Dear Nicole,

Thank you for the opportunity to comment on the Assessment Group Report: Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (review of TA182). Please find below our comments which I hope you find helpful.

If you have any further questions please let me know.

Best regards,

AstraZeneca UK Ltd

Summary

AstraZeneca would like to comment on the applicability of the clinical trial data used in the Assessment Group Report in relation to current UK clinical practice of prasugrel treatment with percutaneous coronary intervention for treating acute coronary syndromes.

- Any recommendation for this appraisal should be reflective of the sub-population of the TRITON trial that is the core clinical cohort (e.g. patients who weigh more than 60kg AND are younger than 75 years of age).
- The recently updated SmPC for prasugrel states "In UA/NSTEMI patients, where coronary angiography is performed within 48 hours after admission, the loading dose should only be given at the time of PCI." Data from the most recent UK BCIS Audit (2012) shows that, in UK real world practice, the median delay from first hospital arrival to PCI in NSTEMI patients is 2.6 days (for those who are admitted directly to a PCI centre) or 4.3 days for those who undergo an inter-hospital transfer. Therefore prasugrel use is appropriate in only a minority of UK NSTEMI patients undergoing PCI, and any recommendation from the appraisal should make this clear.
- In NSTEMI patients in the TRITON study, the loading of prasugrel anti-platelet therapy occurred only after the coronary anatomy was known to be suitable for PCI. Therefore the timing of prasugrel loading (as extrapolated from the TRITON trial) is not representative of the current treatment pathways for many patients presenting with NSTEMI/UA and potentially delays the initiation of dual anti-platelet therapy where an earlier diagnosis of NSTEMI/UA has already been made.
- The significant reduction of events with prasugrel treatment observed in the STEMI cohort of the TRITON study was significantly affected by and benefited from a treatment strategy for STEMI which is no longer clinical practice in the UK.
- The use of 300mg clopidogrel dose in the TRITON study, together with the criteria to exclude patients who may have received 'one or more doses of a thienopyridine within 5 days before PCI' and the delay in timing of anti-platelet therapy not only questions the outcomes as already detailed in section 5 of the assessment report but also challenges the generalisability of the study to the UK population and treatment pathways as detailed in Sections 2 and 3 of this response.
- For the STEMI patient population, an alternative cut of the TRITON study should be used to inform the health economic model, so as to make findings more relevant to UK real world practice.

1. Core Clinical Cohort

- Any recommendation for this appraisal should be reflective of the sub-population of the TRITON trial that is the core clinical cohort (e.g. patients who weigh more than 60kg AND are younger than 75 years of age).

The core clinical cohort comprises a subgroup of patients in the TRITON trial for whom prasugrel is licensed and who may be treated with the full recommended dose of prasugrel (60mg loading dose followed by 10mg daily). These patients have no history of stroke or TIA, are younger than 75 years and weigh more than 60kg and this should be factored into the recommendation. Therefore any recommendation for this appraisal needs to be reflective of this core clinical cohort.

2. NSTEMI/UA Population

- The recently updated SmPC for prasugrel states "In NSTEMI/UA patients, where coronary angiography is performed within 48 hours after admission, the loading dose should only be given at the time of PCI." Data from the most recent UK BCIS Audit (2012) shows that, in UK real world practice, the median delay from first hospital arrival to PCI in NSTEMI patients is 2.6 days (for those who are admitted directly to a PCI centre) or 4.3 days for those who undergo an inter-hospital transfer. Therefore prasugrel use is appropriate in only a minority of UK NSTEMI patients undergoing PCI, and any recommendation from the appraisal should be reflective of this point.
- In NSTEMI patients in the TRITON study, the loading of prasugrel anti-platelet therapy occurred only after the coronary anatomy was known to be suitable for PCI. Therefore the timing of prasugrel loading (as extrapolated from the TRITON trial) is not representative of the current treatment pathways for many patients presenting with NSTEMI/UA and potentially delays the initiation of dual anti-platelet therapy where an earlier diagnosis of NSTEMI/UA has already been made.

