



**Australian Government**

**Department of Health**

Therapeutic Goods Administration

# Australian Public Assessment Report for Ticagrelor

Proprietary Product Name: Brilinta

Sponsor: AstraZeneca Pty Ltd

**June 2017**

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## Common abbreviations

Abbreviation	Meaning
ACS	Acute coronary syndromes
ADP	Adenosine diphosphate
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR-C124910XX	Active metabolite of ticagrelor (formerly AZD6140)
ARR	Absolute risk reduction
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
ATC	Anatomical, Therapeutical, and Chemical
AUC	Area under the plasma concentration-time curve from zero to infinity
AV	Atrioventricular
AZD6140	Former name for ticagrelor
bd	Twice daily
BMI	Body mass index
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CEC	Clinical endpoints committee
CER	Clinical Evaluation Report (CER)
CHD	Coronary heart disease
CI	Confidence interval
CL/F	Apparent clearance
COPD	Chronic obstructive pulmonary disease

Abbreviation	Meaning
CrCL	Creatinine clearance
CSED	Common study end date
CSP	Clinical study protocol
$C_{ss,av}$	Average plasma concentration at steady state
CV	Cardiovascular
CV death	Cardiovascular death
CYP3A	Cytochrome P450 isoenzyme 3A
DME	Designated medical event
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EoS	End of study (visit)
EoT	End of treatment (visit)
EQ-5D	Euro Quality of Life-5 Dimensions
EU	European Union
FAS	Full analysis set
GCP	Good Clinical Practice
GUSTO	<u>G</u> lobal <u>U</u> t ilization of <u>S</u> treptokinase and <u>T</u> issue Plasminogen Activator for <u>O</u> ccluded
HEOR	Health economics outcomes research
HR	Hazard ratio
ICH	International Conference on Harmonisation
IDMC	Independent data monitoring committee
IEC	Independent ethics committee
IPA	Inhibition of platelet aggregation
IRB	Institutional review board

Abbreviation	Meaning
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intention to treat
IVRS	Interactive Voice Response S
IWRS	Interactive Web Response System
JWG	Joint working group
KM	Kaplan-Meier
LS	Least squares
MDRD	Modification of Diet in Renal Disease
MedDRA™	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
NSAID	Non-steroidal anti-inflammatory drug
NSTEMI	Non-ST elevation myocardial infarction
od	Once daily
P-gp	P-glycoprotein
P2Y <sub>12</sub>	A subtype of receptor found on platelets
PAR-1	Protease-activated receptor-1
PCI	Percutaneous coronary intervention
PD	Pharmacodynamics
PEGASUS	AstraZeneca Study D5132C00001: <u>Pr</u> Evention with Tica <u>G</u> relor of <u>Sec</u> ond <u>A</u> ry Thrombotic Events in High-Ri <u>S</u> k Patients with Prior Acute Coronary Syndrome - TIMI Study Group.
PK	Pharmacokinetic
PLATO	AstraZeneca Study D5130C5262: A study of <u>PLA</u> T <u>et</u> inhibition and Patient <u>O</u> tcomes
PRU	P2Y <sub>12</sub> reaction units as assessed using the VerifyNow™ assay
PT	Preferred term
RMP	Risk management plan

Abbreviation	Meaning
RRR	Relative risk reduction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SMQ	Standardised MedDRA queries
SOC	System organ class
STEMI	ST-segment elevated myocardial infarction
TIA	Transient ischaemic attack
TIMI	<u>Thrombolysis In Myocardial Infarction</u> . A cardiology clinical trials study group
UA	Unstable angina
UK	United Kingdom
US	United States

# I. Introduction to product submission

## Submission details

<i>Type of submission:</i>	New indication and new strength
<i>Decision:</i>	Rejected
<i>Date of decision:</i>	25 October 2016
<i>Date of entry onto ARTG</i>	Not applicable
<i>Active ingredient(s):</i>	Ticagrelor
<i>Product name(s):</i>	Brilinta
<i>Sponsor's name and address:</i>	AstraZeneca Pty Ltd 66 Talavera Road, Macquarie Park, NSW 2113
<i>Dose form(s):</i>	Film-coated tablets
<i>Strength(s):</i>	60 mg (new strength), 90 mg (extension of indication)
<i>Container(s):</i>	Blister pack
<i>Pack size(s):</i>	14 and 56 tablets
<i>Approved therapeutic use:</i>	Not applicable
<i>Route(s) of administration:</i>	Oral (PO)
<i>Dosage:</i>	Not applicable
<i>ARTG number (s):</i>	167237

## Product background

This AusPAR describes the application by the sponsor, AstraZeneca Pty Ltd, proposing to:

1. Extend the indications of Brilinta (ticagrelor) to include patients with a history of myocardial infarction at least one year previously and a high risk of developing a atherothrombotic events
2. Register a new 60 mg ticagrelor tablet blister packs containing 14 (sample) and 56 tablets with the same trade name Brilinta.

The same sponsor currently has 90 mg ticagrelor in blister packs of 14 (sample) and 56 tablets registered under the trade name Brilinta.

The sponsor has submitted Study D5132C00001 (Pegasus) to comply with a specific condition of registration for ticagrelor. The sponsor seeks to extend the indication of ticagrelor (Brilinta) based on additional information from this study.

The currently approved indications are (abridged, see PI for full indications):

*Brilinta, in combination with aspirin, is indicated for the prevention of atherothrombotic events (cardiovascular death, myocardial infarction and stroke) in adult patients with acute*



coronary syndromes (unstable angina [UA], non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

The sponsor has proposed the following extension of indications:

*Brilinta, in combination with aspirin, is indicated for the prevention of atherothrombotic events (cardiovascular death, myocardial infarction and stroke):*

- *in patients with acute coronary syndromes (unstable angina [UA], non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG) (refer to Dosage and Administration).*
- *in patients with a history of myocardial infarction (MI occurred at least one year ago) and a high risk of developing a atherothrombotic events (refer to Dosage and Administration).*

Ticagrelor is a non-thienopyridine, reversible inhibitor of adenosine diphosphate (ADP) receptors (P2Y<sub>12</sub>) on platelets. Activated platelets release ADP which binds to ADP platelet receptors causing activation of intracellular glycoprotein IIb/IIIa complex which triggers platelet adherence and aggregation. The aggregation of platelets plays an important role in the growth of atheromatous plaques, potentially leading to arterial occlusion. Ticagrelor does not require metabolic activation for its antiplatelet effects. It is metabolised by cytochrome P450 isozyme CYP3A4 which forms an active metabolite, also a CYP3A4 substrate.

It is in the same class as prasugrel and clopidogrel, but unlike these two agents, the action of ticagrelor is reversible. Platelet transfusion has been proposed to reverse antiplatelet drugs. An in vitro study showed this not to be the case<sup>1</sup> however a study in healthy volunteers and patients with coronary artery disease is underway.

Ticagrelor has a low solubility in aqueous buffers of physiological pH but is soluble in human intestinal fluid, presumably due to solubilisation in mixed micelles of bile salts and phospholipids.

The currently approved dosage regimen is as follows (abridged, see PI for full details):

*In patients with Acute Coronary Syndromes, Brilinta treatment should be initiated with a single 180 mg loading dose (two tablets of 90 mg) and then continued at 90 mg twice daily. Treatment is recommended for at least 12 months unless discontinuation of Brilinta is clinically indicated.*

In addition to the above, the sponsor has proposed the following:

*In patients with a history of Myocardial Infarction (MI occurred at least one year ago) no loading dose of Brilinta is required and the recommended dose is 60 mg twice daily. Long-term treatment is recommended unless discontinuation of Brilinta is clinically indicated.*

*Patients taking Brilinta should take ASA daily unless specifically contraindicated. Following an initial dose of ASA, Brilinta should be used with a recommended maintenance dose of ASA 100 mg daily. If required, the ASA maintenance dose may vary from 75-150 mg according to clinical need.*

<sup>1</sup> Martin AC, Berndt C, Calmette L et al The effectiveness of platelet supplementation for the reversal of ticagrelor-induced inhibition of platelet aggregation : an in-vitro study Eur J Anaesthesiol 2015 Sep 8 [Epub ahead of print]

*Patients may start treatment with Brilinta 60 mg, regardless of their previous anti-platelet regimen, and irrespective if there has been a lapse in therapy or not. Patients should discontinue their current anti-platelet therapy before initiating Brilinta with low dose ASA at the next scheduled dose.*

## Regulatory status

Ticagrelor was first approved in Australia on 9 June 2011 (AUST R 167237).

An extension of indication similar to that proposed in the submission had been requested in Canada, the European Union (EU), Switzerland and the USA.

In the USA an extension of indication was approved on 3 September 2015 and the approved indication is:

*Brilinta is a P2Y12 platelet inhibitor indicated to reduce the rate of cardiovascular death, myocardial infarction and stroke in patient with acute coronary syndrome (ACS) or a history of myocardial infarction (MI). For at least the first 12 months following ACS it is superior to clopidogrel. Brilinta also reduces the rate of stent thrombosis in patient show have been stented for treatment of ACS.*

In the EU an extension of indication was approved on 18 February 2016 and the approved indication is:

*Brilique, coadministered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with*

- *Acute coronary syndromes (ACS) or*
- *A history of myocardial infarction (MI) and a high risk of developing atherothrombotic event.*

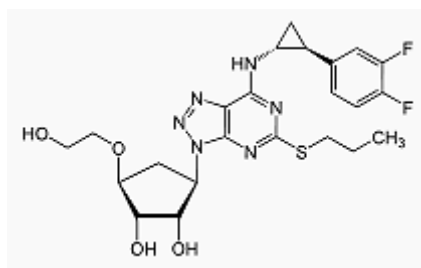
## Product information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

## II. Quality findings

### Drug substance (active ingredient)

No changes have been proposed to aspects of the drug substance. The chemistry, manufacture, quality control and stability of the drug substance are the same as previously approved for ticagrelor 90 mg tablets. The chemical structure of ticagrelor is shown in Figure 1.

**Figure 1: Chemical structure of ticagrelor**

## Drug product

The proposed 60 mg tablets are immediate release film-coated tablets. The cores are made using the same wet granulation process as used for the registered 90 mg tablets and dried, milled, lubricated compressed and coated in the same way. The proposed tablets are packed in Polyvinyl chloride (PVC)/ polyvinylidene chloride (PVDC) blister packs containing 14 (sample packs) and 56 tablets. These are the same pack sizes as the registered 90 mg presentations.

The proposed 60 mg tablet appearance is below:

- Round, biconvex, pink, film-coated tablets, marked with '60' directly above 'T' on one side and plain on reverse

These are distinguishable from the already registered 90 mg tablets which are round, biconvex, yellow film-coated tablets and debossed with the strength '90' without the units on one side and 'T' on the other.

The proposed tablet cores are direct scales of the already registered 90 mg tablet cores. The proposed 60 mg tablet cores are made using the same granule as the registered 90 mg tablets cores. The film-coat utilised for the 90 mg and 60 mg tablets have a similar qualitative composition with the exception of the use of different ferric oxides and talc to provide colour differentiation. The only differences between the different ticagrelor tablets relate to tablet compression weight, tablet debossing and the composition (opacifier and colour) of the non-functional coat.

The proposed tablets contain, apart from ticagrelor, mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate and purified water. The purified water used is removed during the manufacturing process.

The finished product is appropriately controlled using the finished product specifications. The specifications include acceptable tests and limits for appearance, identity, assay, dissolution, related substances, uniformity of dosage units and microbial limits.

A shelf-life of 36 months when stored below 30 °C is recommended for the proposed drug product.

## Biopharmaceutics

No studies were provided.

## Quality summary and conclusions

Registration of the product with respect to chemistry and quality control is recommended.

## III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

## IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

### Introduction

#### Clinical rationale

The sponsor's Clinical Overview included the following rationale for the development of ticagrelor for the proposed indication.

*The continued risk of further CV events in the years following an initial MI represents an unmet need that may be addressed by establishing the optimal duration and combination of antiplatelet therapy with a positive benefit-risk profile. The rationale for investigating ticagrelor in this setting was based on a hypothesis supported by the mechanism of action of ticagrelor, and by the results of the post-hoc analysis of the CHARISMA study with clopidogrel and the PLATO study with ticagrelor. The results of these studies suggest that extended dual antiplatelet therapy targeted to a high-risk population with prior MI may provide clinical benefit. In addition, the more recent studies, TRA2°P-TIMI 50 with the PAR-1 antagonist vorapaxar, and the Dual Antiplatelet Therapy study (the 'DAPT study') provide further support to the hypothesis that intensive antiplatelet therapy over a longer period of time may be beneficial, although the populations studied and the study designs are quite different.*

The sponsor's rationale for the proposed extension of indication is acceptable. Secondary prevention with dual anti-platelet therapy is currently recommended for 1 year following acute coronary syndromes, but the effect of longer-term dual therapy in preventing atherothrombotic events is unclear.<sup>2</sup> The Heart Foundation of Australia guidelines recommend dual anti-platelet therapy with low dose aspirin and a P2Y<sub>12</sub> inhibitor for up to 1 year after a MI (and other acute coronary syndromes).<sup>3</sup> The guidelines also recommend low dose aspirin (75 to 100 mg/day), unless contraindicated, for long-term pharmacological antiplatelet management of all patients with coronary heart disease (CHD), and suggest that clopidogrel be considered in combination with aspirin in patients who have recurrent cardiac ischaemic events. However, clopidogrel is not approved for secondary prevention for patients who have experienced a MI at least 1 year previously and are at high-risk of atherothrombotic events.

