KEY INACCURACIES

Issue 1 Distinguishing between groups of STEMI patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Key issue throughout the report The ERG distinguishes between groups of STEMI patients defining four patient groups: STEMI without stenting; STEMI with BMS, STEMI with DES and STEMI with other. Consideration of these subgroups is outside the remit of the scope and decision problem. This point applies to the following pages and sections: • Page 8, Section 1.3.1 • Page 10, Section 1.4 • Page 63, Section 5.5 • Page 65, Table 22	The report should be restricted to the three subgroups (unstable angina, NSTEMI and STEMI) specified in both the scope and the decision problem	The sub division of STEMI patients is outside of the original scope and the decision problem. The scopes states *'If the evidence allows the following subgroups will be considered: people with unstable angina, NSTEMI, and STEMI'*	The ERG is aware of the disadvantage to the manufacturer with the MS submission date that was prior to the publication of new NICE guidance and working in a field wherein the definition of subgroups is evolving. We understand the perspective of the manufacturer. Although not specified in the final scope issued by NICE, the ERG considers that these four groups are covered by NICE guidance and should therefore be considered by the committee The ERG will include a statement to this effect in its report

Issue 2 Duration of clopidogrel treatment in STEMI patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Throughout the report the ERG distinguishes between STEMI patients	STEMI patients with BMS All reference to NICE recommendations that STEMI	NICE TA 152 recommendations are specific for drug eluting stents only there are no recommendations relating to	The ERG is aware that TA152 is directly relevant to drug eluting stents and is not a NICE

with BMS and STEMI patients without stenting and specifies clopidogrel treatment durations for these two groups. STEMI patients with BMS The duration of clopidogrel treatment for STEMI patients with BMS is stated as 3 months. This specified duration is not based on any NICE guidance recommendations but on the ERG's interpretation of TA152. This is inappropriate - recognised guidelines and evidence based data should be used to specify duration of treatment. STEMI patients with stenting The duration of treatment for STEMI patients without stenting is specified as at least 4 weeks based on NICE CG48. In practice, the duration of clopidogrel treatment for this patient group is much longer. This point applies to the following pages and sections: • Page 8, Section 1.3.1 • Page 10, Sections 1.3.4 and 1.4 • Page 13, Table 1 • Page 18, Section 3.1 • Page 63, Section 5.5 • Pages 67, 68 and 69, Section 5.6	patients with BMS should receive 3 months treatment should be deleted. In the absence of any formal NICE guidance it should be stated that 'in the absence of any formal NICE guidance the European guidelines which state a treatment duration of 12 months were utilised by AstraZeneca'. STEMI patients with stenting • In addition to the NICE CG48 recommendation that patients with STEMI without stenting should receive at least 4 weeks treatment with clopidogrel the ERG report should be updated to reflect current clinical practice and the fact that STEMI patients actually receive treatment for 12 months. All patient groups (UA, NSTEMI and STEMI) At the end of section 1.3.1 a the following statement is recommended for inclusion: 'In clinical practice the median length of treatment of patients with clopidogrel in primary care following admission to hospital with acute coronary syndrome is around 12 months for UA, NSTEMI and STEMI'	BMS. The ERG has assumed a treatment duration of 3 months for STEMI patients - it is not a NICE recommendation. While NICE CG 48 specifies that STEMI patients without stenting should be treated with clopidogrel for at least 4 weeks this does not reflect what happens in clinical practice. We note that the guideline is due for review and recommend that the review takes into account current clinical practice as illustrated by the below GPRD data. [redacted]	recommendation for APT for patients who receive a BMS. However, the text included in the report is taken directly from TA152 . The ERG considered it important that the AC is aware of this text. The ERG will endeavour to make it clear in the ERG report that the text taken from TA152 is the ERG interpretation. The ERG is aware that the guidelines in CG48 may not be followed in clinical practice. This is noted in the ERG report on pg 10, Section 1.4. The ERG will add a further note to this effect in the background section of the ERG report and to section 3.1 The following statement will be added to pg 18 Section 3.1: The manufacturer's view is that In clinical practice the median length of treatment of patients with clopidogrel in primary care following admission to hospital with acute coronary syndrome is around 12 months for UA, NSTEMI and STEMI'

