with primary PCI. This recommendation is adapted from NICE Technology Appraisal No. 236.
Unstable angina and NSTEMI: The early management of unstable angina and non-ST-segment-elevation myocardial Clinical guideline No. 94	2010	Clopidogrel plus aspirin	This guideline recommends: • As soon as the risk of adverse cardiovascular events has been assessed, offer a loading dose of 300 mg clopidogrel in addition to aspirin to patients with a predicted 6-month mortality risk of more than 1.5% and no contraindications (for example, an excessive bleeding risk). • Offer a 300 mg loading dose of clopidogrel to all patients with no contraindications who may undergo PCI within 24 hours of admission to hospital. • Treatment with clopidogrel in combination with low-dose aspirin should be continued for 12 months after the most recent acute episode of NSTEMI. Thereafter, standard care, including treatment with low-dose aspirin alone, is recommended.
ACS, acute coronary syndrome; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction; UA, unstable angina			

[a] NICE technology appraisal No. 236 (ticagrelor) notes that current practice in the UK involves a loading dose for clopidogrel of 600 mg (unlicensed dose)
Source: ERG report (table 1, page 16)

Figure 1 Treatment pathway



Source: ERG report (Figure 2. page 18)

Table 3: Technology

	Rivaroxaban	Clopidogrel	Aspirin
Marketing authorisation	Co administered with acetylsalylic acid (ASA) alone or with ASA plus clopidogel or ticlopidine, for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome with elevated cardiac biomarkers	Adult patients suffering from acute coronary syndrome: • Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA). • ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy	For the secondary prevention of thrombotic cerebrovascular or cardiovascular disease and following by-pass surgery
Administration	Oral	Oral	Oral
Setting	Primary care	Primary care	Primary care
Acquisition cost	£2.10 per day	0.06 per day	0.03 per day
Dose frequency	Twice daily	Once daily	Once daily
Total acquisition cost	Dependent on duration of therapy. Extension beyond 12 months should done on an individual patient basis as experience up to 24 months is limited	The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months	Indefinitely but treatment should be reviewed at regular intervals.
See Summary of Product Characteristics for details on adverse reactions and contraindications.			

3 Comments from consultees

3.1 The patient organisation stated that the side effect profile of rivaroxaban is similar to all other anti-coagulants or antiplatelet therapies. It also stated that rivaroxaban will offer improvements in patient quality of life compared

with warfarin, as it does not require constant measuring of international normalised ratio (INR), which involves regular clinic appointments.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The main evidence in the company's submission came from ATLAS-ACS 2 TIMI 51, which was an international, multi-centre (766 sites in 44 countries including the UK), randomised controlled trial (RCT) comparing rivaroxaban (either 2.5 mg or 5 mg twice daily) with placebo in patients with recent ACS (STEMI, NSTEMI or UA).

4.2 The trial consisted of 3 phases, including a 6-day screening phase, a double blind treatment phase and follow-up phase. Patients were enrolled into the study within 7 days of being admitted to hospital for ACS. After stabilisation of the ACS (and with completion of any initial management strategies such as revascularisation) patients were randomised to receive rivaroxaban 2.5 mg (n=5174), rivaroxaban 5 mg (n=5176) or placebo (n=5176) taken twice daily. Randomisation was stratified according to planned use of a thienopyridine (Stratum 1: aspirin only [n=1053]; Stratum 2: aspirin plus thienopyradine [n=14,473]). Enrolment was neither capped nor fixed and was dependent on regional medical practice. Thienopyridine treatment was clopidogrel or ticlopidine and dosage followed national or local prescribing information. For clopidogrel, the daily maintenance dose was not to exceed 75 mg per day, and for ticlopidine, the daily maintenance dose was not to exceed 250 mg twice daily. Approximately 99% of the patients in stratum 2 received clopidogrel. The length of treatment was not fixed because the trial was event-driven (that is, the time required to obtain at least 983 primary efficacy endpoint events across both strata and at least 728 primary efficacy events in stratum 2). The mean duration of treatment with the study drug was 13.1 months.

4.3 The company considered the baseline patient characteristics to be generally similar between the treatment groups. The mean age of the trial population was 61.8 years (range 22 to 98 years) of which 9.0% were aged over 75 years and 74.7% were men. In the trial population, the index ACS event was 50% STEMI, 25.6% NSTEMI and 23.6% UA. The company stated that that baseline patient characteristics were representative of a moderate-to-high risk population of patients with ACS with the majority of all patients randomised having cardiovascular (CV) risk factors, such as hypertension (67.4%), diabetes (32.0%), history of myocardial infarction (MI, [26.9%]) or hypercholesterolaemia (48.6%). There were 60.5% of patients who had a revascularisation procedure for the index event; the vast majority of these being PCI [redacted].There were 7.1% of patients who had impaired renal function with creatinine clearance less than 50 ml/min. See Table 10, page 51 of the company's submission for further details.

4.4 As one of the listed contraindications in the summary of product characteristics includes those patients with a history of stroke or TIA, the company also presented the baseline characteristics of patients in ATLAS-ACS 2 TIMI 51, excluding those with a history of stroke or TIA and who had elevated biomarkers (that is the licensed population). The company stated

[redacted]

[redacted] See Table 11, page 53 of the company's submission for further details.

4.5 The company also provided supportive evidence from the ATLAS-ACS TIMI 46 trial which compared rivaroxaban once-daily dosing with twice-daily dosing within the same total daily dose range (5-20 mg). This study was a safety and efficacy study to determine the most favourable dose and dosing regimen of rivaroxaban for ATLAS-ACS 2 TIMI 51.

ERG comments

4.6 The ERG stated that the company undertook a comprehensive systematic review of rivaroxaban for the prevention of adverse outcomes in patients after the acute management of ACS. The ERG considered ATLAS-ACS 2 TIMI 51 to be a well designed, multicentre RCT of reasonable quality.