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<sup>2</sup> Keaney JF. Balancing the risk of and benefits of dual antiplatelet therapy (editorial). *N Engl J Med* 2015; 372:19: 1854-55.

<sup>3</sup> National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Reducing risk in heart disease: an expert guide to clinical practice for secondary prevention of coronary heart disease. Melbourne: National Heart Foundation of Australia, 2012

## Guidance

The TGA adopted EU guidelines of direct relevance for this submission are:

- CPMP/EWP/570/98 Points to Consider on the Clinical Investigation of New Medicinal Products in the Treatment of Acute Coronary Syndrome (ACS) Without Persistent ST-Segment Elevation.
- EMEA/CHMP/EWP/311890/2007 Guideline on the Evaluation of Medicinal Products for Cardiovascular Disease Prevention.

## Contents of the clinical dossier

### *Scope of the clinical dossier*

The relevant clinical information provided in the dossier is summarised below:

- 1 pivotal Phase III efficacy and safety study in adult subjects supporting the proposed extension of indication and errata list (PEGASUS TIMI-54).
- 1 population pharmacokinetic (PPK) study based on the data from PEGASUS (Study D5132C00001).
- 1 pharmacodynamic (PD) Phase IV study to assess the anti-platelet effects of ticagrelor versus clopidogrel in patients with coronary artery disease (CAD) who self-identify as Hispanic.

## Paediatric data

No paediatric data were submitted supporting the proposed extension of indication. The sponsor indicated that it had not submitted paediatric data for the proposed indication to either the EU or the USA regulatory authorities. The sponsor indicated that it did not have an agreed Paediatric Investigation Plan (EU) or an agreed Pediatric Plan with the Food and Drug Administration (FDA) under the relevant USA legislation.

The absence of paediatric data is acceptable. The proposed extension is considered to be not relevant to children and adolescents. The FDA's letter to AstraZeneca of 3 September 2015, indicates that it has waived the paediatric study requirement for the application *because necessary studies are impossible or highly impractical because [ACS] rarely occur in the pediatric population. Furthermore, the pathophysiology of [ACS] in children is generally different from its adult counterpart.*

## Good clinical practice

The sponsor stated that its 'procedures, internal quality control measures, and audit programmes provide reassurance that the clinical study programme was carried out in accordance with Good Clinical Practice (GCP), as documented by the International Conference on Harmonisation (ICH)'.

## Pharmacokinetics

### Studies providing pharmacokinetic data

One new population pharmacokinetic (PPK) study (D5132C00001) was submitted. The PPK study also included an exploratory graphical exposure-response analysis relating to both safety and efficacy (PK/PD analysis).

### Evaluator's conclusions on pharmacokinetics

The new PPK study provided both PPK data and exploratory exposure-response data following ticagrelor 60 mg twice a day (BD) and 90 mg BD in the proposed patient population (PEGASUS).

The PPK of ticagrelor and its active metabolite AR-C124910XX were adequately described by one-compartment disposition models with first-order absorption (ticagrelor), formation (AR-C124910XX) and elimination. The sponsor comments that the PK parameter estimates for ticagrelor reported in the new PPK analysis based on data from PEGASUS were generally similar to those reported in the previous PPK analysis based on data from DISPERSE2/PLATO.

The 5 individual covariates identified to have a statistically significant impact on the clearance (CL/F) of ticagrelor and AR-C124910XX were body weight, age, Japanese ethnicity, female sex and current smoking. The covariate effects were qualitatively the same for the CL/F of both ticagrelor and AR-C124910XX, but were generally more pronounced for AR-C124910XX.

In summary the covariate effects were for CL/F that it

- increased with increasing body weight,
- decreased with increasing age,
- was lower in Japanese patients compared to non-Japanese patients,
- was lower in females compared to males; and
- was higher in current smokers compared to non-smokers.

The analysis of Black race on CL/F did not meet the pre-defined statistical significance criterion ( $p < 0.001$ ), and was excluded in the backwards elimination step of the stepwise covariate model building procedure. However, the sponsor comments that patients of Black race have previously been described to have generally higher CL/F<sub>ticagrelor</sub> values than patients of non-Black race (PPK analysis based on DISPERSE2/PLATO).

No exposure-response relationships were demonstrated for ticagrelor exposure (plasma concentration at steady state ( $C_{ss,av}$ )) versus cardiovascular (CV) Death/MI/Stroke (efficacy outcome), or for ticagrelor exposure ( $C_{ss,av}$ ) versus TIMI<sup>4</sup> Major Bleeding (safety outcome). The sponsor considered that a trend towards an exposure-response relationship for TIMI Major Bleeding<sup>5</sup> was observed, with patients in the lower drug exposure range having a slightly lower risk of event compared to patients in the higher drug exposure range. However, based on Kaplan-Meier estimates of patients without TIMI Major Bleeding events, stratified by exposure to ticagrelor and to ticagrelor plus AR-C124910XX versus time after first dose (days), the observed trend is considered to be clinically insignificant. There was a large overlap in ticagrelor exposure in patients with and without both efficacy and safety endpoint events. The sponsor comments that the exploratory graphical exposure-response analyses had some weaknesses and should be interpreted with caution. One issue with the graphical analysis is that it does not control for the distribution of risk factors. It is possible that certain risk factors are correlated with exposure. Without appropriately accounting for such risk factors false exposure-response relationships might be identified or actual true exposure-response relationships might be hidden. A full non-linear mixed effect modelling approach including risk factor assessment based on the placebo cohort could offer a better possibility for an unbiased assessment of the exposure-response relationship.

<sup>4</sup> Thrombolysis In Myocardial Infarction – A cardiology clinical trials study group.

<sup>5</sup> TIMI Major bleeding events: Fatal bleeding directly leading to death within 7 days; Intracranial haemorrhage; Other major bleeding – drop in haemoglobin of  $\geq 5$  g/dL, or a fall in haematocrit of  $\geq 15\%$ .

There were no clinical biopharmaceutical studies comparing the bioequivalence of the proposed ticagrelor 60 mg tablet strength and the approved ticagrelor 90 mg tablet strength. The sponsor submitted an acceptable justification for not submitting such studies.

## **Pharmacodynamics**

### **Studies providing pharmacodynamic data**

The submission included 1 new PD study assessing the antiplatelet effects of ticagrelor versus clopidogrel in Hispanic patients with stable coronary artery disease (CAD) based on P2Y12 inhibition assessed using mean PRU measured by VerifyNow™ (D5130L000120). The study was undertaken in the USA (6 centres). The first patient was enrolled on 17 April 2012, the last patient visit was on 10 May 2013 and the study report was dated 1 April 2014 (Final Version v2.1).

### **Evaluator's conclusions on pharmacodynamics**

In this study, P2Y12 inhibition was statistically significantly greater at 2 hours following the loading dose in the ticagrelor group than in the clopidogrel group (primary PD outcome), and at 0.5 and 8 hours following the loading dose in the ticagrelor group compared to the clopidogrel group (secondary PD outcomes). In addition, P2Y12 inhibition was statistically greater on Day 7 at 2 hours and 8 hours following multiple doses in the ticagrelor group than in the clopidogrel group, as was P2Y12 inhibition at the end of the dosing interval on Day 8 after multiple doses (secondary PD outcomes). The effects of ticagrelor on platelet function in Hispanic patients were stated by the sponsor to be consistent with the effects in non-Hispanic patients.

### **Dosage selection for the pivotal studies**

The sponsor indicated that ticagrelor 90 mg BD was selected based on available data from clinical studies showing that this dose was well tolerated and demonstrated high and consistent levels of inhibition of platelet aggregation (IPA). In PLATO, ticagrelor 90 mg BD reduced major CV events by 16%, CV mortality by 21% and all-cause mortality by 22% compared to clopidogrel 75 mg one a day (QD) in ACS patients also taking Acetylsalicylic acid (ASA) and treated with dual antiplatelet therapy for up to 12 months. Total major bleeding, fatal and fatal/life-threatening bleeding all occurred in a similar proportion of patients in the ticagrelor and clopidogrel groups. However, minor bleeding and non-procedural major bleeding occurred more frequently in patients in the ticagrelor group compared to the clopidogrel group. Overall, the benefit-risk balance for ticagrelor 90 mg BD in combination with ASA was favourable in ACS patients. Consequently, ticagrelor 90 mg BD in combination with ASA was considered to be an appropriate dose for study in stable patients with CAD 1 to 3 years following their most recent MI.

Ticagrelor 60 mg BD in combination with ASA had not been specifically tested in clinical studies prior to PEGASUS. However, since the optimal intensity of platelet inhibition for long-term therapy in CAD is unknown, it was postulated that having outcome data for 2 doses of ticagrelor may allow tailoring of dosing to optimise the benefit-risk benefit ratio in the proposed patient population. The sponsor commented that although the risk of recurrent thrombotic events following an MI persists over time it is higher in the first year post-MI. Consequently, the sponsor postulated that a lower intensity of platelet inhibition than utilised in the ACS setting may be sufficient to prevent major CV events during chronic therapy with ticagrelor.

Based on PK and PD modelling of IPA response and clinical findings in DISPERSE, the 60 mg BD dose of ticagrelor was expected to provide less platelet inhibition than the 90 mg BD dose, but greater mean platelet inhibition and less variability than clopidogrel 75 mg QD daily, with a favourable benefit-risk balance. Ticagrelor doses lower than 60 mg BD were also considered, but modelling predicted that ticagrelor 45 mg BD would not generate a sustained IPA level greater than clopidogrel 75 mg. Furthermore, intra-individual variability in IPA of ticagrelor would be 2 to 3 times greater with 45 mg BD than with 90 mg BD as this PK parameter increases with decreasing ticagrelor dose. Doses higher than 90 mg BD were not considered as this dose has near maximal impact on IPA and efficacy.

Treatment duration of a minimum of 12 months was selected with the goal of demonstrating long-term efficacy and safety. Ticagrelor or placebo were administered on a background of ASA therapy, since ASA is standard therapy for prevention of atherothrombotic events and new therapies are likely to be administered in combination with ASA. The ASA dose of 75 mg to 150 mg once daily was recommended based on clinical trial evidence that higher doses confer no additional antithrombotic protection, but increase the risk of bleeding.<sup>3</sup>

The selection of ticagrelor 90 mg BD and 60 mg BD in combination with low dose ASA for long-term treatment of the proposed population is considered to be acceptable.

## Efficacy

### Studies providing efficacy data

One pivotal efficacy study was submitted: *PEGASUS: A Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, Multinational Trial, to Assess the Prevention of Thrombotic Events with Ticagrelor Compared to Placebo on a Background of Acetyl Salicylic Acid (ASA) Therapy in Patients with History of Myocardial Infarction.*

### Evaluator's conclusions on efficacy

The study demonstrated that both doses of ticagrelor (90 mg BD and 60 mg BD), given in combination with low-dose ASA, reduced the risk of experiencing a primary composite efficacy endpoint event (CV death/MI/stroke) compared to low dose ASA alone in patients with a history of MI (1 to 3 years prior to randomisation) and at high-risk of an atherothrombotic event.

Primary composite efficacy endpoint events (CSED) were reported for 493, 487, and 578 patients on ticagrelor 90 mg, ticagrelor 60 mg, and placebo, respectively, corresponding to Kaplan Meier (KM) percentages at 36 months of 7.8%, 7.8%, and 9.0%: relative risk reduction (RRR) = 15%, hazard ratio (HR) = 0.85 (95% confidence interval (CI): 0.75, 0.96),  $p=0.0080$  for ticagrelor 90 mg relative to placebo; and RRR = 16%, HR = 0.84 (95% CI 0.74, 0.95),  $p=0.0043$  for ticagrelor 60 mg relative to placebo. The higher dose of ticagrelor provided no clinically meaningful increase in efficacy compared to the lower dose of ticagrelor, with the absolute risk reduction for both ticagrelor plus ASA dosage regimens relative to ASA being 1.2%.

The KM plots for the primary composite endpoint for both ticagrelor doses separated from placebo shortly after randomisation and continued to separate throughout the study. The superior treatment effect of both doses of ticagrelor compared to placebo was consistent throughout the study, with a median duration of 33 months to CSED (maximum duration of up to 47 months) for each of the three treatment groups. In an exploratory landmark analysis, the RRR was similar from 1 to 360 days for both ticagrelor 90 mg BD relative to placebo and ticagrelor 60 mg BD relative to placebo (13% and 17% respectively) and from



361 days and onwards (16% for both doses). The results indicate that there was no apparent diminution in effect of either ticagrelor dose relative to placebo through end of treatment.

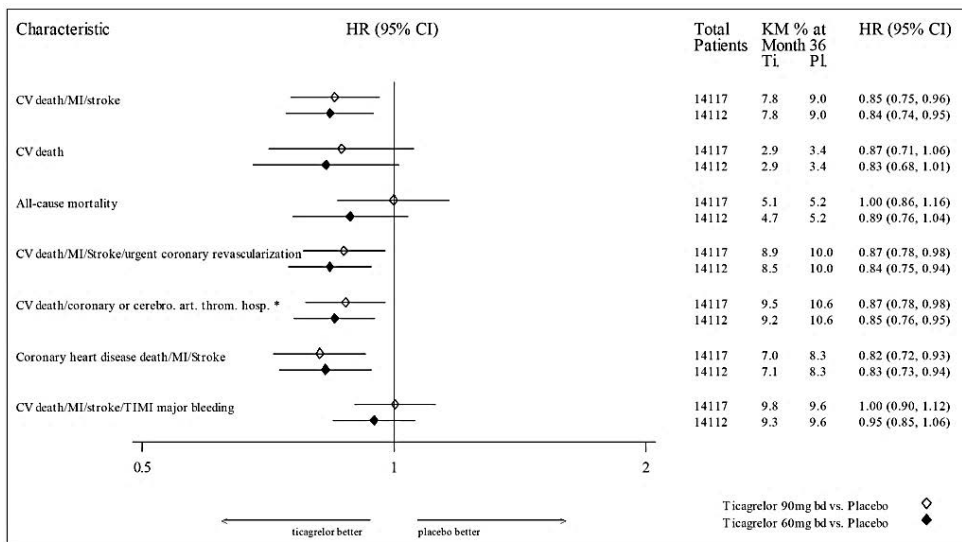
The KM percentages at 36 months numerically favoured ticagrelor (both doses) compared to placebo for each of the three individual components of the composite event. The nominally statistically significant individual events for the ticagrelor versus placebo pairwise comparisons were MI for both ticagrelor 90 mg BD and 60 mg BD dose groups and stroke for the ticagrelor 60 mg BD dose group.