• Page 81, Section 5.10 • Page 84, Section 6			

Issue 3 Inappropriate reference to TA210

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Reference to TA210 is made throughout the document. In discussing the weakness of the model the ERG states 'in the submitted model it is assumed that all patients receive ASA as a long-term preventative treatment; in England and Wales cardiovascular patients with multivascular disease go on to receive long-term clopidogrel treatment' In addition, the ERG states, 'none of the presented analyses recognises that patients with multivascular disease should receive clopidogrel for long-term prevention rather than low-dose ASA, or that patients surviving subsequent stroke/TIA events should be switched from low-dose ASA to clopidogrel for long-term prevention'. These statements both refer to TA210	Reference to TA210 should be removed.	NICE guidance (TA210) refers to the full indications of clopidogrel to include PAD and cerebrovascular disease (stroke). Ticagrelor is not licensed in either of these indications and consequently TA210 is outside the scope of this appraisal. Even it were applicable TA210 was issued after submission of the AstraZeneca document and is outside scope. The model included within the AstraZeneca submission reflects the patient population which will be eligible for treatment with ticagrelor and is in line with NICE CG 48.	The ERG report (pg 12 Section 2.2 notes that TA210 was issued after the submission date of the MS TA210 recommends that patients with MVD go on to long-term treatment with clopidogrel and not ASA as assumed in the manufacturer's model

which is not relevant to the appraisal of ticagrelor and as a consequence are both inappropriate and misleading. This point applies to the following pages and sections: Page 9, Section 1.3.3 Page 13, Table 1 Page 18, Section 3.1 Page 63, Section 5.5 Pages 67,68 and 69, Section 5.6			

Issue 4 Discontinuation of treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10, Section 1.4 The ERG report states that 'in the UK substantial numbers of patients discontinue dual antiplatelet treatment after approximately 90 days' This is incorrect and does not reflect current clinical practice.	It is recommended that the sentence is amended to read 'In the UK substantial numbers of patients discontinue dual antiplatelet treatment after approximately 90 days only [redacted] of patients with UA, NSTEMI or STEMI who are prescribed clopidogrel in primary care discontinue therapy within 90 days (AstraZeneca GPRD Data on File)' (The highlight figure is provided on an academic in confidence)	The current statement is incorrect and does not reflect current clinical practice where only a small proportion of patients discontinue treatment (see GPRD data below). In addition use of the word 'substantial' contradicts a later statement within the ERG report which states (on page 84) that one third of STEMI patients and one quarter of NSTEMI/UA patients discontinue dual antiplatelet therapy after 90 days. We do not have access to this data so have been unable to valid it.	The text of the ERG report to be changed to read 'a not insignificant number of patients'

		The following information is provided on an academic in confidence basis: GPRD data demonstrates that: Fewer than 12% of patients with UA, NSTEMI or STEMI who are prescribed clopidogrel in primary care discontinue therapy within 90 days, the proportion who have discontinued within 6 months is less than 23% in each group. With a median length of treatment 12 months. A data on file can be provided in support of this statement	

OTHER INACCURACIES

Issue 5 Number of events

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 6, Section 1.2 The ERG reports states ....*'After 1780 events had occurred'.* This is incorrect.	The sentence should be amended to read ' *After 1878 events had occurred….'* This figure also requires correcting on page 83, section 6.	Factual correction. 1780 is the number of events needed specified in the protocol while1878 is the number of events that actually occurred by the time the study was concluded and is the correct number which should be cited within the ERG report.	The ERG will amend text to read 1878 events on page 6. The ERG was unable find 1780 on page 83.

Issue 6 Clarification on the length of ventricular pauses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 7, Section 1.2. The ERG report states: 'Statistically significantly increased rates of dyspnoea and, in the first week ventricular pauses detected by Holter monitoring were noted in the ticagrelor arm, in addition to increases in serum uric acid and serum creatinine from baseline values from the beginning to the end of the trial' but does not specify the duration of the ventricular pauses.	Inclusion of the following underlined text, 'Statistically significantly increased rates of dyspnoea and, in the first week ventricular pauses of length greater than or equal to 3 seconds detected by only Holter monitoring were noted in the ticagrelor arm, in addition to increases in serum uric acid and serum creatinine from baseline values from the beginning to the end of the trial.'	The current sentence does not specify the duration of ventricular pauses. There was no increase in ventricular greater or equal to 5 seconds. Ventricular pauses were only detected by Holter monitoring and were asymptomatic.	The ERG will add the suggested text to the ERG report