NSTEMI/UA is an unstable coronary condition prone to ischaemic recurrences and other complications that may lead to death or MI. The diagnosis of NSTEMI is made using a combination of clinical history, symptoms, physical findings, ECG (repeated or continuous ST monitoring), and biomarkers. Risk stratification principles are applied to guide appropriate use and timing of therapy. The invasive strategy (angiography followed, if appropriate, revascularization) has emerged as the dominant strategy in high-risk individuals. One of the key driving forces is the presence of positive biomarkers, indicating the presence of myocardial damage. [1]

Platelet activation and subsequent aggregation play a dominant role in the propagation of arterial thrombosis and consequently are the key therapeutic targets in the management of ACS. According to the ESC guidelines in NSTEMI/UA 'Anti-platelet therapy should be instituted as early as possible when the diagnosis of NSTEMI/UA is made in order to reduce the risk of both acute ischaemic complications and recurrent atherothrombotic events'. [1] In the assessment report the manufacturer reports that 'door to treatment time in the UK is decreasing annually, thereby reducing the opportunity for pre-loading with clopidogrel'. However, the most recent data from the 2012 UK BCIS Audit shows that the median delay from first hospital arrival to PCI in NSTEMI is 2.6 days (for those who are admitted directly to a PCI centre) or 4.3 days for those who undergo an inter-hospital transfer. [2] Furthermore, 34.1% of NSTEMI patients wait more than 96 hours before receiving PCI.

In NSTEMI patients in the TRITON study, the loading of prasugrel anti-platelet therapy occurred only after the coronary anatomy was known to be suitable for PCI.[3,4] Therefore the timing of prasugrel loading (as extrapolated from the TRITON trial) is not representative of the current treatment

pathways for many patients presenting with NSTEMI/UA and potentially delays the initiation of dual anti-platelet therapy where an earlier diagnosis of NSTEMI/UA has already been made.

Furthermore the recently published ACCOAST trial investigated the effect of administering prasugrel at the time of NSTEMI/UA diagnosis rather than after angiography if PCI was indicated. [5] This study demonstrated that when prasugrel was administered at the time of diagnosis (more accurately reflecting UK practice), it did not reduce the rate of major ischaemic events but increased the rates of non CABG TIMI major bleeding and life-threatening bleeding by approximately 3 and 6 fold respectively. The SmPC for prasugrel has since been updated with the following precautionary advice 'Therefore, in UA/NSTEMI patients, where coronary angiography is performed within 48 hours after admission, the loading dose should be given at the time of PCI'. [6]

The licensed use of prasugrel reflects a minority of patients presenting with NSTEMI/UA in England, therefore does not fit the current model of care where $P2Y_{12}$ inhibition is administered as soon as possible after an NSTEMI/UA diagnosis is made; where many patients wait more than two days before receiving PCI (where indicated); and where the earlier use of prasugrel is associated with an higher risk of major bleeding.

3. STEMI Population

- The significant reduction of events with prasugrel treatment observed in the STEMI cohort of the TRITON study was significantly affected by and benefited from a treatment strategy for STEMI which is no longer in clinical practice in the UK.

Increasingly national and international guidelines recommend primary PCI as the preferred reperfusion strategy in patients with STEMI, provided it can be delivered within 120 minutes of the time when fibrinolysis could have been given [7] or 2 hours of the onset of symptoms. [8] Furthermore randomized clinical trials comparing timely primary PCI with in-hospital fibrinolytic therapy have shown that primary PCI is superior to hospital fibrinolysis. However, in settings where primary PCI cannot be performed within 2 hours of symptom onset then fibrinolysis should be considered. 'Rescue' PCI or routine angiography following fibrinolysis could also be considered if indicated.

The ambition to deliver primary PCI as the preferred treatment strategy for STEMI in the UK is now almost complete. The UK BCIS Audit 2012 shows that nearly 97% of the 24,631 patients with a diagnosis of STEMI were managed with a primary PCI strategy. [2] Indeed, 90.1% and 74.5% had door-to-balloon times of <90 and <60 minutes respectively, for direct admission to a Primary PCI centre. Importantly only 3% of STEMI patients in the UK had fibrinolysis followed by rescue PCI. This compares with the 2007 BCIS Audit data (the year that the TRITON trial was published) where 32% of patients received rescue PCI. [2]

The STEMI cohort of the TRITON trial made up 26% of the overall (13,608) trial participants.[4] This population comprised two separate treatment strategies: patients enrolled within 12 hours of symptom onset (primary PCI); and those enrolled between 12 hours and 14 days after symptom onset (defined as secondary PCI). [9] It is unclear as to what is meant by 'secondary PCI' or the delay experienced by this cohort as fibrinolytic pre treatment accounted for only 29% of the secondary PCI population. The latter group accounted for 31% of the total STEMI cohort and may have been more reflective of UK clinical practice at the time. The 'all STEMI' cohort demonstrated a benefit of prasugrel treatment versus clopidogrel (12.4% vs. 10.0%, 2.4% ARR, 21% RRR, P=0.0221) for the primary composite endpoint. [9] However, this clinical benefit was driven by the secondary PCI cohort (14.1% vs. 9.6%, 4.5% ARR, 35% RRR, P=0.0154). The primary PCI cohort demonstrated a non significant difference. We are unaware of any publications that provide primary or secondary PCI information or outcomes data for the NSTEMI population in TRITON.