The confirmatory hierarchical analysis of the primary and secondary endpoints failed to show that the observed differences between both doses of ticagrelor (90 mg BD and 60 mg BD) and placebo for the first secondary efficacy endpoint of CV death. Consequently, formal statistical of the second efficacy endpoint of all-cause mortality did not proceed.

There were a number of exploratory efficacy endpoints (including subgroup analyses) and these consistently showed a numerical advantage for both doses of ticagrelor compared to placebo.

The HRs for the primary, secondary and other efficacy endpoints of interest are summarised in Figure 2.

**Figure 2: PEGASUS - Hazard ratios and rates for primary, secondary, and other efficacy endpoints; FAS**



Source: Figure 11.2.15  
 CV death/coronary or cerebrovascular arterial thrombosis hospitalisation.  
 CI Confidence interval; HR Hazard ratio; KM Kaplan-Meier; MI Myocardial infarction; PL Placebo; Ti Ticagrelor; TIMI Thrombolysis In Myocardial Infarction.

## Safety

### Studies providing safety data

The relevant safety data for the proposed ticagrelor dosing regimen for the proposed indication were provided by the pivotal Phase III study (PEGASUS). The safety objective of PEGASUS was to assess the safety and tolerability of long-term therapy with ticagrelor compared to placebo on a background of ASA in patients with history of MI and high risk of developing atherothrombotic events. The overall safety focus in the study was: (1) time to first TIMI Major bleeding event following the first dose of study drug, as well as time to first TIMI Major or Minor bleeding event and time to first PLATO Major bleeding event; (2)

time to discontinuation of study drug due to any bleeding event; and (3) evaluation of adverse events (AEs).

### Patient exposure

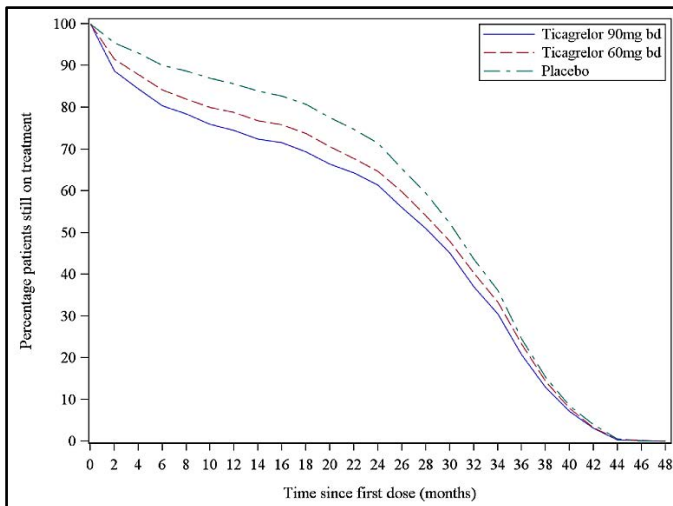
A total of 20942 patients (99.0% of randomised patients) received at least 1 dose of randomised study drug, including 6988 patients in the ticagrelor 90 mg group, 6958 patients in the ticagrelor 60 mg group, and 6996 patients in the placebo group.

For the ticagrelor 90 mg, ticagrelor 60 mg, and placebo groups, mean  $\pm$  standard deviation (SD) *total duration of exposure to study drug* from first to last dose in months was  $23.9 \pm 13.7$  (range: 0.3, 48.0),  $25.3 \pm 13.1$  (range: 0.03, 47.4), and  $27.3 \pm 11.6$  (range: 0.03, 47.4), respectively, and median total duration of exposure was 28.3, 29.4, and 30.4 months, respectively. Total treatment years were 13936, 14663, and 15939, respectively.

For the ticagrelor 90 mg, ticagrelor 60 mg, and placebo groups, mean  $\pm$  SD *actual duration of exposure to study drug*, defined as total exposure excluding prescribed temporary interruptions, in months was  $23.5 \pm 13.6$  (range: 0.3, 47.9),  $24.9 \pm 13.1$  (0.03, 47.4), and  $27.0 \pm 11.6$  (range: 0.03, 47.4), respectively, and median total duration of exposure was 27.8, 28.9, and 30.1 months, respectively. Total actual treatment years were 13710, 14440, and 15766, respectively.

The percentage of patients still on treatment over time is presented in Figure 3. The total exposure time for patients in the ticagrelor groups was shorter than in the placebo group due to the higher rates of discontinuation in the two ticagrelor groups. Cumulative exposure to the study drug is summarised below in Table 1.

**Figure 3: PEGASUS - Percentage of patient still on treatment over time; safety analysis**



At a given time, the curve shows the percentage with exposure time >1.

**Table 1: PEGASUS - Cumulative exposure over time; safety analysis set**

Time on Study drug <sup>a</sup>	Number(%) of patients		
	Ticagrelor 90 mg bd (N=6988)	Ticagrelor 60 mg bd (N=6958)	Placebo (N=6996)
0 days	6988 ( 100%)	6958 ( 100%)	6996 ( 100%)
1 day	6988 ( 100%)	6958 ( 100%)	6996 ( 100%)
30 days	6434 (92.1%)	6527 (93.8%)	6799 (97.2%)
4 months	5899 (84.4%)	6110 (87.8%)	6505 (93.0%)
8 months	5476 (78.4%)	5705 (82.0%)	6204 (88.7%)
12 months	5203 (74.5%)	5481 (78.8%)	5992 (85.6%)
18 months	4842 (69.3%)	5126 (73.7%)	5643 (80.7%)
24 months	4291 (61.4%)	4505 (64.7%)	4996 (71.4%)
30 months	3142 (45.0%)	3328 (47.8%)	3653 (52.2%)
36 months	1445 (20.7%)	1620 (23.3%)	1716 (24.5%)
42 months	216 ( 3.1%)	222 ( 3.2%)	270 ( 3.9%)

a. Number of patients on treatment at the start of the interval.

### Postmarketing data

No post-marketing experience is available for the proposed indication.

### Evaluator's conclusions on safety

The safety profile of patients treated with ticagrelor 90 mg BD and 60 mg BD in combination with ASA (that is, ticagrelor groups) was inferior to that of patients treated with ASA alone (that is, placebo group). Furthermore, the safety profile of ticagrelor 90 mg BD in combination with ASA was inferior to that ticagrelor 60 mg BD in combination with ASA.

The safety of ticagrelor compared to placebo for the proposed indication was assessed in 6988 patients in the ticagrelor 90 mg group, 6958 patients in the ticagrelor 60 mg group, and 6996 patients in the placebo group. Based on the 'rule of threes', it can be estimated that adverse drug reactions to ticagrelor with an incidence of 1 in 4,655 patients would likely to have been detected in the 13,946 patients treated with the drug.

In the ticagrelor 90 mg, ticagrelor 60 mg, and placebo groups, the mean±SD total duration of exposure to the study drug was 23.9±13.7 (range: 0.3, 48.0), 25.3±13.1 (0.03, 47.4), and 27.3±11.6 (range: 0.03, 47.4) months, respectively, and the median total duration of exposure was 28.3, 29.4, and 30.4 months, respectively. Actual exposure to the study drugs was marginally lower than total exposure in the three treatment groups due to temporary treatment interruptions.

Patients in the ticagrelor groups were at a greater risk of experiencing TIMI major bleeding events (fatal, intracerebral haemorrhage (ICH), or 'Other') than patients in the placebo group. The majority of TIMI major bleeding events were categorised as 'Other' major haemorrhages, rather than either intracranial or fatal haemorrhages. Intracranial haemorrhages occurred in a smaller proportion of patients in each of the three treatment groups than 'Other' major haemorrhages, and more commonly in the two ticagrelor groups than in the placebo group. Fatal haemorrhages were reported in a smaller proportion of patients in each of the three treatment groups than either 'Other' or ICHs, with the frequency of fatal haemorrhages being similar across the three treatment groups.

The risk of TIMI major bleeding events was greater in patients in both ticagrelor groups than in the placebo group, and in the higher compared to the lower dose ticagrelor group. TIMI major bleeding events were reported in 127, 115, and 54 patients in the ticagrelor 90 mg, ticagrelor 60 mg, and placebo groups, respectively, corresponding to KM percentages

at 36 months of 2.6%, 2.3%, and 1.1%: HR = 2.69 (95% CI: 1.96, 3.70),  $p < 0.0001$  for ticagrelor 90 mg relative to placebo; and HR = 2.32 (95% CI: 1.68, 3.21),  $p < 0.0001$  for ticagrelor 60 mg relative to placebo. The absolute difference in TIMI major bleeding events based on the KM percentages at 36 months between the ticagrelor 90 mg and placebo groups was 1.5%, and between the ticagrelor 60 mg and placebo groups was 1.2%.

For further details on TIMI bleeding events, AEs, SAEs and discontinuations of treatment please see Attachment 1 (*Evaluator's conclusion on safety* (Attachment 1) and the *First round assessment of risks* and *Overall conclusion and benefit-risk assessment, Safety* below.

In addition to bleeding events and dyspnoea known to be associated with ticagrelor, gout and hyperuricaemia have also been reported to be associated with ticagrelor and these events occurred in a greater proportion of patients in both ticagrelor groups than in the placebo group. However, bradyarrhythmias and renal-related AEs, which have also been reported with an increased incidence in ticagrelor treated patients, occurred in a similar proportion of patients in the three treatment groups. In addition, no particular safety concerns with ticagrelor relative to placebo were identified in the analysis of designated medical events (on-treatment), with all events occurring with a frequency of  $\leq 1.0\%$  in each of the three treatment groups and with a similar frequency across the groups.

## First round benefit-risk assessment

The sponsor proposes that ticagrelor 60 mg BD co-administered with ASA be approved for treatment of the proposed patient population. The sponsor is not seeking approval of ticagrelor 90 mg BD co-administered with ASA for the proposed extension of indication. The sponsor comments that although the efficacy profiles of ticagrelor 90 mg and 60 mg were similar, there is evidence that the lower dose has a better safety profile in relation to the risk of bleeding and dyspnoea. Consequently, as ticagrelor 90 mg BD in combination with ASA is not being proposed for approval the benefit-risk assessment relates only to ticagrelor 60 mg BD in combination with ASA for the proposed usage.

### First round assessment of benefits

In the pivotal study (PEGASUS), ticagrelor 60 mg compared to placebo demonstrated a statistically significant reduction in the risk of experiencing a composite cardiovascular efficacy endpoint event of CV death, MI or stroke in the proposed patient population ( $p=0.0043$ ). The reduction in risk for each of the components of the composite endpoint was numerically greater in the ticagrelor 60 mg group than in placebo group.

Composite efficacy endpoint events at the CSED were reported for 487 and 578 patients on ticagrelor 60 mg and placebo, respectively, corresponding to KM percentages at 36 months of 7.8%, and 9.0%, respectively: that is, RRR = 16%; HR = 0.84 (95% CI 0.74, 0.95),  $p=0.0043$ . The absolute risk reduction (ARR) for ticagrelor compared to placebo was 1.2%, based on KM percentages at 36 months.

In an exploratory 'landmark' analysis of the composite primary efficacy endpoint, the RRR for ticagrelor 60 mg compared to placebo was similar from 1 to 360 days (17%) and from 361 days and onwards (16%), suggesting no diminution of treatment effect over time through end of treatment.

The majority of composite first events in both the ticagrelor 60 mg and placebo groups were MIs (58.1% versus 58.0%, respectively), followed by CV deaths (23.8% versus 22.1%, respectively) and strokes (18.1% versus 19.9%, respectively). The KM percentages at 3 years for ticagrelor 60 mg versus placebo, respectively were 4.5% versus 5.2% for MI, 2.9% versus 3.4% for CV death, and 1.5% versus 1.9% for stroke. Based on KM percentages at 36 months, the absolute risk reduction due to ticagrelor 60 mg relative to

placebo for each of the three individual components of the composite endpoint was 0.7% for MI, 0.5% for CV death and 0.4% for stroke.

In a pre-specified hierarchical confirmatory statistical analysis involving the primary efficacy endpoint and the two key secondary efficacy endpoints, the difference in CV death (first secondary efficacy endpoint) between ticagrelor 60 mg and placebo was not significant (KM percentages at 36 months 2.9% versus 3.4%, respectively;  $p=0.0676$ , which is greater than the pre-specified significance level  $p=0.02478$ ). Therefore, formal confirmatory analysis of all-cause mortality (second secondary efficacy endpoint) between ticagrelor 60 mg and placebo did not proceed (KM percentages at 36 months 4.7% versus 5.2%, respectively; nominal  $p=0.1350$ ). However, the incidence of both CV death and all-cause mortality was numerically lower in the ticagrelor 60 mg group compared to the placebo group, based on KM percentages at 36 months.