4.7 The ERG noted that the company had stated [redacted]

4.8 The ERG questioned the generalisibity of the population enrolled in ATLAS-ACS 2 TIMI 51 study to the population seen in clinical practice in England. The ERG noted that of all patients randomised in ATLAS-ACS 2 TIM 51, 74% were men, and the mean age was 61.8 years ([redacted]). The ERG commented that patients with ACS in England are usually older with a mean age of 65 years and 72 years for patients with STEMI and NSTEMI respectively. It highlighted that the EMA's assessment report noted that patients in the trial were considered to be at low risk. Patients in the trial had little co-morbidity, lower than usual use of PCI and included a relatively small proportion of people aged over 75 years or who had impaired renal impairment with creatinine clearance less than 50 ml/min. As a result, the

findings from ATLAS-ACS 2 TIMI 51 may not be applicable to an older population or those with a greater incidence of renal impairment and a higher baseline bleeding risk.

4.9 The ERG commented that mean treatment duration with rivaroxaban in ATLAS-ACS 2 TIMI 51 was 13.1 months. As a result the efficacy and safety of rivaroxaban 2.5 mg twice daily beyond this time is limited. The ERG noted that this is reflected in the summary of product characteristics, which recommends that extension of treatment beyond 12 months should be done on an individual patient basis because experience up to 24 months is limited.

4.10 The ERG stated that the terminology ‘elevated cardiac biomarker’ is less sensitive than if a patient exhibits a rise or fall in their cardiac biomarkers (preferably troponins) as many patients have persistently raised biomarkers outside the context of ACS and in current practice, the diagnosis of NSTEMI requires evidence of myocardial ischaemia with a rise or fall in the blood level of a cardiac biomarker (troponin). In addition the sensitivity of biomarker assays has increased since the trial was conducted, and therefore the use of more sensitive assays in ATLAS-ACS 2 TIMI 51 might have led to the reclassification of patients with unstable angina and included in the licensed population.

4.11 The ERG commented that although ATLAS-ACS 2 TIMI 46 was designed to select the most favourable dose and dosing regimen of rivaroxaban in patients receiving aspirin with or without a thienopyridine for further assessment in ATLAS-ACS 2 TIMI 51, the 2.5 mg twice daily dose (or 5 mg twice daily) was the lowest effective dose tested. The ERG stated that it remains unclear whether alternative, lower dosage regimens, such as 2 mg twice daily or 1.5 mg twice daily may have been clinically effective with fewer adverse events.

Clinical trial results

4.12 The primary efficacy endpoint in ATLAS-ACS 2 TIMI 51 was the composite of death from CV causes (CV death), MI or stroke (ischaemic, haemorrhagic or stroke of uncertain cause). There were 4 secondary endpoints. These were: composite of death from any cause, MI or stoke; net clinical outcome (composite of CV death, MI, ischaemic stroke and non-CABG TIMI [non-coronary artery bypass grafting {CABG} Thrombolysis in Myocardial Infarction {TIMI}] major bleeding); composite of CV death, MI, stroke or severe recurrent ischaemia requiring revascularisation; and composite of CV death, MI, stroke or severe recurrent ischaemia leading to hospitalisation.

4.13 The efficacy analysis was based on the modified intention-to-treat (mITT) analysis set, which included all randomised patients (except those from 3 excluded sites which had issues with potential trial misconduct) and the endpoint events that occurred from randomisation up to the earlier date of the global treatment end date, or 30 days after last dose of study drug (for patients who discontinued study drug prematurely), or 30 days after randomisation (for patients who were randomised but never treated).The exclusion of the data from the 3 sites was considered to be acceptable by the EMA. The intention-to-treat (ITT) analysis set, which included all randomised patients and endpoint events occurring at or after randomisation until global treatment end date was conducted as an efficacy sensitivity analysis.

4.14 The company presented results based on the whole trial population and for the licensed population (post hoc subgroup analysis of patients after an ACS with elevated cardiac biomarkers without a prior history of stroke or TIA). For conciseness this document presents the results for the licensed population only. For details of the results for the whole trial population, see tables 14 and 15, pages 79-81 and 88-92 of the company's submission.

4.15 A summary of the primary efficacy endpoints for the licensed population (all strata, n=12,353, 80% of the total trial population) in ATLAS-ACS 2 TIMI 51 is provided in table 4. The company presented the results for the 2.5 mg rivaroxaban twice daily and 5 mg rivaroxaban twice daily doses separately and combined. The company explained that its submission focused on the results for the 2.5 mg twice daily dose since this is the licensed dose.

4.16 A summary of the results for the secondary endpoints for the licensed population is provided in table 5.

Table 4: Effect of rivaroxaban compared with placebo on the primary endpoint (mITT analysis excluding 3 sites): Licensed population

Stratum	**Rivaroxaban**			**Placebo**	**2.5mg bd vs. placebo**		**5mg bd vs. placebo**		**Combined vs. placebo**	
	2.5mg bd	**5mg bd**	**Combined**							
Endpoint	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
All strata	*N=4104*	*N=4089*	*N=8193*	*N=4160*						
Primary Endpoint: Composite of CV death, MI, stroke	[redacted] (6.2)	[redacted] (6.1)	[redacted] (6.2)	[redacted] (7.9)	0.80 (0.68-0.94)	0.007	0.79 (0.67-0.93)	0.004	0.79 (0.69-0.91)	0.001
CV Death	[redacted] (1.7)	[redacted] (2.6)	[redacted] (2.1)	[redacted] (3.1)	0.55 (0.41-0.74)	<0.001	0.89 (0.69-1.15)	0.360	0.72 (0.57-0.90)	0.004
MI	[redacted] (4.3)	[redacted] (3.6)	[redacted] (3.9)	[redacted] (4.9)	0.88 (0.72-1.08)	0.215	0.75 (0.61-0.92)	0.007	0.81 (0.68-0.97)	0.021
Stroke	[redacted] (0.9)	[redacted] (0.9)	[redacted] (0.9)	[redacted] (0.7)	1.23 (0.75-2.02)	0.403	1.38 (0.85-2.24)	0.190	1.30 (0.85-2.01)	0.225
Stratum 1: Aspirin	[redacted]	[redacted]	[redacted]	[redacted]						
Primary Endpoint: Composite of CV death, MI, stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CV Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratum 2: Aspirin plus thienopyridine	[redacted]	[redacted]	[redacted]	[redacted]						
Primary Endpoint: Composite of CV death, MI, stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CV Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

bd, bis die (twice daily); CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; mITT, modified intention to treat