Issue 7 Inclusion of enzymatic MIs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 8, Section 1.3.2 The report states 'Only clinical MI's were included in the analysis' This statement requires amending in order to reflect the fact that in PLATO small number of enzymatic MIs were included.	Change 'only' to 'mainly'	There were a small number of enzymatic MIs included in the PLATO study endpoint analyses.	The ERG will amend the ERG report accordingly

Issue 8 Reversibility of ticagrelor

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10, Section 1.3.4 The following statement is inaccurate: 'The rapid reversibility of the clinical effects of ticagrelor will be advantageous for patients in a number of clinical scenarios (e.g. patients undergoing planned CABG or other surgery)'	This statement should be deleted	This statements is inaccurate and outside of license. The BRILIQUE SmPC states 'If a patient is to undergo elective surgery and antiplatelet effect is not desired, Brilique should be discontinued 7 days prior to surgery (SmPC. Section 4.4)'.	The ERG to remove statement

Issue 9 Reversibility of ticagrelor

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10, Section 1.3.4 The ERG report states '… if patients do not take all (twice daily) planned doses, then the rapid reversibility of ticagrelor may in fact be a disadvantage compared with clopidogrel (daily)'	This statement should be deleted	This statement is incorrect and misleading. The only data in relation to the offset of action of ticagrelor in inhibiting platelet function comes from a phase II study (Onset-Offset) in a non-licensed patient population (stable coronary artery disease) (Gurbel et al; Circulation 2009, 120, 2577-2585 – reference 46 of the AstraZeneca submission document). In this study trough IPA 24 hours after a ticagrelor dose (e.g., if a dose is missed) is similar to trough IPA 24 hours after a clopidogrel dose (e.g. prior to the next scheduled dose of clopidogrel taken once daily). There is	The ERG to remove statement

		no apparent difference in IPA relative to clopidogrel as a result of missing a dose. If a patient misses multiple doses, the effect on IPA is unknown.	

Issue 10 Incorrect citation of TA152 recommendations

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13, Section 2.2., Table 1 With the exception of TA152 the recommendations for other technology appraisals and clinical guidelines are in line with the published documents. For TA152 the TA recommendations are not cited and the ERG has selected text from the guidance document.	For TA152 the table should be deleted or amended to accurately reflect the guidance recommendations	The current text does not reflect the recommendations cited within TA152.	The text is taken directly from Section 2.12 of TA152

Issue 11 Outcomes – Need for Revascularisation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 19, Section 3.4 In relation to the clinical outcome the need for revascularisation the ERG considers that 'the scope is ambiguous and the manufacturer's explanation is acceptable if the scope is interpreted as referring to changing the immediate mode of treatment (i.e.	The opinion of the ERG should be deleted.	This interpretation of the ERG does not reflect the discussions between AstraZeneca and NICE in both relation to the scope or the decision problem. Throughout the appraisal process AstraZeneca has consistently highlighted that the outcome on the need for revascularization was not appropriate	The ERG were not party to any of these discussions and therefore cannot comment on this further

revascularisation) within the trial'. The ERG then states that in their opinion of 'this outcome was intended to refer to additional, unplanned revascularisation following any index procedure' and went on to state that 'this has not been addressed by the manufacturer'.		for this appraisal on the basis that 'nearly all patients with STEMI received revascularization whilst for patients with NSTEMI or UA it was left to the investigators' discretion as to whether the patient was medically managed or revascularised'. This was discussed with NICE during the decision problem meeting and at no point was the interpretation of this outcome deemed incorrect.	

Issue 12 Patients identified for early conservative strategy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 20, Section 3.6 The ERG report states 'In the clinical effectiveness section.....patients who were identified at randomisation as being intended for early conservative strategy (UA and NSTEMI patients)...'	The text should be amended as follows: 'In the clinical effectiveness section.....: patients who were identified at randomisation as being intended for early invasive strategy (angiography followed by PCI/CABG) (i.e. from all ACS subgroups); patients who were identified at randomisation as being intended for early conservative strategy (UA and NSTEMI patients); patients with STEMI (treated with primary or planned PCI).	The current text does not reflect the study protocol.	The ERG to amend text as suggested

Issue 13 Economic and clinical subgroups

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 20, Section 3.6 The ERG makes reference to the fact this there is a mismatch between the subgroups of interest in the economic evaluation and the clinical subgroups in the clinical section. Details on this mismatch are not provided. A similar comment is made on page 63, section 5.5 which states 'the subgroups in the economic evaluation do not reflect the subgroups of interest in the clinical section of the MS.	Details on the mismatch should be clarified in both sections.	Without further details is it not possible to evaluate the ERGs view on the mismatches between the subgroups.	In the clinical effectiveness section, the outcomes for UA/NSTEMI patients are combined. In the economic evaluation, ICERS for UA/NSTEMI are presented separately