In general, pairwise comparisons of numerous other secondary efficacy and exploratory efficacy endpoints all numerically favoured ticagrelor 60 mg compared to placebo but there were no confirmatory statistical analyses of the differences between the treatment groups with all  $p$ -values being nominal.

### First round assessment of risks

The most clinically significant risk associated with ticagrelor 60 mg compared to placebo in the proposed patient population relate to TIMI major bleeding events. The majority of TIMI major bleeding events were categorised as 'Other' (that is, neither ICH nor fatal haemorrhages), and were most commonly gastrointestinal in origin. 'Other' TIMI major haemorrhages were associated with significant morbidity in the majority of patients in both the ticagrelor 60 mg and placebo groups, characterised by hospitalisation and blood transfusions. TIMI major bleeding events categorised as ICH and fatal haemorrhages were reported in a similar proportion of patients in the ticagrelor 60 mg and placebo groups. The most clinically significant non-bleeding risk associated with ticagrelor 60 mg was dyspnoea (unknown cause). Discontinuation of the study drug due to AEs was higher in the ticagrelor group 60 mg group than in the placebo group.

TIMI major bleeding events were reported in 115 and 54 patients in the ticagrelor 60 mg and placebo groups respectively, corresponding to KM percentages at 36 months of 2.3% and 1.1%, respectively: HR = 2.32 (95% CI: 1.68, 3.21),  $p < 0.0001$ . The results indicate that there was a 2.3 fold increased risk of TIMI major bleeding in the ticagrelor 60 mg group compared to the placebo group. The absolute risk difference in TIMI major bleeding events between ticagrelor 60 mg and placebo was 1.2% in the safety analysis set, based on KM percentages at 36 months.

The observed increased risk of TIMI major bleeding in the ticagrelor 60 mg group compared to placebo was primarily driven by 'Other' TIMI major bleeding events (that is, neither ICH nor fatal haemorrhages). TIMI major bleeding events (other) were reported in 83 patients in the ticagrelor 60 mg group and 25 patients in the placebo group, corresponding to KM percentages at 36 months of 1.6% and 0.5%, respectively (HR = 3.61 [95% CI: 2.31, 5.65],  $p < 0.0001$ ). Intracranial haemorrhage was reported in 28 and 23 patients in the ticagrelor 60 mg and placebo groups, respectively, corresponding to KM percentages at 36 months of 0.6% and 0.5%, respectively (HR = 1.33 [95% CI: 0.77, 2.31],  $p < 0.3130$ ). Fatal haemorrhage was reported in 11 and 12 patients in the ticagrelor 60 mg and placebo groups, respectively, corresponding to a KM percentage at 36 months of 0.3% in both treatment groups (HR = 1.00 [95% CI: 0.44, 2.27],  $p < 1.000$ ).

The observed higher frequency of 'Other' TIMI major bleeding events in the ticagrelor 60 mg group compared to the placebo group was driven primarily by 'gastrointestinal disorders' (system organ class (SOC)), which were reported in 51 (0.7%) and 12 (0.2%) patients, respectively. 'Other' TIMI major bleeding events by SOC in  $\geq 10$  patients in the

ticagrelor 60 mg group (versus placebo) were 'injury, poisoning and procedural complications' (32 [0.5%] versus 19 [0.3%]) and 'nervous system disorders' (10 [0.1%] versus 14 [0.2%]). The most commonly reported 'Other' TIMI major bleeding events by preferred term in  $\geq 5$  patients in the ticagrelor 60 mg group (versus placebo) were, gastrointestinal haemorrhage (12 [0.2%] versus 3 [ $<0.1\%$ ]), and gastric ulcer haemorrhage (7 [0.1%] versus 2 [ $<0.1\%$ ]).

'Other' TIMI major bleeding events categorised as serious AEs (SAEs) were reported in 64 (0.9%) patients in the ticagrelor 60 mg group and 24 (0.3%) patients in the placebo group, and 'Other' TIMI major bleeding events leading to discontinuation of the study drug were reported in 28 (0.4%) and 10 (0.1%) patients, respectively. 'Other' TIMI major bleeding events were associated with significant morbidity in both treatment groups, with 75.9% (63/83) of patients in the ticagrelor 60 mg group being hospitalised compared to 68.0% (17/25) of patients in the placebo group, while 77.1% (64/83) of patients in the ticagrelor 60 mg group required blood transfusion compared to 80.0% (20/25) of patients in the placebo group.

TIMI major or minor bleeding events on-treatment were reported in 168 patients in the ticagrelor 60 mg group and 72 patients in the placebo group, corresponding to KM percentages at 36 months of 3.4%, and 1.0%, respectively: HR = 2.54 (95% CI: 1.93, 3.35),  $p < 0.0001$ . TIMI minor bleeding events were reported in 0.8% (n=55) of patients in the ticagrelor 60 mg group and 0.3% (n=18) of patients in the placebo group. TIMI minor bleeding events (Preferred term (PT)) reported in  $\geq 2$  patients in the ticagrelor group (versus the placebo group) were gastric ulcer haemorrhage (n=3 [ $<0.1\%$ ] versus n=3 [ $<0.1\%$ ]), duodenal ulcer haemorrhage (n=3 [ $<0.1\%$ ] versus n=0 [0.0%]), diverticulum intestinal haemorrhage (n=2 [ $<0.1\%$ ] versus n=0 [0.0%]), and haematuria (n=2 [ $<0.1\%$ ] versus n=0 [0.0%]).

AEs (any bleeding event) occurring on-treatment were reported more frequently in patients in the ticagrelor 60 mg group compared to the placebo group (29.1% [n=2028] versus 11.5% [n=807], respectively). The most commonly reported AEs (any bleeding event) occurring on-treatment in  $\geq 1\%$  of patients in the ticagrelor group 60 mg group (versus placebo) in decreasing order of frequency were: epistaxis (6.0% versus 2.2%); increased tendency to bleed (6.0% versus 0.9%); contusion (4.9% versus 1.5%); spontaneous haematoma (3.1% versus 0.6%); traumatic haematoma (2.2% versus 0.6%); haematuria (1.7% versus 0.9%); and ecchymosis (1.5% versus 0.2%);

SAEs (any bleeding event) occurring on-treatment were reported more frequently in patients in the ticagrelor 60 mg group compared to the placebo group (3.9% [n=271] versus 2.2% [n=157], respectively). SAEs (any bleeding event) reported in  $\geq 0.2\%$  of patients in the ticagrelor 60 mg group (vs placebo) were epistaxis (0.2% versus  $> 0.1\%$ ), gastrointestinal haemorrhage (0.2% versus  $> 0.1\%$ ), gastric ulcer haemorrhage (0.2% versus  $< 0.1\%$ ), and traumatic intracranial haemorrhage (0.2% versus 0.1%).

Hospitalisations due to AEs (any bleeding events) were reported in 3.1% and 1.6% of patients in the ticagrelor 60 mg BD and placebo groups, respectively, while blood transfusions due to AEs (any bleeding event) were reported in 3.1% and 1.7% patients in the ticagrelor 60 mg and placebo groups, respectively.

Discontinuations due to AEs (any bleeding event) were reported more frequently in the ticagrelor 60 mg group than in the placebo group (5.1% [n=335] versus 1.3% [n=88], respectively). The most commonly reported discontinuations due to AEs (any bleeding event) reported in  $\geq 0.5\%$  of patients in the ticagrelor 60 mg group (versus placebo) were increased tendency to bruise (0.8% versus 0.1%), epistaxis (0.7% versus 0.2%), and spontaneous haematoma (0.6% versus  $< 0.1\%$ ).

Adjudicated fatal bleeding AEs on-treatment was reported in 0.2% of patients in both the ticagrelor 60 mg group (11 patients) and the placebo group (12 patients). The most

commonly reported fatal bleeding events reported in  $\geq 2$  patients in either treatment group were ICH (6 patients [0.1%] in the ticagrelor 60 mg group and 5 [0.1%] patients in the placebo group) and gastrointestinal system (3 patients [ $< 0.1\%$ ] in the ticagrelor 60 mg group and 3 [ $< 0.1\%$ ] patients in the placebo group). The majority of fatal haemorrhages in patients in both the ticagrelor 60 mg and placebo groups were spontaneous (8/11 versus 9/12, respectively), with the other fatal haemorrhages being either procedural or traumatic.

The risk of patients experiencing at least 1 AE (including bleeding) on-treatment was similar in the ticagrelor 60 mg and placebo groups (75.7% [36.0/100 patient years] and 69.1% [30.4/100 patient years], respectively). The most commonly reported AE (including bleeding) in the ticagrelor 60 mg group was dyspnoea (unknown mechanism), which occurred in 12.4% of patients (5.9/100 patient years) in the ticagrelor 60 mg group and 4.4% of patients (1.94/100 patient years) in the placebo group. In addition to dyspnoea, other AEs (including bleeding) reported on-treatment in  $\geq 5\%$  of patients in the ticagrelor 60 mg group (versus placebo group) were epistaxis (6.2% versus 2.2%), increased tendency to bruise (6.0% versus 0.9%), contusion (5.0% versus 1.5%), and nasopharyngitis (5.0% versus 5.0%).

The risk of patients experiencing at least 1 SAE (any) on-treatment was similar in the ticagrelor 60 mg and placebo groups (21.5% [10.22/100 patients] versus 21.6% [9.48/100 patients], respectively). SAEs (any) reported on-treatment in  $\geq 0.5\%$  of patients in the ticagrelor 60 mg group (versus placebo group) were non-cardiac chest pain (1.3% versus 1.3%), atrial fibrillation (1.1% versus 0.7%), pneumonia (0.6% versus 0.8%), cardiac failure (0.6% versus 0.5%), osteoarthritis (0.6% versus 0.8%), cardiac failure congestive (0.5% versus 0.4%), and angina pectoris (0.5% versus 0.7%).

The risk of permanent discontinuation of the study drug due to AEs (any) occurred more frequently in the ticagrelor 60 mg group than in the placebo group (16.1% and 8.5% of patients, respectively). The most common reason for permanent treatment discontinuation (any) in the ticagrelor 60 mg group was dyspnoea. Permanent discontinuation of the study drug due to AEs (any) reported in  $\geq 0.5\%$  of patients in the ticagrelor 60 mg group (versus placebo group) were dyspnoea (4.0% versus 0.7%), atrial fibrillation (1.2% versus 1.1%), increased tendency to bruise (0.9% versus 0.1%), epistaxis (0.7% versus 0.2%), and spontaneous haematoma (0.6% versus  $< 0.1\%$ ).

The risk of adjudicated CV death (on and off treatment) was lower in the ticagrelor 60 mg group than in the placebo group (2.5% [n=176] versus 3.1% [n=219], respectively). The most frequently reported CV death in each of the two treatment groups was sudden cardiac death, which occurred in 1.2% (n=82) of patients in the ticagrelor 60 mg group and 1.5% (n=106) of patients in the placebo group. Death due to acute MI was reported in 0.3% (n=22) of patients in the ticagrelor 60 mg group and 0.4% (n=26) of patients in the placebo group, death due to heart failure or cardiogenic shock was reported in 0.3% (n=18) and 0.3% (n=22) of patients, respectively, and death due to intracranial haemorrhage was reported in 0.1% (n=7) and 0.1% (n=9) of patients, respectively. No CV deaths were reported more frequently in the ticagrelor 60 mg group than in the placebo group.

The risk of adjudicated non-CV death (on and off treatment) was similar in the ticagrelor 60 mg and placebo groups (1.7% [n=116] versus 1.6% [n=115], respectively). The most frequently reported non-CV deaths in the two treatment groups were malignancy, which was reported in 0.9% (n=63) of patients in the ticagrelor 60 mg group and 0.8% (n=53) of patients in the placebo group. The only other non-CV death reported with a greater incidence in the ticagrelor 60 mg group than in the placebo group was infection (includes sepsis), which was reported in 0.4% (n=23) and 0.3% (n=24) of patients, respectively.

In addition to bleeding events and dyspnoea, gout and hyperuricaemia have also been reported to be associated with ticagrelor. The risks of gout and hyperuricaemia were greater in the ticagrelor 60 mg BD group than in the placebo group but the increased risks were small. Bradyarrhythmias and renal related AEs have also been reported to be associated with ticagrelor but in PEGASUS the risks of these events were similar in the ticagrelor 60 mg and placebo groups. There were no clinically significantly increased risks of designated medical events (on-treatment) in patients in the ticagrelor 60 mg group compared to the placebo group.

### First round assessment of benefit-risk balance

It is considered that the data from PEGASUS demonstrate that the benefit-risk balance of ticagrelor 60 mg BD in combination with ASA is favourable for the treatment of patients with a history of MI at least 1 year previously and at high risk of atherothrombotic events.

In the Clinical Study Protocol (PEGASUS), analysis of net clinical benefit was defined as the time to first occurrence of any event after randomisation from the composite of CV death, MI, stroke, or TIMI major bleeding. In the FAS, there were 585 (8.3%) events in the ticagrelor 60 mg group and 618 (8.7%) events in the placebo group, corresponding to KM percentages at 36 months of 9.3% and 9.6%, respectively; HR = 0.95 (0.85, 1.06), p=0.3412. The results indicate that the net clinical benefits of ticagrelor 60 mg and placebo were similar, with a numerically small risk reduction in favour of ticagrelor 60 mg relative to placebo based on KM percentages at 36 months (that is, RRR = 5%; ARR = 0.3%). The complete results of the analysis of net clinical benefit are summarised in Table 2.