Table 5: Effect of rivaroxaban compared with placebo on the secondary endpoints and components (mITT analysis excluding 3 sites): Licensed population

Stratum	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
Endpoint	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
All strata	*N=4104*	*N=4089*	*N=8193*	*N=4160*						
Secondary endpoint 1: Composite of all cause death, MI, stroke	[redacted] (6.4)	[redacted] (6.2)	[redacted] (6.3)	[redacted] (8.1)	0.80 (0.68-0.94)	0.007	0.79 (0.67-0.93)	0.004	0.79 (0.69-0.91)	<0.001
Secondary endpoint 2: Net clinical outcome	[redacted] (7.2)	[redacted] (7.2)	[redacted] (7.2)	[redacted] (8.1)	0.90 (0.77-1.05)	0.166	0.90 (0.77-1.05)	0.184	0.90 (0.78-1.03)	0.110
Secondary endpoint 3: Composite of CV death, MI, stroke, SRIR	[redacted] (8.5)	[redacted] (7.9)	[redacted] (8.2)	[redacted] (9.8)	0.87 (0.76-1.01)	0.059	0.81 (0.70-0.94)	0.006	0.84 (0.75-0.95)	0.006
Secondary endpoint 4: Composite of CV death, MI, stroke, SRIH	[redacted] (7.1)	[redacted] (7.4)	[redacted] (7.2)	[redacted] (8.9)	0.80 (0.68-0.93)	0.004	0.84 (0.72-0.98)	0.026	0.82 (0.72-0.93)	0.002
Individual outcomes										
Death (all-cause)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-CABG TIMI major bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRIR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRIH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stent thrombosis [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Stratum	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
Endpoint	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Stratum 1: Aspirin	[redacted]	[redacted]	[redacted]	[redacted]						
Secondary endpoint 1: Composite of all cause death, MI, stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary endpoint 2: Net clinical outcome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary Endpoint 3: Composite of CV death, MI, stroke, SRIR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary endpoint 4: Composite of CV death, MI, stroke, SRIH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Individual outcomes										
Death (all-cause)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-CABG TIMI major bleeding	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	[redacted]	-	[redacted]
SRIR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRIH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stent thrombosis [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratum 2: Aspirin plus thienopyridine	[redacted]	[redacted]	[redacted]	[redacted]						

Stratum	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
Endpoint	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Secondary endpoint 1: Composite of all cause death, MI, stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary endpoint 2: Net clinical outcome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary Endpoint 3: Composite of CV death, MI, stroke, SRIR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary endpoint 4: Composite of CV death, MI, stroke, SRIH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Individual outcomes										
Death (all-cause)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-CABG TIMI major bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRIR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRIH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stent thrombosis [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

bd, bis die (twice daily); CABG, coronary artery bypass grafting; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IS, Ischaemic stroke; MI, myocardial infarction; mITT, modified intention to treat; SRIR, Severe recurrent ischaemia requiring revascularisation; SRIH; Severe recurrent ischaemia requiring hospitalisation; TIMI, Thrombolysis in Myocardial Infarction

[a] Defined as definite, probable or possible by Academic Research Consortium definitions; method of analysis using ITT approach (p95-96, company submission)

Stratum	Rivaroxaban			Placebo	2.5mg bd vs. placebo		5mg bd vs. placebo		Combined vs. placebo	
	2.5mg bd	5mg bd	Combined							
Endpoint	n (%)	n (%)	n (%)	n (%)	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value

Source: tables 4 and 5, ERG report (tables 6 and 7, pages 41 and 43)

4.17 In its submission, the company provided results on the primary efficacy endpoint across a number of subgroups for the whole trial population only (combined 2.5 mg twice daily and 5 mg twice daily doses of rivaroxaban). These included age, sex, creatinine clearance, previous MI, stroke or TIA and index event (STEMI, NSTEMI or UA). The company stated that in general, rivaroxaban treatment was consistently associated with improved outcomes across all major subgroups (with the exception of the subgroup analysis of prior history of stroke or TIA). For further details of the subgroup analyses, see figure 15, page 99 of the company's submission. The company also stated that as the licensed population was a subgroup of the ATLAS-ACS 2 TIMI 51, any further subgroup analysis would be subgroup data of a subgroup, and therefore not statistically robust. This was because the trial was not powered to draw conclusions about post-hoc subgroups of subgroups.

4.18 In response to a clarification request, the company provided subgroup analysis data for the following groups (as per the final scope issued by NICE): people with NSTEMI, people with STEMI, people with diabetes, people who received prior primary PCI; and people who did not receive prior primary PCI in the acute phase of management. A favourable hazard ratio 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 twice daily and 5 mg twice daily doses individually compared with placebo. For the majority of analyses, interaction p values were >0.05. For further details of the results, see the company's clarification response to question A20.

4.19 The company did not report any data in relation to treatment compliance or premature discontinuation of study treatments for the licensed population (as data was not currently available). For the whole trial population (that is, the primary safety analysis population [see section 4.25 for a definition of the primary safety analysis population]) 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. The most common reasons for discontinuation of study treatment were adverse events (rivaroxaban 2.5 mg twice daily 8.8%; rivaroxaban 5 mg twice daily 10.9%; placebo 7.3%), consent withdrawal (rivaroxaban 2.5 mg twice daily 4.7%; rivaroxaban 5.0 mg twice daily 4.3%; placebo 4.3%) and 'other' (rivaroxaban 2.5 mg twice daily11.5%; rivaroxaban 5 mg twice daily 11.3%; placebo 11.8%).

4.20 Of the 15,526 patients randomised, 13,124 (84.5%) patients completed the trial alive (patients who completed the follow-up period were considered to have completed the trial) and 537 patients (3.5%) died. The remaining 1,865 (12.0%) patients were categorised as having 'incomplete follow-up'. 11,026 (71.0%) randomised patients completed both the double-blind treatment period and the trial. At trial end, of the 1,294 patients who withdrew consent, vital status remained unknown for 1,117 (86.3%) patients. During discussions with the US Food and Drug Administration (FDA) concerns were raised about the level of missing data as a result of the incomplete follow-up of patients who prematurely discontinued from the trial for reasons other than death. The company therefore undertook an extensive plan to obtain vital status information on patients who withdrew consent. This resulted in the proportion of patients with unknown vital status reducing to 3.2% (495 patients) in the ITT analysis set and 1.8% (278 patients) in the mITT analysis set.