Issue 14 Aspirin doses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 25, Section 4.2, Table 6 In the table column headed 'Intervention/comparator' under ASA dosing it states 'All patients received 75 to 100 mg daily'...this is not correct.	Statement to be amended to read 'Most patients received 75 to 100 mg daily...'	Not all patients received 75 to 100 mg aspirin daily and in line with the study protocol some patients received other doses of ASA at the discretion of the investigator.	ERG to correct Table 6

Issue 15 Third party monitoring

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 26, Section 4.3 The ERG notes that concerns were expressed in the US that whilst manufacturer appointed third parties monitored most sites involved in the trial, this did not occur for sites in the US, Russia or Georgia (all locations in which trial results favoured clopidogrel over ticagrelor). This is incorrect	This statement should be deleted	This statement is based on a quote from the following heartwire (non peer reviewed) article (http://www.theheart.org/article/1164221.do) and is factually incorrect. All sites were monitored (by AstraZeneca or an appointed third-party CRO). There is no correlation between the PLATO results in a particular country and the company performing the monitoring (AstraZeneca vs. third-party CRO) and there is no evidence that for specific locations clopidogrel was statistically superior to ticagrelor.	The ERG to remove statement from the report

Issue 16 Revision of adverse events to adverse effects

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 27, Section 4.3 – Trial conduct The ERG report states 'There were differences in the .frequencies of some adverse events (AEs) (e.g dyspnoea, ventricular pausing and syncope were more frequent in the ticagrelor arm of the trial)…...'	In order to accurately reflect reporting, 'adverse events' should be revised to 'adverse effects'.	Ventricular pauses are not adverse events reported by investigators and are only detected by Holter monitoring. "Adverse effects" is a more general term which could be used.	The ERG to change the ERG report as suggested

Issue 17 Correction of ventricular pausing to ventricular pauses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 27, Section 4.3 – Trial conduct The ERG report states 'There were differences in the .frequencies of some adverse events (AEs) (e.g. dyspnoea, ventricular pausing and syncope were more frequent in the ticagrelor arm of the trial)…...'	'Ventricular pausing' should be corrected to 'ventricular pauses'	Factual inaccuracy	The ERG to change the ERG report as suggested

Issue 18 Duration of action

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 27, Section 4.3 – Trial conduct The ERG report states that 'in addition short-acting ticagrelor is more vulnerable to underperformance compared with longer-acting clopidogrel' This statement is inaccurate and appears to be based on the opinion of the ERG.	The statement should be deleted.	The statement 'short-acting ticagrelor is more vunerable to underperformance compared with longer-acting clopidogrel; is inaccurate and appears to be based on the opinion of the ERG. Ticagrelor is not a short acting drug. Trough IPA 24 hr after a ticagrelor dose (e.g., if a dose is missed) is similar to trough IPA with clopidogrel taken once daily. There is no disadvantage relative to clopidogrel as a result of missing a dose, especially in light of IPA at 24 hours vs. clopidogrel as per earlier comment (see issue 9).	The ERG will remove the statement

Issue 19 Applicability of the trial results to the UK population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 28, Section 4.2, Applicability to UK and UK clinical practice The ERG question whether or not the results of the trial are fully applicable to the UK population stating that this 'is uncertain because there are no patients in the trial who received clopidogrel for less than 12 months as recommended by NICE' Page 49, Section 4.9.1 The ERG state 'Clinical effectiveness analyses of the PLATO21 data were restricted to patients with 12 months dual antiplatelet treatment.' Both statements are misleading.	Both statements require amending to accurately reflect the fact that clinical effectiveness analyses of the PLATO data were conducted for several lengths dual antiplatelet treatment including durations less than 12 months.	Data on observation periods shorter than 12 months was provided by AstraZeneca. Page 35, figure 2 of the ERG report document cites this data stating that 'the early benefits of ticagrelor compared to clopidogrel are seen within the first 30 days of treatment and that these are maintained across the course of the treatment'.	The protocol-intended treatment period in the PLATO trial was for 12 months

Issue 20 Clarification on absolute rates of stroke and MI

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 29, Section 4.3.1 The ERG note that it is not possible from the data provided in the MS to compare absolute rates of stroke and MI across the two arms of the trial; only time to first event data are	Delete statement	The statement is factually incorrect. The primary endpoint counts time to first event, but the secondary endpoints of MI and stroke count all these events (i.e. multiple events in the same patient) .	The ERG to delete this statement

presented This is not correct.			