**Table 2: PEGASUS Analysis of net clinical benefit, the composite of CV death, MI, stroke, and TIMI major bleeding; FAS**

Characteristic	Ticagrelor 90 mg bd N = 7050				Ticagrelor 60 mg bd N = 7045				Placebo N= 7067	
	Patients (%) with events	KM %	HR (95% CI)	p-value	Patients (%) with events	KM %	HR (95% CI)	p-value	Patients (%) with events	KM %
Composite of CV death / MI/ stroke/ TIMI Major bleeding	618 ( 8.8%)	9.8%	1.00 (0.90, 1.12)	0.9563	585 ( 8.3%)	9.3%	0.95 (0.85, 1.06)	0.3412	618 ( 8.7%)	9.6%
CV death	182 ( 2.6%)	2.9%	0.87 (0.71, 1.06)	0.1547	174 ( 2.5%)	2.9%	0.83 (0.68, 1.01)	0.0676	210 ( 3.0%)	3.4%
MI	275 ( 3.9%)	4.4%	0.81 (0.69, 0.95)	0.0100	285 ( 4.0%)	4.5%	0.84 (0.72, 0.98)	0.0314	338 ( 4.8%)	5.2%
Stroke	100 ( 1.4%)	1.6%	0.82 (0.63, 1.07)	0.1403	91 ( 1.3%)	1.5%	0.75 (0.57, 0.98)	0.0337	122 ( 1.7%)	1.9%
TIMI Major bleeding	159 ( 2.3%)	2.5%	2.05 (1.57, 2.69)	<.0001	138 ( 2.0%)	2.2%	1.78 (1.35, 2.35)	<.0001	78 ( 1.1%)	1.3%

Source: Table 11.2.6.4

Hazard ratio and p-value calculated separately for each ticagrelor dose vs. placebo from Cox proportional hazards model with treatment group as the only explanatory variable.

Kaplan-Meier percentage is calculated at 36 months.

Note: The number of first events for the components is the actual number of first events for each component, and does not add up to the number of events in the composite endpoint.

bd Twice daily; CI Confidence interval; CV Cardiovascular; KM Kaplan-Meier; HR Hazard ratio; MI Myocardial infarction; N Number of patients in treatment group

PEGASUS also included an ad hoc analysis of net clinical benefit by irreversible harm (that is, composite of all-cause mortality/MI/stroke/ICH/fatal bleeding). In the FAS, there were 600 (8.5%) events in the ticagrelor 60 mg group and 686 (9.7%) events in the placebo group, corresponding to KM percentages at 36 months of 9.6% and 10.6%, respectively; HR = 0.87 (0.78, 0.97), p=0.0139. Based on KM percentages at 36 months, the results indicate a numerical risk reduction in irreversible harm in the ticagrelor 60 mg group compared to the placebo group (that is, RRR = 13%; ARR = 0.9%). The complete results of the analysis of net clinical benefit by irreversible harm are summarised in Table 3.



**Table 3: PEGASUS Analysis of net clinical benefit by irreversible harm, the composite of all-cause mortality, MI, stroke, ICH, and fatal bleeding; FAS**

Characteristic	Ticagrelor 90 mg bd N = 7050				Ticagrelor 60 mg bd N = 7045				Placebo N = 7067	
	Patients (%) with events	KM %	HR (95% CI)	p-value	Patients (%) with events	KM %	HR (95% CI)	p-value	Patients (%) with events	KM %
Composite of all-cause mortality/MI/stroke, intracranial haemorrhage and fatal bleeding	643 (9.1%)	10.1%	0.93 (0.84, 1.04)	0.2194	600 (8.5%)	9.6%	0.87 (0.78, 0.97)	0.0139	686 (9.7%)	10.6%
All-cause mortality	326 (4.6%)	5.1%	1.00 (0.86, 1.16)	0.9851	289 (4.1%)	4.7%	0.89 (0.76, 1.04)	0.1350	326 (4.6%)	5.2%
MI	275 (3.9%)	4.4%	0.81 (0.69, 0.95)	0.0100	285 (4.0%)	4.5%	0.84 (0.72, 0.98)	0.0314	338 (4.8%)	5.2%
Stroke (excluding intracranial haemorrhages)	86 (1.2%)	1.4%	0.84 (0.63, 1.12)	0.2435	79 (1.1%)	1.3%	0.77 (0.58, 1.04)	0.0872	102 (1.4%)	1.6%
Intracranial haemorrhage	41 (0.6%)	0.6%	1.25 (0.79, 1.97)	0.3483	35 (0.5%)	0.5%	1.06 (0.66, 1.71)	0.8051	33 (0.5%)	0.6%
Fatal bleeding	13 (0.2%)	0.2%	0.86 (0.41, 1.82)	0.7011	13 (0.2%)	0.2%	0.87 (0.41, 1.82)	0.7049	15 (0.2%)	0.3%

Source: Table 11.2.6.10

Hazard ratio and p-value calculated separately for each ticagrelor dose vs. placebo from Cox proportional hazards model with treatment group as the only explanatory variable.

Kaplan-Meier percentage calculated at 36 months.

Note: The number of first events for the components is the actual number of first events for each component, and does not add up to the number of events in the composite endpoint.

bd Twice daily; CI Confidence interval; CV Cardiovascular; KM Kaplan-Meier; HR Hazard ratio; MI Myocardial infarction; N Number of patients in treatment group

Based on the absolute risk difference in primary composite efficacy events (CV death/MI/stroke) between ticagrelor 60 mg and placebo in the *ITT analysis (FAS)* (1.2% in favour of ticagrelor 60 mg BD), it can be estimated that 84 patients need to be treated with ticagrelor 60 mg BD for 3 years in order to prevent 1 composite event, and that treatment of 1000 patients with ticagrelor 60 mg for 3 years will prevent 12 composite events. Based on the absolute risk difference for primary safety outcome of TIMI major bleeding events between ticagrelor 60 mg and placebo in the *ITT analysis (FAS)* (0.9% in favour of placebo), it can be estimated that 112 patients treated with ticagrelor 60 mg for three years will experience 1 TIMI major bleeding event due to treatment, and 9 events will be caused by ticagrelor 60 mg BD in 1000 patients treated for 3 years. Therefore, based on the analysis in the *ITT analysis (FAS)* the benefit-risk balance (composite efficacy endpoint versus TIMI major bleeding event) for ticagrelor 60 mg BD in combination with ASA is favourable, with the benefit marginally outweighing the risk.

The primary benefit of treatment with ticagrelor 60 mg compared to placebo was a statistically significant reduction in the primary composite efficacy endpoint event rate (CV death/MI/stroke). In patients in the ticagrelor 60 mg (487 events) and placebo groups (578 events), KM percentages at 36 months for composite events were 7.8% and 9.0%, respectively (HR = 0.84 [95% CI: 0.74, 0.95], p=0.0043). The risk of each separate component of the primary composite efficacy endpoint was numerically lower in the ticagrelor 60 mg group than in the placebo group. The benefits observed with ticagrelor 60 mg compared to placebo relating to the composite endpoint are considered to be clinically meaningful.

There was no confirmatory evidence that ticagrelor 60 mg statistically significantly reduced the risk of the key secondary efficacy endpoints of CV death and all-cause mortality compared to placebo. However, based on KM percentages at 36 months the risk of both of these mortality outcomes was numerically lower in the ticagrelor 60 mg group than in the placebo group. Other secondary and exploratory cardiovascular and mortality endpoints consistently numerically favoured treatment with ticagrelor 60 mg compared to placebo.

The most clinically significant risks associated with ticagrelor 60 mg compared to placebo in the proposed patient population relate to TIMI major bleeding events. In patients in the ticagrelor 60 mg BD (115 events) and placebo groups (54 events), KM percentages at 36

months for TIMI major bleeding events were 2.3% and 1.1%, respectively (HR = 2.32 [95% CI: 1.68, 3.21],  $p < 0.0001$ ). The increased risk of TIMI major bleeding events in the ticagrelor 60 mg group was primarily driven by 'Other' TIMI major bleeding events (predominantly gastrointestinal haemorrhage), which were associated with significant morbidity characterised by hospitalisation and blood transfusions in both the ticagrelor 60 mg and placebo groups. TIMI major bleeding events categorised as ICH and fatal were both reported in a similar proportion of patients in the ticagrelor 60 mg and placebo groups.

Adjudicated fatal bleeding AEs (any) on-treatment was reported in 0.2% of patients in both the ticagrelor 60 mg BD group and the placebo group. Adjudicated CV deaths (on and off treatment) were reported in a greater proportion of patients in the placebo group than in the ticagrelor 60 mg BD group, and adjudicated non-CV deaths (on and off treatment) were reported in a similar proportion of patients in both treatment groups. Overall, the mortality data indicate that patients treated with ticagrelor 60 mg BD plus ASA are not at an increased risk of death compared to patients treated with ASA.

The risk of experiencing at least one AE (any) was higher for patients in the ticagrelor 60 mg group than the placebo group (75.7% [36.0 events/100 patient years] versus 69.1% [30.4 events/100 patient years, respectively). The most frequently reported AE (any) in the ticagrelor 60 mg group was dyspnoea, which was reported in 12.4% of patients (5.9/100 patient years) in the ticagrelor 60 mg group and 4.4% of patients (1.94/100 patient years) in the placebo group. SAEs (any) were reported in a similar proportion of patients in both the ticagrelor 60 mg group and the placebo group (21.4% [10.2 events/100 patient] years versus 21.6% [9.5 events/100 patient years], respectively). SAEs reported in  $\geq 1\%$  of patients in the ticagrelor 60 mg group (versus placebo) were non-cardiac chest pain (1.3% versus 1.3%, respectively) and atrial fibrillation (1.1% versus 0.7%, respectively), with dyspnoea being reported in 0.3% of patients in the ticagrelor 60 mg group and 0.1% in the placebo group.

The risk of permanent discontinuation of the study drug due to AEs (any) was notably greater in the ticagrelor 60 mg group than in the placebo group (16.1% versus 8.5% of patients, respectively), with the most frequently reported AE resulting in permanent treatment of ticagrelor 60 mg being dyspnoea. Permanent discontinuation of the study drug due to AEs (any) reported in  $\geq 0.5\%$  of patients in the ticagrelor 60 mg group (versus placebo group) were dyspnoea (4.0% versus 0.7%), atrial fibrillation (1.2% versus 1.1%), an increased tendency to bruise (0.9% versus 0.1%), epistaxis (0.7% versus 0.2%) and spontaneous haematoma (0.6% versus  $< 0.1\%$ ).

The favourable benefit-risk balance relating to ticagrelor 60 mg BD in combination with ASA observed in PEGASUS cannot be extrapolated to all patients with a previous history of MI. Consequently, careful selection of patients to be treated with the proposed dosage regimen will be required in order to avoid potentially harmful effects of the combination resulting in an unfavourable benefit-risk balance.

The pivotal study (PEGASUS) included patients aged  $\geq 50$  years with a history of MI occurring more than 1 year previously and with at least one of the following high risk factors for a further atherothrombotic event: age  $\geq 65$  years; diabetes mellitus requiring medication; angiographic evidence of significant multi vessel CAD; or chronic non-end stage renal dysfunction defined as CrCL  $< 60$  mL/min. The study specifically excluded patients at risk for bleeding events and patients with a significant history of bleeding (for example, ICH at any time; gastrointestinal tract (GIT) bleeding within the previous 6 months). In addition, the study excluded patients with a history of intracranial haemorrhage at any time, a history of ischaemic stroke at any time and severe liver disease. The study also excluded patients needing chronic oral anti-coagulant therapy or chronic Low-molecular-weight heparin (LMWH) therapy at venous thrombosis treatment doses but not prophylaxis doses. Patients requiring concomitant treatment with strong

CYP3A4 inhibitors were excluded, as were patients at an increased risk of bradycardia and patients with renal impairment requiring dialysis. There were also exclusions relating to the time interval between previous specified treatments and enrolment in the study, including coronary artery by-pass graft (CABG) surgery, intracranial and spinal surgery, other major surgery and gastrointestinal bleeding.

### **First round recommendation regarding authorisation**

It is recommended that the application to register ticagrelor 60 mg BD in combination with ASA for the prevention of atherothrombotic events (CV death, MI, stroke) in patients with a history of MI occurring at least 1 year previously and a high risk of developing an atherothrombotic event be approved.

### **Second round evaluation**

No clinical questions were raised by the evaluator and no new data were submitted by the sponsor for evaluation.

The sponsor provided comments on the first round clinical evaluation report and a response to the matters raised by the clinical evaluator relating to the clinical aspects of the draft PI, together with an updated draft PI. The sponsor's response also included additional proposals relating to amendments to the PI, which had not been discussed in the original submission. The sponsor's response relating to the PI was considered but the details are beyond the scope of an AusPAR.

### **Second round benefit-risk assessment**

#### **Second round assessment of benefits**

No new clinical information was submitted in the sponsor's response to the first round clinical evaluation report. Accordingly, the benefits of ticagrelor for the proposed extension of indication are unchanged from those identified in the first round evaluation.

#### **Second round assessment of risks**

No new clinical information was submitted in the sponsor's response to the first round clinical evaluation report. Accordingly, the risks of ticagrelor for the proposed extension of indication are unchanged from those identified in the first round evaluation.

#### **Second round assessment of benefit-risk balance**

The benefit-risk balance of ticagrelor, given the proposed usage, is favourable.

### **Second round recommendation regarding authorisation**

It is recommended that the application to register ticagrelor 60 mg BD in combination with ASA for the prevention of atherothrombotic events (CV death, MI, stroke) in adult patients with a history of myocardial infarction (MI occurred at least 1 year ago) and a high risk of developing an atherothrombotic event be approved.