4.21 Health-related quality of life was assessed in ATLAS-ACS 2 TIMI 51 using the EuroQoL (EQ-5D) utility index. EQ-5D data was collected from sites in eight countries including the UK at baseline, 4 weeks, 24 weeks, 48 weeks, 72 weeks and 96 weeks. Health-related quality of life data was collected for all of the participants in the trial. The company stated that the utility values obtained from the trial were not used in the economic model

as they did not differentiate between the tunnel states defined in the model. The company also stated that the low numbers of observations for some of the estimates from the trial (for example stroke and TIMI major bleed were based on fewer than 35 observations) meant that the data were not robust enough for use in the economic base case analysis. The company presented the average utility values after each health state event from ATLAS-ACS 2 TIMI 51 (see table 53, page 243 of the company's submission for further details).

ERG comments

4.22 The ERG noted that there were numerical inconsistencies between the 2 dose groups (2.5 mg twice daily and 5 mg twice daily) for the components of the composite efficacy endpoints in the licensed population. When the components of the primary efficacy endpoint were analysed individually, rivaroxaban 2.5 mg twice daily significantly reduced the risk of death from CV causes compared with placebo (hazard ratio [HR] 0.55, 95% CI: 0.41 to 0.74, p<0.001), but did not reduce the risk of MI (HR 0.88, 95% CI: 0.72 to 1.08, p=0.215) or stroke (HR 1.23, 95% CI: 0.75 to 2.02, p=0.403). In contrast, rivaroxaban 5 mg twice daily significantly reduced the risk of MI (HR 0.75, 95% CI: 0.61 to 0.92, p=0.007), but did not reduce the risk of CV death (HR 0.89, 95% CI: 0.69 to 1.15, p=0.360) or stroke (HR 1.38, 95% CI: 0.85 to 2.24, p=0.190). A similar pattern was also observed for the total trial population in ATLAS-ACS 2 TIMI 51 (see table 14, page 79-81 of the company's submission). The ERG noted that the numerical inconsistencies between the two dose groups had been extensively discussed in a US FDA briefing document (albeit in the whole trial population of ATLAS-ACS 2 TIMI 51, rather than the licensed population) which states that 'the proposition that a lower dose of an antithrombotic drug is significantly more effective than a higher dose lacks biological plausibility' and concludes with 'Hence analyses which suggest efficacy results are superior for the 2.5 mg bid dose should be viewed as likely spurious'. The ERG also noted that the EMA's assessment report concluded that these findings may partly have been due to chance. The

ERG therefore considered the hazard ratios from the combined dose to be more plausible than those of the individual doses.

4.23 The ERG considered the validity of the results from ATLAS-ACS 2 TIMI 51 to be questionable as a result of the high discontinuation rates from the trial. The ERG noted that 15.5% of the total randomised population (n=15,526) prematurely discontinued from the trial (2.5 mg rivaroxaban twice daily 15%[redacted]5 mg rivaroxaban twice daily 16.3%[redacted] placebo 15.1%[redacted] The ERG highlighted that the rates of premature withdrawal in the ATLAS-ACS 2 TIMI 51 trial were higher than other similar randomised trials in patients with ACS: APPRAISE-2 (apixaban, 1.8% [131/7392]); TRACER (vorapaxar, 5.9% [761/12,944]); PLATO (ticagrelor, 3.0% [562/18,624]) and TRITON (prasugrel, 5.9% [804/13,619]).

4.24 The ERG commented that because of the missing data from those who discontinued from the trial (proportion of patients with unknown vital statistics 3.2% [495/15,526]), there was a potential risk that this may lead to informative censoring (that is, patients who drop out, and therefore censored, are more or less likely to experience the primary outcome of interest compared with those remaining in the study in a non-random manner), which may be compounded if the reason for, or frequency of, drop out differs between treatment groups. The ERG highlighted that no detailed discussion was provided in the EMA's assessment report regarding this issue. The ERG considered that the efficacy analyses were at risk of bias as prognoses may differ in those patients who discontinued from the trial. The ERG highlighted that the likely bias introduced by informative censoring in the clinical outcomes and cost-effectiveness analyses were unknown.

Adverse effects of treatment

4.25 The primary safety analysis set was the Treatment-Emergent Safety analysis set, including all patients who were randomised and who

received at least one dose of the study drug with all events from first dose up to the date of the last dose of study drug plus 2 days for each patient. This was used for the primary safety analysis of non-CABG TIMI major bleeding events, key adverse event summaries and the benefit-risk analysis.

4.26 The company presented results on the Primary Safety Endpoint and other bleeding related endpoints based on the whole trial population and for the licensed population (that is adult patients after an ACS without prior stroke or TIA). The total number of patients valid for the safety analysis from ATLAS-ACS 2 TIMI 51 was15, 350 (Safety analysis set, n=5115 rivaroxaban 2.5 mg twice daily; n=5110 rivaroxaban 5 mg twice daily; n=5125 placebo). For conciseness this document presents the results for the licensed population only. For details of the results for the whole trial population and other bleeding related secondary endpoints, see table 18, page 108 of the company's submission.

4.27 A summary of the Primary Safety Endpoint and other bleeding events for the post-hoc subgroup analysis of patients after an ACS with elevated cardiac biomarkers without prior stroke or TIA is provided in table 6. The company presented the results for the 2.5 mg rivaroxaban twice daily and 5 mg rivaroxaban twice daily doses separately and combined.