Issue 21 Cardiac and non-cardiac causes of death

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 30, Section 4.4 The ERG report states 'Finally, cardiac and non-cardiac causes of death are competing risks; this does not appear to have been addressed by the manufacturer'	Delete or add clarification as to why cardiac or non-cardiac causes of death are considered to be completing risks.	It is unclear as to why cardiac and non-cardiac death are considered to be competing risks	If two different risks exist, then both should be considered. No change will be made to the ERG report

Issue 22 Correction to sample size

Description of problem	Description of proposed amendment	Justification for amendment	
Page 30, Section 4.4 The ERG report states: '*The sample size calculation for the trial was based on an expected primary composite endpoint (death from vascular causes, MI or stroke) with an event rate of 11% in the clopidogrel group and a relative risk reduction of 13.5% for ticagrelor. The ERG considers this to be inappropriate as the definition of the primary endpoint was time to first occurrence of the composite of death*	Paragraph to be deleted	The sample size was based on a test using the logrank statistic and was calculated using a generalization of the Lakatos method (Lakatos E et al 1986, Lakatos E et al 1988). Please see section 5.7.3 of the CSR for more details and references.	The ERG does not question the method of calculating the sample size The ERG considers that as the primary endpoint was defined as time to first occurrence of death from vascular causes, MI or stroke, the sample size should be based on HRs rather than a measure of whether patients had experienced an event or not

from vascular causes, MI or stroke and it would therefore have been more appropriate to use a survival measure such as a hazard ratio rather than a measure of simply whether patients experienced an event or not. ' It is not correct to assume the sample size calculation is inappropriate			

Issue 23 Clarification on endpoints

Description of problem	Description of proposed amendment	Justification for amendment	
Page 31, Section 4.4 The endpoints are currently listed as: *'i. time to first occurrence of any event of the composite of death from vascular causes, MI, or stroke for the subgroup of patients with intent for invasive management at randomisation; the time for first occurrence of any event of the composite of death from any cause*, *MI or stroke'* *'v. the time to first occurrence of stroke; the time for occurrence of all-cause mortality'* These are both incorrect and require amending to fully reflect the hierarchy of endpoints	Points i and v need to be subdivided . The complete pre-specified order of the secondary endpoints should be documented as: i. time to first occurrence of any event of the composite of death from vascular causes, MI, or stroke for the subgroup of patients with intent for invasive management at randomisation ii. the time to first occurrence of any event of the composite of death from any cause, MI or stroke iii. the time for first occurrence of any event of the composite of death from vascular causes, MI. stroke, severe recurrent cardiac ischaemia, recurrent cardiac ischemia, transient ischemic attack or other arterial thrombotic events iv. ~~the time to~~ first occurrence of MI v. ~~the time to~~ first occurrence of stroke	Distinction between the specified endpoints and the hierarchy followed is required.	The ERG to amend accordingly

	vi. ~~the time for~~ occurrence of all-cause mortality		

Issue 24 Treatment comparisons

Description of problem	Description of proposed amendment	Justification for amendment	
Page 31, Section 4.4 The ERG reports states that the treatment comparisons were examined in an exploratory manner but does not specify the order *'These treatment comparisons were examined in an exploratory manner and therefore any results from such comparisons should be treated with caution'*	In order to accurately reflect how the treatment comparisons were performed the text should be amended as follows: *'~~These~~ Treatment comparisons with the first non statistically significant comparison in the hierarchy were examined in an exploratory manner and therefore any results from such comparisons should be treated with caution.'*	The current statement is incorrect in that it implies that none of the tests beyond the primary endpoint would be confirmatory in nature. This is not true since a closed test procedure was used to maintain control overall type I error.	The ERG will amend the ERG report to read *Treatment comparisons starting with the first non statistically significant comparison in the hierarchy*

Issue 25 Correction of table heading

Description of problem	Description of proposed amendment	Justification for amendment	
Page 33, Section 4.5.1, Table 7 The table headings '*No events'* is incorrect.	Heading to be corrected to read: No. patients with events	The numbers in the table are the number of patients with events, not the total number of events.	The ERG will amend the ERG report accordingly