## V. Pharmacovigilance findings

### Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP version 9 dated 27 February 2015 (data lock point 14 February 2015) and the Australian Specific Annex version 3 dated 27 May 2015; updated Australian Specific Annex version 3.1 dated 17 February 2016) which was reviewed by the RMP evaluator.

### Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown in Table 4.

**Table 4: Summary of safety concerns**

Safety concern	
Important identified risks	<p>Increased risk of bleeding</p> <p>Dyspnoea</p> <p>Drug-drug interactions: Strong inhibitors/inducers of CYP3A4; moderate inhibitors of CYP3A4; drugs metabolised through CYP3A4 (eg, simvastatin), digoxin (inhibition of P-gp transporter by ticagrelor) and cyclosporine (P-gp and CYP3A inhibitor)</p>
Important potential risks	Bradyarrhythmias
Missing information	<p>Use in patients with moderate or severe hepatic impairment</p> <p>Use in patients with risk factors for bleeding</p> <p>Use in children</p> <p>Use in pregnant or lactating women</p> <p>Long-term use in patients with prior ischaemic stroke</p> <p>Use in patients with renal failure requiring dialysis</p>

### Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance to monitor all the safety concerns. Study D5130N00010 has been proposed as additional pharmacovigilance for all the safety concerns except missing information - 'Use in children', 'Use in pregnant or lactating women', 'Long-term use in patients with prior ischaemic stroke', and 'Use in patients with renal failure requiring dialysis'.

### Risk minimisation activities

The sponsor proposes routine risk minimisation for all the safety concerns. No additional risk minimisation has been proposed.

## Reconciliation of issues outlined in the RMP report

Table 5 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA and an evaluation of the sponsor's responses.

**Table 5: Reconciliation of issues outlined in the first round RMP evaluation report**

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>1. Safety considerations may be raised by the non-clinical and clinical evaluators through request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.</p>	<p><i>The sponsor acknowledges this comment. The Nonclinical and Clinical Evaluation reports do not include comments warranting revision of the Risk Management Plan (RMP).</i></p>	<p>The sponsor's response is noted.</p>
<p>2. As the TGA has previously evaluated RMPs, the focus of this evaluation is on the differences between the RMP versions that could have an impact on the safety profile and any new safety related information since the last review.</p>	<p><i>The sponsor acknowledges this comment.</i></p>	<p>The sponsor's response is noted.</p>
<p>3. EU-RMP version 8 with ASA version 2 appear to be the most recent RMP documents that were reviewed and accepted by the TGA as part of the post-authorisation update. The evaluator has noted the following differences in the summary of safety concerns between EU-RMP version 8 with ASA version 2 and EU-RMP version 9 with ASA version 3:</p> <p><i>Important identified risks:</i> Serum creatinine increases</p>	<p><i>The completed PEGASUS study has contributed extensive long-term data, which provides a better understanding of the overall risk profile of ticagrelor. Therefore, a number of safety concerns have been removed, updated or reworded in Version 9 of the European Union (EU) RMP (dated 09 February 2015) and consequently Australian Specific Annex (ASA) Version 3.0, as follows:</i></p> <p><i>After review of the PEGASUS data, the following changes have been made:</i></p> <p><i>The following terms are no longer considered to be important identified</i></p>	<p>The evaluator has noted the discussion on Study D5132C0001 in the updated EU-RMP. The sponsor's response is acceptable.</p>

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>(renal impairment) and hyper-uricaemia were listed in ASA version 2, they are no longer listed in the current RMP.</p> <p>Bradyarrhythmias (including Holter detected ventricular pauses) was an important identified risk in ASA version 2, it is downgraded to important potential risk in the current EU-RMP and the ASA.</p> <p><i>Important potential risks:</i> Gout/gouty arthritis and urate nephropathy were listed in ASA version 2, it is no longer listed in the current EU-RMP and the ASA.</p> <p><i>Missing information:</i> Use in patients beyond one-year treatment duration was listed in ASA version 2, it is no longer listed in the current EU-RMP and the ASA.</p> <p>The evaluator has also noted that routine and additional pharmacovigilance activities including Study D5130N00010 (DUS) and Study D5132C00001 (PEGASUS) were proposed in the ASA version 2 to monitor these safety concerns. The sponsor should provide justification to why these changes have been made including relevant study findings.</p>	<p><i>risks:</i></p> <ul style="list-style-type: none"> <li>- Serum creatinine increased (renal impairment)</li> <li>- Hyperuricaemia</li> <li>- Bradyarrhythmias (including Holter-detected ventricular pauses), which are now categorised as an important potential risk.</li> </ul> <p><i>The following terms are no longer considered to be important potential risks:</i></p> <ul style="list-style-type: none"> <li>- Gout/gouty arthritis</li> <li>- Urate nephropathy</li> <li>- Use of ticagrelor in patients beyond the recommended 1-year treatment duration is no longer considered to be missing information.</li> </ul> <p><i>Please refer to EU RMP version 9, for a detailed summary of the results and justification of RMP changes.</i></p> <p><i>Study D5130N00010 (Drug Utilisation Study [DUS]), which is now completed, monitored safety concerns in ASA Version 3. Since the PEGASUS study is completed, it is consequently not included as an additional pharmacovigilance activity in the ASA Version 3. The impact of PEGASUS on the safety concerns is presented above.</i></p>	
<p>4. The final report for Study D5130N00010 is scheduled in 2015. The sponsor should provide an update to the safety findings from the study. The sponsor should justify in the ASA whether findings from this study are applicable to Australia.</p>	<p><i>The Swedish Drug Utilization Study (D5130N00010) was a retrospective cohort study using national Swedish health registries, representing a general population. The sponsor therefore considers that the findings of this study are applicable to Australia.</i></p> <p><i>The study included 49332 P2Y12 antagonist users aged 20 to 84 years. It comprised a drug utilization</i></p>	<p>The sponsor's response is acceptable. Dyspnoea is a listed important identified risk in the RMP. The current PI also includes advice about this risk under 'Precautions'. At this stage, these are considered acceptable measures from the RMP perspective.</p>

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	<p><i>component and a follow-up of selected outcomes. The study period was 01 June 2011 to 31 December 2012. There were 3 study cohorts:</i></p> <ul style="list-style-type: none"> <li><i>- First time users of ticagrelor (n=6945)</i></li> <li><i>- First time users of clopidogrel (n=42319)</i></li> <li><i>- First time users of prasugrel (n=1428).</i></li> </ul> <p><i>Participants were followed-up from date of first qualifying prescription until a first occurrence of a selected outcome, 85th birthday, death, or end of follow-up (31 December 2013).</i></p> <p><i>A large majority of each cohort were drug-naïve, or had not taken a P2Y12 antagonist in the prior 12 months.</i></p> <p><i>The co-morbidity pattern among naïve ticagrelor and prasugrel users were generally similar, but naïve clopidogrel users showed less cardiovascular (CV) disease (MI/ACS/CABG/PCI 54% versus &gt;95% for ticagrelor and prasugrel, respectively) and more cerebrovascular disease (34% versus 4% for ticagrelor and prasugrel, respectively).</i></p> <p><i>The estimated duration of ticagrelor use was close to the recommended 12 months, with median duration of the first continuous use period of 10.5 months. Corresponding duration was 11.0 months for clopidogrel users and 12.0 months for prasugrel users.</i></p> <p><i>There was no clear difference in crude incidence rates of intracranial bleeding, gastrointestinal bleeding, respiratory bleedings, other bleedings, bradyarrhythmias, pacemaker insertion, cardiac arrest, heart failure, acute renal failure, acute liver injury, syncope, or gout between naïve current users of the P2Y12 receptor antagonists with similar therapy indications, eg, with history of MI and/or ACS.</i></p> <p><i>In patients with a history of MI and/or ACS (which was used as a proxy for treatment indications), the crude incidence rate (incidence rate [95%</i></p>	



Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	<p><i>confidence interval]) of dyspnoea per 1000 person-years was elevated in naïve current users of ticagrelor 26.3 (22.1-31.0) versus naïve current users of clopidogrel 15.8 (14.2-17.6) and prasugrel 9.4 (4.3-17.8). A similar pattern was observed in the stratified analysis by history of MI and/or chronic obstructive pulmonary disease, showing a higher incidence rate of dyspnoea in current naïve users of ticagrelor 26.8 (22.4-31.8) versus current naïve users of clopidogrel 17.7 (15.8-19.7) and prasugrel 8.8 (3.8-17.3). There was no safety outcome signal other than that for dyspnoea.</i></p> <p><i>The full study report for the DUS study is available on request.</i></p>	
<p>5. Table 2 in ASA version 2 - 'PI and CMI wording pertaining to safety concerns' has been removed from ASA version 3. The ASA template (4 May 2015) as found on the TGA website includes a table comparing all planned risk minimisation measures for Australia with those proposed in the EU (<a href="https://www.tga.gov.au/book/australian-specific-annex-template">https://www.tga.gov.au/book/australian-specific-annex-template</a>). This table should include a comparison of the actual content and wording of the EU SmPC and the proposed Australian PI and CMI for all of the specified ongoing safety concerns and missing information to identify and provide reasons for any observed differences, particularly where it appears the EU SmPC is more restrictive.</p>	<p><i>Please refer to the ASA, Version 3.1.</i></p>	<p>The evaluator has noted the inclusion of Table 3 'Summary of Proposed Routine Risk Minimisation Activities in Australia and Europe' in the updated ASA. The sponsor's response is acceptable.</p>
<p>6. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft product information</p>	<p><i>a) The sponsor acknowledges this comment and proposes that the word 'adult' be reintroduced into the indication statement. The revised proposal for the indication is provided below:</i></p>	<p>The sponsor's response is satisfactory for recommendation 6-a) and 6-c). The evaluator has noted the sponsor's argument and evidence on</p>



Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>document be revised as follows:</p> <p>6-a). The evaluator has noted the deletion of 'adult' from the proposed indication statement in the draft PI. The sponsor's note in the draft PI states that this is because 'Precautions and Dosage and Administration sections indicate safety and efficacy in children has not been established'. This difference is highlighted to the Delegate.</p> <p>6-b). The evaluator has noted that use in patients with moderate hepatic impairment has been removed from the list of contraindications. However, no advice on dosage adjustment or hepatic function monitoring is provided in the draft PI other than 'there is limited experience with Brilinta in patients with moderate hepatic impairment, therefore, caution is advised in these patients'. It is recommended that the Delegate considers the adequacy of PI advice on this special patient group given the importance of the hepatic metabolic pathway for ticagrelor.</p> <p>6-c). The evaluator has noted that in most part of the PI, references to aspirin have been changed to acetylsalicylic acid/ASA. However, the indication still refers to aspirin. It is recommended that for clarity, references to drug names are internally consistent.</p>	<p><i>Brilinta, in combination with aspirin, is indicated for the prevention of atherothrombotic events (cardiovascular death, myocardial infarction and stroke) in adult patients with:</i></p> <p><i>- acute coronary syndromes (unstable angina [UA], non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG) (refer to DOSAGE and ADMINISTRATION).</i></p> <p><i>- a history of myocardial infarction (MI occurred at least one year ago) and a high risk of developing an atherothrombotic event (refer to Dosage and Administration).</i></p> <p><i>b) Patients with moderate hepatic impairment were allowed to participate in the PEGASUS study. Those patients with moderate or severe elevations in liver function tests at baseline were identified and data analysed. Exposure to ticagrelor and AR-C124910XX (active metabolite) were similar or only slightly higher in patients with, compared to patients without, moderate or severe elevations in liver function tests at baseline. There were small exposure differences, with large overlap between groups. AstraZeneca considers the proposed Precautions in the PI appropriately detailed to enable a physician to determine suitability of Brilinta for an individual patient based on their medical condition and history.</i></p> <p><i>c) The sponsor acknowledges this comment and will use consistent wording in future updates of the Australian Specific Annex (ASA). Please note the PI has been amended to replace the abbreviation for acetylsalicylic acid with the AAN aspirin (Refer to response to 2 above).</i></p>	<p>recommendation 6-b) relating to dosage adjustment in hepatic impairment. The evaluator considers that stating 'caution is advised' alone does not provide sufficient advice to prescribers. In comparison, the updated EU SmPC includes the following statement: 'Only limited information is available in patients with moderate hepatic impairment. Dose adjustment is not recommended, but ticagrelor should be used with caution' (<a href="http://www.medicines.org.uk/emc/medicine/23935">http://www.medicines.org.uk/emc/medicine/23935</a>). For antiplatelet drugs used as secondary prevention for atherothrombotic events, inappropriate dosage adjustment can become a safety issue if the protective effects are compromised by suboptimal dosing. Therefore, the recommendation remains for the Delegate's determination.</p>

## Summary of recommendations

It is considered that the sponsor's response to the TGA has adequately addressed most of the issues identified in the RMP evaluation report. Outstanding issues for the Delegate's consideration are detailed below.

### ***Outstanding issues***

#### *Issues in relation to the RMP*

**Recommendation 6:** The sponsor's response is satisfactory for recommendation 6-a) and 6-c). The evaluator has noted the sponsor's argument and evidence on recommendation 6-b) relating to dosage adjustment in hepatic impairment. The evaluator considers that stating 'caution is advised' alone does not provide sufficient advice to prescribers. In comparison, the updated EU SmPC includes the following statement: '*Only limited information is available in patients with moderate hepatic impairment. Dose adjustment is not recommended, but ticagrelor should be used with caution*'. For antiplatelet drugs used as secondary prevention for atherothrombotic events, inappropriate dosage adjustment can become a safety issue if the protective effects are compromised by suboptimal dosing. Therefore, the recommendation remains for the Delegate's determination.