Table 6: Effect of Rivaroxaban compared with Placebo on the Primary Safety Endpoint & other bleeding-related secondary endpoints (treatment emergent safety analysis set[a]) – Licensed population

Stratum	**Rivaroxaban**			**Placebo**	**2.5mg bd vs. placebo**		**5mg bd vs. placebo**		**Combined vs. placebo**	
	2.5mg bd	**5mg bd**	**Combined**							
Endpoint	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
All strata	*N=4096*	*N=4072*	*N=8168*	*N=4157*						
Primary safety endpoint:[b] Non-CABG TIMI major bleeding	[redacted] (1.3)	[redacted] (1.6)	[redacted] (1.5)	[redacted] (0.4)	3.44 (1.97-6.01)	<0.001	4.40 (2.55-7.60)	<0.001	3.91 (2.32-6.59)	<0.001
Secondary safety endpoint: Clinically significant bleeding (composite of TIMI major bleeding, TIMI minor bleeding and bleeding requiring medical attention)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Individual outcomes										
Fatal bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TIMI major bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TIMI minor bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TIMI bleeding requiring medical attention	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intracranial haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

bd, bis die (twice daily); CI, confidence interval; HR, hazard ratio; TIMI, Thrombolysis in Myocardial Infarction

[a] Treatment-emergent safety analysis set included all events from first dose up to the date of last dose of study drug plus 2 days [redacted] [b] Stratum 1: [redacted] Stratum 2 [redacted]

Source: ERG report (table 8, page 49)

4.28 [redacted]. For further details see Table 21, page 117 of the company's submission.

ERG comments

4.29 The ERG commented that the reporting of treatment-emergent adverse events was not well reported or transparent for the licensed (post hoc analysis) and the total population of the ATLAS-ACS 2 TIMI 51 trial.

5 Cost-effectiveness evidence

Model structure

5.1 The company submitted a de novo Markov cohort model comparing rivaroxaban 2.5 mg twice daily with standard care (clopidogrel plus acetylsalicylic acid [ASA] or ASA alone) in adults with a recent ACS who were biomarker positive and had not had a previous stroke or TIA. 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 respectively and the remaining cycles used a cycle length of 12 weeks. The company based the analysis from an NHS and personal social services perspective, and costs and benefits were discounted at an annual rate of 3.5%. Half cycle correction was performed on the markov trace.

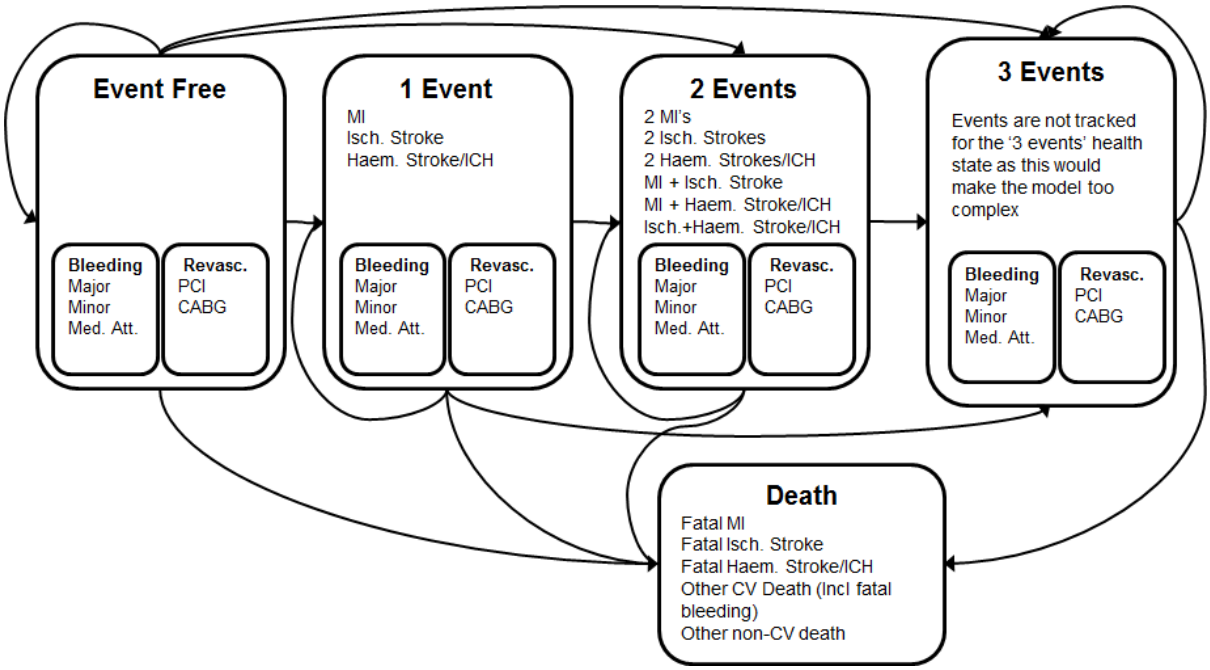
5.2 The company's model consisted of a number of health states corresponding to whether no further ACS event occurred or whether the patient suffered an ACS event. The ACS events considered in the model were: MI, ischaemic stroke (IS), haemorrhagic stroke or intracranial haemorrhage (HS/ICH); a bleeding 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.

5.3 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 patient's health related quality of life to improve over time, and for the cost of treatment 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 occurred, it was assumed that one event of each type (that is an MI, an IS and a HS/ICH) had occurred to the patients in this health state.

5.4 The health states corresponding to bleeding and revascularisations were assumed to be transient health states and when a patient entered 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 were comparable after rivaroxaban treatment was discontinued for all patients at the end of the second year. The model structure is provided in figure 2.

Figure 2 Model Structure



MI = Myocardial Infarction, Isch. Stroke = Ischaemic Stroke, Haem. Stroke = Haemorrhagic Stroke, ICH = Intracranial Haemorrhage, Med. Att. = Medical Attention, CV = Cardiovascular
Source: company's submission (figure 19, page 174)

ERG comments

5.5 The ERG stated that the structure of the company's model led 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 suffered from two events in one time cycle were not distinguished from those patients who suffer multiple events in separate time cycles. Secondly, for patients who suffered from multiple events in separate time cycles any improvement over time that they may have experienced was ignored. Finally, for those patients who

transition into the multiple event states from the single event states, the first event was not tracked. The ERG commented that there were 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.

5.6 The ERG commented that its clinical advisers agreed that the time horizon of the transient events was appropriate but that this approach ignored the possibility that multiple bleeding events could occur in one time cycle.