Issue 26 Incorrect table footnote

Description of problem	Description of proposed amendment	Justification for amendment	
Page 33, Section 4.5.1, Table 7 The following footnote to table 7 is incorrect: ** The ERG notes that the sum of the strokes in the ticagrelor arm is equal to 129 (96+23+10), not 125. If 129 is the correct number then the HR would be higher.	The footnote should be deleted	The stroke component was analysed as all of the other time to first event variables. In the case of stroke there were a small number of patients who suffered more than one type of stroke. The HR stated in the table is correct and does not require any clarification by means of a footnote.	The ERG to remove the footnote

Issue 27 Correction of table figures

Description of problem	Description of proposed amendment	Justification for amendment	
Page 40, Section 4.5.3, Table 10 The HR and CI estimates for PLATO-DIABETES stated as: • 0.83(0.74 to 0.93) – with DM and • 0.88(0.76 to 1.03) – without DM are incorrect	Figures should be corrected to • 0.88(0.76 to 1.03) – with DM • 0.83 (0.74-0.93) – without DM	HR and CI estimates are presented incorrectly	The ERG to amend ERG report accordingly

Issue 28 Description of ventricular pauses

Description of problem	Description of proposed amendment	Justification for amendment	
Page 42, Section 4.7 – Safety/adverse events The current ERG statement on increases in ventricular pauses does not specific the duration of ventricular pauses and how these were detected.	The statement should be clarified by the addition of the following underlined text: *'Statistically significantly increased rates are noted in the ticagrelor arm for dyspnoea and ventricular pauses <u>of length greater than or equal to 3 seconds (identified by Holter monitoring during the first week)</u>… to the end of the trial'*	The current sentence does not specify the two types of pauses presented or the asymptomatic nature of the effect. Ventricular pauses were only detected by Holter monitoring and were asymptomatic.	The ERG to amend ERG report accordingly

Issue 29 Description of MIs

Description of problem	Description of proposed amendment	Justification for amendment	
Page 46, Section 4.8 – Differences in MI Assessment The current ERG statement *'In TRITON-TIMI 38 [16] ....., while in PLATO[21] only clinical MIs were included in the primary composite endpoint'* should be amended to reflect that the MIs included were mainly clinical MIs	Change *'only'* to '*mainly*' '	There were a small number of enzymatic MIs included in the analysis of the PLATO study endpoints In TRITON-TIMI 38, almost half of the *"MI"s were purely enzymatic events (triggered for adjudication by lab values only), while in PLATO less than 20% of all MIs were purely enzymatic events' (See AstraZeneca submission document page 62)."*	The ERG to amend ERG report accordingly

Issue 30 Description of ventricular pauses

Description of problem	Description of proposed amendment	Justification for amendment	
Page 49, Section 4.9 The ERG report states:	Sentence to be revised as follows with the underlined text added: *'Statistically significantly increased rates of dyspnoea*	While there were more pauses in general, statistical significance only applies to those greater than or equal to 3 seconds.	The ERG to amend ERG report accordingly

'Statistically significantly increased rates of dyspnoea were noted in the ticagrelor arm, as were increased numbers of patients with ventricular pauses (in the first week of treatment). Clarification is required on the duration of ventricular pauses which were increased and the fact these were identified by Holter monitoring.	*were noted in the ticagrelor arm as were increased numbers of patients with ventricular pauses <u>of length greater than or equal to 3 seconds</u>* <u>identified by Holter monitoring during the first week</u> *(in the first week of treatment).'*	Ventricular pauses were only detected by Holter monitoring and were asymptomatic.	

Issue 31 Provision of AstraZeneca Model

Description of problem	Description of proposed amendment	Justification for amendment	
Page 51, Section 5.3 The ERG comment that a copy of the electronic model comparing ticagrelor with prasugrel was not provided. This is not correct.	Text to be revised to state that a copy of the model has been provided	A copy of the economic model for ticagrelor vs. prasugrel was provided on the same CD as the ticagrelor vs. clopidogrel model. Please contact the AstraZeneca project lead in the event a further copy of the model is required.	The statement will be removed from ERG report

Issue 32 Removal of confidentiality

Description of problem	Description of proposed amendment	Justification for amendment	
Page 57, Section 5.3.7 – Intervention of cost comparators The price of ticagrelor is currently marked up as confidential but is no	Confidentiality restrictions can be removed	The price of ticagrelor is no longer confidential	Thank you

longer confidential			