The significant reduction of events with prasugrel treatment observed in the STEMI cohort of the TRITON study was significantly affected by and benefited from a treatment strategy for STEMI which is no longer in practice in the UK.

4. Clopidogrel Dosing

- The use of 300mg clopidogrel dose in the TRITON study, together with the criteria to exclude patients who may have received 'one or more doses of a thienopyridine within 5 days before PCI' and the delay in timing of anti-platelet therapy not only questions the validity of outcomes as already detailed in section 5 of the assessment report but also challenges the generalisability of the study to the UK population and treatment pathways as detailed in Sections 2 and 3 of this response.

Whilst there may be uncertainly within clinical outcome studies with respect to the appropriate loading and subsequent maintenance dose of clopidogrel for patients with ACS, following a greater understanding of the pharmacokinetics of clopidogrel and appraisal of the latest clinical evidence, the latest guidelines clearly stipulate the following:

- ESC guidelines 2012 - STEMI* 'Loading dose of 600 mg orally, followed by a maintenance dose of 75 mg/day'. [8]
- ESC guidelines 2011 Non STE ACS* - 'A 600-mg loading dose of clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option'. [1]
- NICE 2013 - 'The GDG were aware that a clopidogrel loading dose of 600mg is not licensed in the UK but is used widely in current practice, especially in people undergoing PPCI'[7] - as captured in the assessment report.

* These guidelines made specific reference to the clinical evaluation of OASIS 7 trial used in the assessment report.

The use of 300mg clopidogrel dose in the TRITON study, together with the criteria to exclude patients who may have received 'one or more doses of a thienopyridine within 5 days before PCI' and the delay in timing of anti-platelet therapy not only questions the validity of outcomes as already detailed in section 5 of the assessment report but also challenges the generalisability of the study to the UK population and treatment pathways as detailed in Sections 2 and 3 of this response.

5. Health Economic Critique of the AG Cost effectiveness Model

- For the STEMI patient population, an alternative cut of the TRITON study should be used to inform the health economic model, so as to make findings more relevant to UK real word practice.

For the STEMI, with or without diabetes populations - in line with the above comments relating to clinical-effectiveness, use of the data from the 'core' TRITON clinical cohort is likely to overestimate the benefits of prasugrel vs. clopidogrel in preventing CV events in STEMI patients, relative to what would be achieved in UK real world practice, due to the contribution of patients who underwent secondary or 'rescue' PCI to the overall efficacy outcome observed in STEMI patients in TRITON.[9] Instead, data to inform the model should be restricted to the subset of STEMI patients in TRITON who underwent primary PCI.

References

1) Hamm CW *et al.* ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2011; 32:2999-3054.

2) BCIS National Audit of Percutaneous Coronary Interventional Procedures Public Reports Available at http://www.bcis.org.uk/pages/page_box_contents.asp?pageid=697&navcatid=11

3) Wiviott SD *et al.* Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38). Am Heart J. 2006; 152:627-35.

4) Wiviott SD *et al.* Prasugrel versus clopidogrel in patients with acute coronary syndromes. New Engl J Med. 2007; 357:2001-15.

5) Montelascot G et al. Pretreatment with prasugrel in non ST segment elevation acute coronary syndromes. New Engl J Med. 2013;369:999-1010

6) Summary of Product Characteristics Efient 5 and 10mg tablets. Available from http://www.medicines.org.uk/emc/medicine/21504/SPC

7) NICE Clinical Guideline CG167. Myocardial infarction with ST-segment-elevation (STEMI): Full guideline available http://guidance.nice.org.uk/CG167

8) Steg PG *et al.* ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012; 33:2569-619.

9) Montalescot G *et al*. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet 2009; **373:** 723-731

Abbreviations

ACCOAST	Pretreatment with Prasugrel in Non–ST-Segment Elevation Acute Coronary Syndromes
BCIS	British Cardiovascular Intervention Society
CABG-TIMI	Coronary Artery Bypass -Thrombolysis In Myocardial Infarction
ESC	European Society of Cardiology
NSTEMI	non-ST segment elevation myocardial infarction
STEMI	ST segment elevation myocardial infarction
TRITON	TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel–Thrombolysis In Myocardial Infarction
UA	Unstable Angina