Model details

Population modelled

5.7 The population modelled was the subgroup of patients who were biomarker positive and had not experienced a prior stroke or TIA in the ATLAS-ACS 2 TIMI 51 trial. The data in the rivaroxaban model arm was not pooled from both rivaroxaban trial arms. As such, the population for rivaroxaban was limited to those patients who received 2.5 mg rivaroxaban twice daily. Data from both trial strata were used to inform the model data. In accordance with ATLAS-ACS 2 TIMI 51, it was assumed that in the base case 93% of patients received clopidogrel plus aspirin and 7% of patients received aspirin alone. A scenario analysis was presented considering only those patients who received clopidogrel and aspirin.

Transition probabilities

5.8 In the base case the transition probabilities for future ACS-related events in the observation period (2 years) were determined by fitting a Weibull distribution to the trial data. This was undertaken for both the rivaroxaban 2.5 mg twice daily data and for the placebo data. The company stated that as patient numbers diminished over time, particularly visible towards the end of ATLAS-ACS 2 TIMI 51, it was difficult to estimate transition

probabilities directly from the data for the later cycles within the observation period. The company commented that by fitting a Weibull distribution to the ATLAS-ACS 2 TIMI 51 trial data, it was able to remove the data fluctuations caused by a decline in the numbers of observations over the trial. A comparison of the trial data for the licensed population with the interpolated data obtained by the company when a Weibull distribution was applied to estimate the transition probabilities is provided in table 7.

Table 7: Summary of model results compared with clinical data for the observation period

	Clinical trial result (licensed population)	**Model result (from interpolation)**
Rivaroxaban		
MI	4.24%	5.92%
IS	0.58%	0.80%
HS/ICH	0.19%	0.27%
OCD	1.54%	3.41%
NCD	0.39%	0.90%
Comparator	**Clinical trial result**	**Model result (from interpolation)**
MI	4.83%	6.42%
IS	0.50%	0.72%
HS/ICH	0.10%	0.17%
OCD	2.60%	4.57%
NCD	0.46%	0.96%
MI, myocardial infarction; IS, ischaemic stroke; HS/ICH, haemorrhagic stroke or intracranial haemorrhage; OCD, other cardiovascular death; NCD, non-cardiovascular death		

Source: company's submission (table 70, page 325)

5.9 The transition probabilities for the transient event state were obtained from the event rates in ATLAS-ACS 2 TIMI 51. For each transient event, the number of events in the trial period was added together. The event rate was then calculated by dividing through by the total number of patients in the trial. The transient event states were only applied in the observation period. This was equivalent to assuming that any differences in bleeding risks between the 2 populations were equivalent after rivaroxaban has been discontinued.

5.10 The transition probabilities in the extrapolation period were estimated from the trial data assuming that the underlying rates in the last cycle were maintained but then subjected to changes as a result of patients aging and the increased risk of case fatalities as a result of aging. The company calculated the initial case fatality values for fatal MI, fatal stroke and non-cardiovascular mortality from a variety of sources.

Continuation rates

5.11 In the model it was assumed that patients could discontinue treatment in the observation period after they had suffered an ACS event. The probability of discontinuation following an ASC event was obtained from ATLAS-ACS 2 TIMI 51. This was calculated by using the whole trial population, not the licensed population.

5.12 The UK marketing authorisation for rivaroxaban states that 'extension of treatment beyond 12 months should be done on an individual patient basis as experience up to 24 months is limited. To reflect this, the company adjusted the efficacy and cost of rivaroxaban after 48 weeks. The change in efficacy and costs were calculated by selecting numbers which ensured that 19% of patients continued on rivaroxaban after 48 weeks. The change in efficacy and costs reflected the proportion of the costs and efficacy that were assumed to remain in the rivaroxaban group, for those patients who have continued rivaroxaban treatment. No treatment effect or cost was applied to those patients who discontinued rivaroxaban treatment.

Costs

5.13 In the model patients received clopidogrel (75 mg once per day), aspirin (75 mg once per day) and rivaroxaban (2.5 mg twice daily) where appropriate. As rivaroxaban entered the treatment pathway after stabilisation of an ACS any further differences in costs between the intervention and comparator were a result of ACS events and

discontinuations related to an ACS event occurring. The acquisition costs of rivaroxaban, clopidogrel and aspirin are provided in table 8.

Table 8: Acquisition costs associated with the drugs in the economic model

Drug	Loading dose	Daily Dose (maintenance)	Pack size	Pack Price (£)	Cost of loading dose (£)	Cost per day (£)
Rivaroxaban	None	2 x 2.5mg	56-tablets	58.80	None	2.10
Clopidogrel	300mg	75mg	28-tablets	1.74	0.25	0.06
Aspirin	300mg	75mg	28-tablets	0.82	0.12	0.03

Source: ERG report (table 21, page 74)

5.14 Costs of ACS events were determined by the NHS reference costs 2012-13 of treating the ACS event and the cost of follow up for the patient. An assumption was made that if a patient suffered from multiple long term ACS events then the cost of hospitalisation and the follow-up of both events were applied. This was the case irrespective of the time between the ACS events. It was assumed that on average, patients experienced 5, 14 and 28 days rehabilitation after a MI, IS and HS/ICH respectively. These rehabilitation costs occurred in the first 3 months after an ACS event. Transient event costs were also included in the model.

Utility values

5.15 The utility values associated with long-term health states were obtained from the literature, primarily from NICE technology appraisal 236 (Ticagrelor for the treatment of acute coronary syndromes). A study by Ara and Brazier was used to calculate the improvement in health-related quality of life that patients would experience in the stroke health states. The study was used to obtain the utility values of patients with stroke in the UK at baseline and 12 months after the stroke occurred. Based on the utility values from the 2 time points a 33% improvement in health-related quality of life over 12 months was calculated for patients with strokes. To calculate the utility values for patients with a stroke 6 months after a stroke, the average of the stroke 1st 6 months and the stroke (post 12 months) health states was taken. Utility values were assumed to be the same for both rivaroxaban and standard care following any particular

event. For multiple event states, the utility values of both events which had occurred were multiplied together. The company stated that this allowed for worsening health-related quality of life following multiple events to be taken into account. The utility value for the event free health state was assumed to remain constant over time. A summary of the utility values applied to the long-term health states in the model are provided in table 9.