#### *Advice from the Advisory Committee on the Safety of Medicines (ACSOM)*

ACSOM advice was not sought for this submission.

### ***Suggested wording for conditions of registration***

#### *RMP*

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

*Implement EU-RMP version 9 dated 27 February 2015 (data lock point 14 February 2015) with the Australian Specific Annex version 3.1 dated 17 February 2016 and any future updates as agreed with the TGA.*

## VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

### **Quality**

The quality evaluator had no objection to the registration of the 60 mg film-coated tablet (new strength) of ticagrelor.

The evaluator noted that ticagrelor is an immediate release preparation, taken twice daily. The 60 mg strength tablet is a round biconvex pink tablet with a '60' marked directly over a 'T' on one side and plain on the other, distinguishable from the round, biconvex, yellow 90 mg tablet with a '90' marked directly about the 'T'.

The evaluator has accepted the sponsor's justification for not providing a bioequivalence study based on the very similar dissolution profiles of the 60 mg clinical trial tablets (white), 60 mg commercial tablets (pink) and 90 mg tablets, that the tablets cores are

made from the same granule using the same wet granulation method as the 90 mg tablets and that the proposed tablet core is a direct scale of the 90 mg tablet core. The non-functioning film coat differs only in the ingredients used to produce the colour.

The excipients in both the 60 mg and 90 mg tablets are conventional substances with well-known properties and functions. The container closure system (blister pack) is the same as that for the registered 90 mg presentation.

A shelf-life of 36 months 'Stored below 30°C' is recommended for the 60 mg presentation in the blister pack.

## Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

## Clinical

The clinical evaluator has recommended approval for ticagrelor 60 mg BD in combination with aspirin, for the prevention of atherothrombotic events (CV death, MI, stroke) in patients with a history of MI occurring at least 1 year previously and a high risk of developing an atherothrombotic event.

The clinical dossier included the following data:

- 1 population pharmacokinetic (PPK) study
- 1 pharmacodynamic study
- 1 pivotal Phase III study

## Pharmacology

The studies with pharmacokinetic results noted the following:

- Based on data from the PEGASUS study (see below) the population pharmacokinetics (PPK) of ticagrelor 60 mg BD and 90 mg BD ticagrelor and its active metabolite AR-C124910XX were adequately described by one-compartment disposition models with first-order absorption (ticagrelor), formation of the active metabolite (AR-C124910XX) and elimination.
- The PPK were generally similar to those reported for the DISPERSE2 and PLATO studies from previous submissions.
- CL/F (for ticagrelor and AR-C124910XX) was higher in patients with greater body weight, current smoking and decreased by age, Japanese ethnicity, and female sex.
- No exposure-response relationships were demonstrated for ticagrelor exposure ( $C_{ss,av}$ ) and cardiovascular death (CV death)/MI/stroke (efficacy outcome) or for ticagrelor exposure and TIMI Major bleeding, although there was a trend towards lower risk in patients with lower exposure.
- There was a large overlap in ticagrelor exposure in patients with and without both efficacy and safety endpoints.
- The flaws in the model lead to the conclusion that a full non-linear mixed effect modelling approach including factor assessment based on the placebo cohort could offer a better unbiased assessment of the exposure-response relationship.
- There were no differences in PK for ticagrelor and AR-C124910XX in a Hispanic population compared with populations previously studied.

- No clinical biopharmaceutical studies comparing the bioequivalence of the proposed 60 mg tablet with the 90 mg approved tablet were provided however the sponsor's justification was accepted by the evaluator.

The pharmacodynamic study comparing on-treatment platelet reactivity of ticagrelor compared with clopidogrel in 40 adult Hispanic patients with documented coronary artery already taking aspirin (75 or 100 mg daily) disease noted the following:

- Platelet inhibition (assessed in P2Y<sub>12</sub> Reaction Units – PRU) was significantly greater at 2 hours (primary endpoint), and 0.5 and 8 hours after a 180 mg loading dose of ticagrelor than a 600 mg loading dose of clopidogrel.
- Platelet inhibition was also greater in the ticagrelor group after multiple twice daily doses of 90 mg twice daily than with clopidogrel 75 mg once daily.

## **Efficacy**

### ***PEGASUS study***

This was an event-driven, Phase III multinational, multicentre, randomised, double-blind, controlled, 3 arm, parallel group study in 21162 patients with a history of myocardial infarction (MI) 1 to 3 years prior to randomisation and at high risk of an atherothrombotic event. The study was designed to assess the prevention of cardiovascular events following dual antiplatelet therapy with 60 mg BD ticagrelor with aspirin 75 to 150 mg daily (n=7045), or 90 mg BD ticagrelor with 75 to 150 mg aspirin daily (n=7050) compared with aspirin alone (n=7067). The study was run until the common study end date when all patients had been treated for a minimum of 12 months and the pre-estimated number of primary events had occurred.

Patients were aged  $\geq 50$  years, with a history of MI 1 to 3 years previously and at least one of the following risk factors for CV disease (age  $\geq 65$  years, diabetes mellitus requiring medication, a second prior MI, evidence of multi-vessel disease CAD or chronic non-end-stage renal dysfunction that is, creatinine clearance (Cr CL)  $< 60$  mL/min).

Exclusion criteria were extensive and included conditions that would have increased the risk of bleeding, although patients with moderate hepatic dysfunction were included. ADP receptor blockers were not permitted unless the patient already enrolled in the study developed a condition specifically requiring this therapy (such as acute coronary syndromes (ACS) or percutaneous coronary intervention (PCI)). In such circumstances, modified blinded study drug was given for the duration that indication (ticagrelor 90 mg given in place of ticagrelor 60 mg in the ticagrelor 60 mg group and clopidogrel given instead of placebo in the placebo group). All patients continued to receive aspirin. After ADP treatment was no longer indicated the patient resumed treatment with the allocated treatment from the initial randomisation. Alternatively, open-label clopidogrel or prasugrel could be given prescribed and the patient was temporarily stopped from their study medication.

Post-randomisation 13.3% of patients took clopidogrel (13.0%/13.7%/13.2% in the ticagrelor 90 mg/ticagrelor 60 mg/placebo groups, respectively) and 10.9%/11.0%/11.0% of the ticagrelor 90 mg/ticagrelor 60 mg/placebo patients took medications in the heparin group. GPIIb/IIIa receptor antagonist and short term treatment with parenteral anticoagulants was permitted but the use of oral anticoagulants and long term use of LMWH was not.

Premature discontinuations occurred more frequently in the ticagrelor 90 mg BD group (32.3% n=2233) and ticagrelor 60 mg BD group (28.7%, n=1999) than in the placebo group (21.4%, n=1496), with annualised discontinuation rates of 12.1%/year, 10.8%/year and 8.1%/year. Most (n=3475) were due to AEs or SAEs. One hundred and two patients

(0.5%) with a history of stroke discontinued after a protocol amendment to exclude these patients 4 months into the study.

Baseline characteristics were similar in the three groups. The mean age of the total population was 65.3 years (range 47, 95), with 45.5% aged < 65 years, and 12.1% aged > 75 years. Most were male (76.1%), Caucasian (86.8%) or Asian (10.8%), with a mean weight of 82.0 kg and a mean BMI of 28.5 kg/m<sup>2</sup>. Most were current (16.7%) or former smoker (48.3%). The qualifying event was a ST-segment<sup>6</sup> elevation myocardial infarction (STEMI) in 53.5%, and a Non-ST-segment elevation myocardial infarction (NSTEMI) in 40.6% and the mean time from qualifying event to randomisation was 21.8 months (range 0.7 to 146 months) and for 60.7% the event occurred more than 1 year but less than 2 years from enrolment. The additional risk factors included aged ≥ 65 years (54.4%), diabetes mellitus requiring medication (28.5%), history of a second spontaneous MI (16.5%), multiple vessel CAD on angiogram (59.3%) and chronic non-end stage renal dysfunction (5.9%). Across the study, 0.6% had no risk factor, 51.6% had 1 risk factor, 33.2% had 2 risk factors, and 14.6% had ≥ 3 risk factors. Most (83%) had had a PCI, and 79.8% had stent insertion (42.1% bare metal stent and 39.2% drug-eluting). Previous stroke was reported for 0.6%, transient ischaemic attack (TIA) in 1.2% and cerebrovascular revascularisation in 0.4%.

Prior to randomisation (in addition to the protocol-mandated aspirin) 24% patients were taking clopidogrel ≤ 7 days prior to randomisation, and 89% had had previous ADP receptor blocker treatment [clopidogrel (83.7%), prasugrel (4.4%), ticlopidine (0.5%), ticagrelor (0.4%)]. Anti-thrombotic therapy taken post-randomisation outside the protocol included clopidogrel (13.3%) and ticagrelor (1.3%). Overall, 10.4% received prohibited medications. Heparin products were taken by 10.9%.

Based on randomisation of 21,000 patients and 1360 accrued events, the study had an 89.2% power for 90 mg versus placebo and 82.5% power for 60 mg versus placebo at 2.59% significance level based on 14 months minimum follow-up. Assumptions made for the power calculation included an expected primary composite event rate of 3.5%/year, a target RRR for ticagrelor 90 mg BD of 20% (HR 0.791). Based on the inhibition of platelet aggregation (IPA) data from a Phase II study and assuming the log hazard ratio is proportional to the ratio of mean IPA for the 60 mg dose relative to the 90 mg dose an estimated hazard ratio for 60 mg BD was 0.814.

Primary efficacy variable analysis was conducted using the full analysis set, used Cox proportional hazards model with a factor for treatment group, and KM estimates of the cumulative percentage of patients with an event per treatment group calculated at 36 months. Sensitivity analyses to determine the possible effects of censoring, to replace CV death with all-cause mortality, and to include all patients who had withdrawn consent, were conducted. Secondary and other variables were handled in a similar way. A hierarchical approach to testing of primary and secondary endpoints was utilised.

Four months after the study commenced the protocol was changed to exclude patients with a history of ischaemic stroke based on increasing data from other studies that suggested intensive antiplatelet therapy increased the risk of intracranial haemorrhage in patients with a history of ischaemic stroke, resulting in the discontinuation of 102 patients. Major protocol deviations: occurred in 11.5% overall, and were in similar proportions of patients across the groups.

The primary efficacy endpoint was the time to first occurrence of any event from the composite endpoint of CV death, MI or stroke. Fatal MI or stroke was counted as a death.

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<sup>6</sup> The ST segment is the flat, isoelectric section of the ECG between the end of the S wave (the J point) and the beginning of the T wave. It represents the interval between ventricular depolarization and repolarisation.

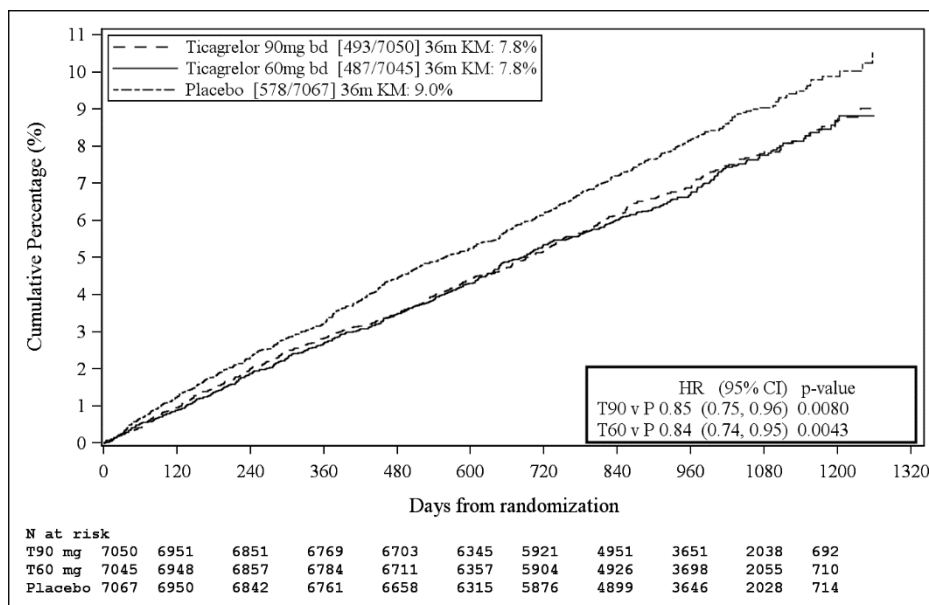
The results for the composite endpoint and the individual components of the endpoint are summarised in Table 6 below.

**Table 6: PEGASUS study Composite primary efficacy endpoint and individual components**

Characteristic	Ticagrelor 90 mg bd N = 7050				Ticagrelor 60 mg bd N = 7045				Placebo N = 7067	
	Patients with events	KM %	HR (95% CI)	p-value	Patients with events	KM %	HR (95% CI)	p-value	Patients with events	KM %
Composite of CV Death/MI /stroke	493 ( 7.0%)	7.8%	0.85 (0.75, 0.96)	0.0080 (s)	487 ( 6.9%)	7.8%	0.84 (0.74, 0.95)	0.0043 (s)	578 ( 8.2%)	9.0%
CV death	182 ( 2.6%)	2.9%	0.87 (0.71, 1.06)	0.1547	174 ( 2.5%)	2.9%	0.83 (0.68, 1.01)	0.0676	210 ( 3.0%)	3.4%
MI	275 ( 3.9%)	4.4%	0.81 (0.69, 0.95)	0.0100	285 ( 4.0%)	4.5%	0.84 (0.72, 0.98)	0.0314	338 ( 4.8%)	5.2%
Stroke	100 ( 1.4%)	1.6%	0.82 (0.63, 1.07)	0.1403	91 ( 1.3%)	1.5%	0.75 (0.57, 0.98)	0.0337	122 ( 1.7%)	1.9%

The Kaplan-Meier plot of the results shows an early divergence of the ticagrelor and placebo groups, and very similar curves for the two ticagrelor treatment groups (see Figure 4).