Table 9: Summary of utility values used in the company's base case

State	Utility Value	Standard Error	Reference in company submission
No event	0.842	0.002	NICE technology appraisal 236 (Ticagrelor for the treatment of acute coronary syndromes).
Non-fatal MI	0.779	0.10	As above
Post MI	0.821	0.038	As above + Lacey
Non-fatal stroke	0.703	0.010	As above
Post stroke	0.748	0.038	As above + assumption
Dead	0.000	Not applicable	Not applicable

Source: adapted from ERG report (table 26, page 82)

5.16 In the company's base case the utility values associated with the transient health states were taken from the literature. To calculate the quality of life decrement associated with bleeding the utility values 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 state. The utility values associated with the transient health states are provided in table 10.

Table 10: Utility values associated with the transient health states

Health State / Event	Value from the trial	Values from the literature (which were used in the model).	Assumed length of utility decrement (days) (page 275, Table 58, company	Literature reference

			submission)	
Major bleed	0.77	0.75	30	Crespin *et al.* 2011
Minor bleed	0.84	0.80	2	Kazi *et al.* 2014
Bleeding requiring medical attention	0.87	0.80	2	Sullivan *et al.* 2006
PTCA / PCI	N/A	0.792	30	Latour-Perez 2008
CABG	N/A	0.742	84	Latour-Perez 2008
PTCA/PCI, Percutaneous transluminal coronary angioplasty/ Percutaneous coronary intervention; CABG, coronary artery bypass graft				

Source: ERG report (Table 27, page 82)

ERG comments

5.17 The ERG stated that the population modelled was the patient subgroups who were biomarker positive and had not experienced a prior stroke or TIA. Therefore all issues with the generalisability of the population in ATLAS-ACS 2 TIMI 51 (highlighted in sections 4.8 and 4.10 of this document) and informative censoring (highlighted in section 4.24 of this document) apply to the economic model results.

5.18 The ERG stated that the approach used by the company to calculate the transition probabilities for the transient health states was inappropriate as cost and QALYs of the events which occur in the second year were not appropriately discounted. Also, there was no clear adjustment for the number of additional patients who were assumed to discontinue rivaroxaban in year 2 or for those patients who were assumed to discontinue clopidogrel or rivaroxaban treatment after an ACS event.

5.19 The ERG commented that is was not clear in the submission as to how the patients who continued rivaroxaban treatment after 1 year were selected from the rest of the patient population. The ERG stated that it was unknown whether the base case parameters for the change in efficacy and costs to represent patient discontinuation in the second year

of treatment (see table 18, page 71 of the ERG report) would be applicable to the UK population.

5.20 The ERG had concerns with the methodology used by the company to calculate the utility values for patients with a stroke. The ERG stated that it was unclear why the values from Ara and Brazier were appropriate to calculate the improvement in health-related quality of life of patients who experienced a stroke but not considered appropriate to be used as the utility values in the economic model.

5.21 The ERG had concerns about how the improvement in utility values over time was modelled in the multiple event states. If the patient transitions into the multiple event states from a single event state their utility in the multiple event state could be understated as their improvement in utility after the first event has been ignored. The ERG stated that that this problem was again related to the model structure's inability to distinguish when events had occurred. The ERG noted that this was not the only assumption which the company could have made to calculate the utility value in the multiple event states. It could have been assumed that the lowest utility value of the 2 applied to the patients or if the model could track the chronicity of events it could be assumed that the utility of the most recent event applied.

Company's base case results and sensitivity analysis

5.22 The base case deterministic results for the licensed population are shown in table 11. The company also presented the base case probabilistic results for in the licensed population. The base case probabilistic results were not substantially different from the deterministic results (for further details, see table 76, page 332 of the company's submission).

Table11: Base-case deterministic results for rivaroxaban compared with clopidogrel plus ASA or ASA alone in the licensed population

	Rivaroxaban	**Clopidogrel +ASA or ASA alone**
Total costs (£)	14,767	14,004

	Rivaroxaban	**Clopidogrel +ASA or ASA alone**
Total QALYs	9.56	9.44
Incremental costs (£)	764	-
Incremental QALYs	0.12	-
ICER (£) incremental QALYs	**6,203**	-
ASA, aspirin; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year		

Source: adapted from company's submission (table 75, page 332)

5.1 The company conducted a series of one-way deterministic sensitivity analyses (for further details, see tables 77 and 78, pages 334-335 of the company's submission). Changes to the cost parameters, discount rates, utility values and risk estimates for MI impacted on the base case ICER, but no factor increased the ICER to over £10,000 per quality-adjusted life year (QALY) gained.

5.2 The company's probabilistic analysis showed that if the maximum acceptable amount for an additional QALY was £30,000 then rivaroxaban would have a 99.9% probability of being cost effective compared with clopidogrel plus ASA or ASA alone.

ERG comments

5.3 The ERG expressed concerns about the appropriateness of the methods used to model the costs of rivaroxaban, clopidogrel and aspirin and the efficacy data (shape and scale parameters of the Weibull curve). The ERG recalculated the PSA and found the PSA results were generally more favourable to rivaroxaban producing more incremental QALYs at a lower incremental cost. For further details see table 29 page 85 of the ERG report.

Company's scenario analyses

5.4 The company conducted a series of scenario analyses. The following parameter groups were considered: strata and transition probabilities, utility values, cost of events and increased risk of events as a result of age and relative risk of suffering subsequent events following an event. Table

12 shows that none of the scenarios tested increased the ICER to over £10,000 per QALY gained.

Table 12: Results from the company's scenario analyses applied to the 40 year time horizon

Parameters tested	Rivaroxaban		"standard of care"		Incremental		ICER
	Costs	QALYs	Costs	QALYs	Costs	QALYs	
Strata and transition probabilities (proportional hazards)							
Stratum 2	£15,362	9.52	£14,479	9.40	£883	0.12	£7,404
Transition probabilities							
Non-parametric	£16,290	9.75	£15,431	9.62	£858	0.13	£6,468
Clopidogrel efficacy							
Clopidogrel RRR=1	£13,794	10.09	£13,044	9.96	£749	0.13	£5,824
Utilities							
Utility values from trial	£14,767	9.83	£14,004	9.71	£763.58	0.13	£5,935
Utility values return to the baseline utility value in the post event cycles	£14,767	9.61	£14,004	9.49	£763.58	0.12	£6,195
Utility values applied to fatal events	£14,767	13.39	£14,004	13.28	£763.58	0.10	£7,147
Cost of events							
Cost of death = £0.00	£13,522	9.56	£12,707	9.44	£814.70	0.12	£6,618
Increased risk of events due to age and subsequent events							
RR = 1 for all subsequent events following a MI, IS or HS	£15,960	9.81	£15,169	9.68	£790	0.12	£6,439
Increased risk due to age = 0	£31,093	14.09	£30,194	13.91	£898	0.18	£4,927
RR = 1 and increased risk due to age = 0	£29,633	14.34	£28,704	14.16	£928	0.18	£6,745
ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year; RR, relative risk; RRR, relative risk reduction							

Source: Company's submission (table 80, page 339)

5.5 The company also presented additional scenario analyses in response to clarification requests. These were: age adjusted utility values using different formulas, most costly event applied to the multiple ACS event states, different formula applied to the costs in the observation period and all patients were assumed to discontinue rivaroxaban after 1 year. None

of the additional scenarios tested increased the ICER to over £10,000 per QALY gained. For further details see table 34 page 99 of the ERG report.

ERG comments and exploratory analyses

5.6 The ERG commented that there were a number of key parameters that could not be adjusted within the model that may have changed the ICER to a greater extent. These included: amendments to the hazard ratio for fatal bleeds; using pooled efficacy data rather than the 2.5 mg rivaroxaban twice daily dose alone; and adjusting for the possibility of informative bias.

5.7 The ERG conducted an exploratory probabilistic sensitivity analysis where published levels of uncertainty around the utility value estimates and the reference costs rather than an arbitrary range were taken into account. The ERG noted that the resulting probabilistic ICER was similar to the company's deterministic ICER. For further details see pages 99-102 of the ERG report.

5.8 The ERG conducted a 'crude' exploratory sensitivity analysis to explore the effects on the ICER of increasing the number of patients who experienced a fatal bleeding event with rivaroxaban, assuming that the event occurred immediately upon taking rivaroxaban. To conduct this sensitivity analysis, the ERG adjusted the total discounted costs and QALYs for those patients who received rivaroxaban. No adjustments were made to the total discounted costs or QALYs of those patients who did not receive rivaroxaban. The ERG considered a range of additional fatal bleeding events ranging from no additional fatal bleeding events (company's base case) to 20 additional bleeding events. As there were 21 fatal bleeding events in the combined rivaroxaban treatment arms of the total population in ATLAS-ACS 2 TIMI 51, the ERG considered that 20 additional fatal bleeding events was an unfavourable scenario for rivaroxaban 2.5 mg twice daily dose. The result of the ERG's exploratory analysis showed that even if rivaroxaban 2.5 mg twice a day caused an additional 20 fatal bleeding events compared with the event rate observed

in the trial the ICER was not estimated to be greater than £10,000 per QALY gained.

5.9 The ERG also undertook a series of exploratory analyses. When all the changes to the model were implemented the ERG's base case was lower than the company's base case. The ERG's exploratory analyses are provided in table 13.

Table 13: ERG's exploratory scenario analyses

Code	Change from company's base case	Total costs		Total QALYs		Incremental costs	Incremental QALYs	ICER
		Rivaroxaban plus ASA with or without CLOP	ASA with or without CLOP	Rivaroxaban plus ASA with or without CLOP	ASA with or without CLOP			
Company's base case	-	£14,767.63	£14,004.05	9.56	9.44	£763.58	0.12	£6,203
1	The transition probabilities are estimated from the trial data	£16,290.40	£15,431.41	9.75	9.62	£858.99	0.13	£6,468
2	The treatment duration of rivaroxaban is limited to one year	£14,628.81	£14,004.05	9.56	9.44	£624.73	0.12	£5,323
3	The utilities are age adjusted, using Ara and Brazier's formula for the whole population	£14,767.63	£14,004.05	9.07	8.95	£763.58	0.12	£6,536
4	Only one cost is applied to the multiple event states. Where there are two different costs added together in the company's base case, the maximum of the two costs is applied	£13,592.041	£12,818.43	9.56	9.44	£768.15	0.12	£6,240
5	No improvement over time in the stroke utility is modelled	£14,767.63	£14,004.05	9.53	9.41	£763.58	0.12	£6,289
6	The relative risk of suffering a subsequent event is given by Table 37, page 106 of the ERG report	£15,007.30	£14,234.54	9.59	9.47	£772.76	0.12	£6,250
7	The life years gained matrix and the costs are adjusted	£14,804.12	£14,026.06	9.49	9.37	£778.06	0.12	£6,357

	for the 12 week cycle length in the observation period							
8	There are 5 times as many bleeding events. (Excluding deaths due to bleeding)	£14,873.51	£14,049.43	9.56	9.44	£824.08	0.12	£6,714
9	The relative risk of a further ACS event following the first ACS event is one in the extrapolation period(i.e. all cells in Table 37, page 106 of the ERG report would be one)	£15,960.00	£15,169.14	9.80	9.68	£790.86	0.12	£6,439
10	The relative risk of a further ACS event following the first ACS event is five in the extrapolation period(i.e. all cells in Table 37, page 106 of the ERG report would be five)	£12,292.55	£11,606.37	9.04	8.92	£686.19	0.13	£5,412
ERG base case 1+2+3+4+5+6+7		£14,650.11	£13,947.41	9.17	9.05	£702.70	0.12	£5,622
ASA, aspirin ;Clop, clopidogrel; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year								

Source: ERG report (table 38, pages 107-108)

5.10 The ERG concluded that if all the identified errors in the model were corrected, the ICER for rivaroxaban would not be above £10,000 per QALY qained.

Innovation

5.11 Justifications for considering rivaroxaban to be innovative:

- The company stated that rivaroxaban was innovative because there is a residual risk of further ACS events despite treatment with currently available antiplatelet therapy, which may be attributed to higher thrombin levels after ACS. The company stated that low dose rivaroxaban offers a novel mechanism of action by blocking the thrombin generation after ACS.

6 Equalities issues

6.1 No potential equality issue were raised at the scoping workshop, or in the evidence submitted.

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