**Figure 4: PEGASUS study – Kaplan-Meier plots of the primary efficacy endpoint; full analysis set**



The RRR for ticagrelor 90 mg BD versus placebo was 15%, HR 0.85 [95% CI: 0.75, 0.96], p=0.008, and for ticagrelor 60 mg BD versus placebo the RRR was 16%, HR 0.84 [95% CI: 0.74, 0.95], p=0.0043. The ARR for both ticagrelor groups and aspirin versus aspirin alone was 1.2%, being 1.19% for the 90 mg BD groups and 1.27% for the 60 mg BD group.

The majority (80% to 90%) of first event strokes in the three treatment groups were ischaemic strokes.

The treatment compliance analysis showed best results compared to placebo (aspirin) with  $\geq 92.1\%$  compliance with the study medication for both the 90 mg BD and 60 mg BD doses.

The first secondary endpoint was the time from randomisation to the first occurrence of CV death. The second secondary endpoint was the time from randomisation to the first occurrence of all-cause mortality.

**Table 7: PEGASUS study Composite Primary Efficacy Endpoint, CV Death and All-Cause Mortality**

Characteristic	Ticagrelor 90mg bd (N=7050)				Ticagrelor 60mg bd (N=7045)				Placebo (N=7067)	
	Patients (%) with events	KM%	HR (95% CI)	p-value <sup>a</sup>	Patients (%) with events	KM%	HR (95% CI)	p-value <sup>a</sup>	Patients (%) with events	KM%
Composite of CV death/MI/stroke	493 ( 7.0%)	7.8%	0.85 (0.75, 0.96)	0.0080 (s)	487 ( 6.9%)	7.8%	0.84 (0.74, 0.95)	0.0043 (s)	578 ( 8.2%)	9.0%
CV Death	182 ( 2.6%)	2.9%	0.87 (0.71, 1.06)	0.1547	174 ( 2.5%)	2.9%	0.83 (0.68, 1.01)	0.0676	210 ( 3.0%)	3.4%
All-cause mortality	326 ( 4.6%)	5.1%	1.00 (0.86, 1.16)	0.9851	289 ( 4.1%)	4.7%	0.89 (0.76, 1.04)	0.1350	326 ( 4.6%)	5.2%

There was no statistically significant difference between either of the ticagrelor dose groups versus placebo for the first secondary endpoint in the hierarchical testing. The secondary endpoints do not confirm a survival benefit for ticagrelor and aspirin compared to aspirin alone.

### Safety

In the submission a total of 20982 patients were exposed to at least one dose of study drug and 13,986 were exposed to ticagrelor, and of those, 6958 were exposed to the proposed dose for this indication. The safety data were dominated by the safety outcomes from the PEGASUS study (described from hereon).

The duration of exposure ranged from 0.3 to 48 months, with the median durations of total exposure approximately 28.3, 29.4 and 30.4 months in the ticagrelor 90 mg BD, ticagrelor 60 mg BD and placebo groups, respectively. Across the groups about 61%/65%/71% patients in the 90 mg/60 mg/placebo groups, respectively were exposed for at least 24 months.

AEs occurred in 76.2%/75.7%/69.1% in the ticagrelor 90 mg BD/ticagrelor 60 mg BD/placebo groups, respectively, and 18.7%/16.1%/8.5% of the ticagrelor 90 mg BD/ticagrelor 60 mg BD/placebo groups, respectively had an AE that lead to the discontinuation of the study drug. Apart from bleeding events the most common were dyspnoea (15.6%/12.4%/4.4%), nasopharyngitis (4.9%/5.0%/5.0%) and non-cardiac chest pain 4.5%/4.9%/5.3%). Of the bleeding AEs epistaxis (7.3%/6.1%/2.2%), increased tendency to bruise (6.6%/6.0%/0.9%), contusion (5.4%/5.0%/1.5%), spontaneous haematoma (3.8%/3.1%/0.6%) and traumatic haematoma (2.8%/2.3%/0.6%) were the most common bleeding events with a notable difference between the ticagrelor 90 mg BD/ticagrelor 60 mg BD/placebo groups.

Deaths were reported for 961 patients, with 8 occurring after withdrawal of consent and one in the follow-up period. Including bleeding events, AEs with an outcome of death were reported in 2.3%/2.1%/2.9% with death, sudden cardiac death, acute myocardial infarction and myocardial infarction being the most common causes. CV death was reported in 2.7%/2.5%/3.1% ticagrelor 90 mg BD/ticagrelor 60 mg BD/placebo groups, respectively with sudden cardiac death the most common. Most common among the non-CV deaths were malignancies (1.1%/0.9%/0.8%, ticagrelor 90 mg BD/ticagrelor 60 mg BD/placebo groups, respectively) and infection including sepsis (0.4%/0.4%/0.3%, ticagrelor 90 mg BD/ticagrelor 60 mg BD/placebo groups, respectively).

SAEs including bleeding occurred in 21.7%/21.5%/21.6% (10.86/10.22/9.48 events per 100 patient years) of the ticagrelor 90 mg BD/ticagrelor 60 mg BD/placebo groups, respectively. The most common disorders (PT) were non-cardiac chest pain, atrial fibrillation, pneumonia, Chronic Obstructive Pulmonary Disease (COPD), congestive cardiac failure and angina pectoris. Apart from non-cardiac chest pain (1.3% in each group) the remainder occurred in a frequency of <0.1% in each group.



AEs leading to discontinuations occurred in 18.7%/16.1%/8.5% ticagrelor 90 mg BD/ticagrelor 60 mg BD/placebo groups, respectively, with dyspnoea (6.7%/4.0%/0.7%) increased tendency to bruise (1.3%/0.9%/0.1%) and epistaxis (1.0%/0.7%/0.2%). Temporary interruptions of the study drug because of bleeding occurred in 3.4%/2.8%/0.8% ticagrelor 90 mg BD/ticagrelor 60 mg BD/placebo groups, respectively.

### ***Safety events of special interest***

Of the events of special interest bleeding was the main concern. Deaths from bleeding events occurred in 0.2% of all groups. Bleeding SAEs occurred in 4.6%/3.9%/2.2% of ticagrelor 90 mg BD/ticagrelor 60 mg BD/placebo groups, respectively. Hospitalisations because of bleeding were reported in 3.7%/3.1%/1.6% and blood transfusion was required in 3.2%/3.1%/1.7%. The most frequently reported events were epistaxis (7.3%/6.0%/2.2%), increased bruising tendency (6.5%/6.0%/0.9%), contusion (5.3%/4.9%/1.5%), spontaneous haematoma (3.8%/3.1%/0.6%), traumatic haematoma (2.7%/2.2%/0.6%), ecchymosis (2.1%/1.5%/0.2%) and haematuria (1.3%/1.7%/0.9%).

TIMI major bleeding occurred in 127 patient (1.8%), KM 2.6%, HR versus placebo 2.69 [95%CI: 1.96, 3.70] in the ticagrelor 90 mg BD group; 115 patient (1.7%), KM 2.3%, HR versus placebo 2.32 [95%CI: 1.68, 3.21] in the ticagrelor 60 mg BD group; and 54 (0.8%), KM 1.1% in the placebo group. The most common three events (PT) in the on-treatment patient groups were intracranial haemorrhage (0.2% of each ticagrelor group and 0.1% of the placebo group), gastric ulcer haemorrhage and gastrointestinal haemorrhage. TIMI minor bleeding<sup>7</sup> occurred in 0.9%/0.8%/0.3% in the ticagrelor 90 mg BD, ticagrelor 60 mg BD and placebo groups, respectively. The most common sites were gastrointestinal and urinary tract, and mostly spontaneous. When bleeding events were classified according to the PLATO bleeding criteria a similar pattern of increased bleeding on the ticagrelor groups compared with the placebo group was noted, and more bleeds were reported in the 90 mg BD group than the 60 mg BD group.

Fatal bleeding on treatment was infrequent occurring in 0.1%/0.2%/0.2% in the ticagrelor 90 mg BD, ticagrelor 60 mg BD and placebo groups, respectively. Intracranial haemorrhage was reported in 0.6% /0.6%/0.5% in the ticagrelor 90 mg BD, ticagrelor 60 mg BD and placebo groups, respectively, with the differences due to trauma and procedural events.

Dyspnoea, thought to be triggered by reduced clearance of adenosine through adenosine deaminase inhibition, has been seen in other studies with ticagrelor. In PEGASUS 17.2%/14.2%/5.5% of the ticagrelor 90 mg BD, ticagrelor 60 mg BD and placebo groups, respectively reported dyspnoea, mostly of mild to moderate intensity. Dyspnoea SAEs were infrequent (0.3%/0.3%/0.1%), and there were no deaths in the ticagrelor group but 1 death in the placebo group. Dyspnoea resulted in discontinuations in 6.2%/4.3%/0.7% of the ticagrelor 90 mg BD, ticagrelor 60 mg BD and placebo groups, respectively and 49.5%/43.9%/23.5% of permanently study discontinuations were due to dyspnoea.

Bradycardias have been noted in previous studies with ticagrelor but occurred in similar proportions to the placebo group in PEGASUS.

### **Additional changes to the PI proposed (responses to questions).**

In addition to the responses to the clinical evaluator's questions, the sponsor indicated it proposed to make amendments to the safety information:

1. Remove the precautionary statement about hyperuricaemia
2. Remove the precautionary statement about increased serum creatinine

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<sup>7</sup> TIMI minor bleeding: Clinically apparent with 3 to <5 g/dL decrease in haemoglobin or fall of 9 to 15% in haematocrit.



**Hyperuricaemia:** From baseline to last observation on treatment, uric acid increased 6.3% and 5.6% in the ticagrelor 90 mg BD and 60 mg BD groups and decreased 1.5% in the placebo group, and exceeded the ULN in 9.1%/8.8%/5.5% of the ticagrelor 90 mg BD, ticagrelor 60 mg BD and placebo groups, respectively. Gout and gouty arthritis occurred more frequently in the ticagrelor groups: 90 mg BD HR 1.77 [95% CI: 1.32, 2.37]; 60 mg BD HR 1.48 [95% CI: 1.10, 2.00]. No urate nephropathy was reported. A similar pattern of increased uric acid was seen in the PLATO study that supported initial approval of ticagrelor. The sponsor has argued that the hyperuricaemia is reversible after discontinuation of ticagrelor even after long-term treatment and has proposed removal of the precautionary statement regarding hyperuricaemia from the PI, considering that a mention of gout in the Adverse effects section of the PI is sufficient. The clinical evaluator has considered a precautionary statement to be required to draw attention to the risk of hyperuricaemia and the risk of gout with ticagrelor.

**Creatinine clearance:** The sponsor proposed to move the information about increased creatinine to the adverse effects section based on the findings from the PLATO study (that supported initial registration) and PEGASUS study. The sponsor's view is that the changes in serum creatinine were non-progressive, did not translate to renal-related SAEs or clinically important renal outcomes, that few patients had an increase in maximum serum creatinine >50% or >100% from baseline, and therefore that a Precautionary statement is not warranted. The advisory committee will be asked for comment on this proposal.

#### **Removal of contraindication to use in moderate hepatic impairment**

The sponsor, in the draft PI, removed moderate hepatic impairment<sup>8</sup> from the list of Contraindications. A justification was sought and the sponsor stated that there were patients included in the PEGASUS study with moderate liver impairment and that this population is not contraindicated in the EU and the US.

In the PEGASUS study moderate hepatic impairment (as judged by the investigator) was not an exclusion criterion, and 165 patients (49/55/61 in the ticagrelor 90 mg/ticagrelor 60 mg/placebo groups) included in the study had moderate or severe increases in LFT at baseline. The frequency of AEs was similar and 7 patients (4 in the placebo group) had hepatic-related AEs. Five patients had TIMI major bleeding events (2/1/2 in the ticagrelor 90 mg/ticagrelor 60 mg/placebo groups).

#### **Post market data**

No post-market data specific for the proposed indication and dose were provided in the submission.

#### **Net clinical benefit**

In the PEGASUS study protocol the net clinical benefit was defined as the time to first occurrence of any event after randomisation from the composite of CV death, MI, stroke or TIMI major bleeding. In the 60 mg BD ticagrelor these events occurred in 8.3% of the ticagrelor 60 mg BD group and 8.7% of the placebo group (KM% at 36 months 9.3% and 9.6%, respectively; HR 0.95 (95% CI 0.85, 1.06; p=0.34). Based on KM% at 36 months the RRR = 5% and the ARR = 0.3%.

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<sup>8</sup> Moderate or severe hepatic impairment was defined as one or more baseline liver function test moderately increased (as judged by the investigator) – ALT > 3x ULN, AST > 3x ULN, ALP > 2.5 x ULN, bilirubin > 1.5 x ULN.

## Risk management plan

The Pharmacovigilance and Special Access Branch has accepted EU-RMP version 9 dated 27 February 2015 (data lock point 14 February 2015) with the Australian Specific Annex version 3.1 dated 17 February 2016.

The only outstanding matter is that of the removal of moderate hepatic impairment as a contraindication to the use of ticagrelor and its replacement with a precautionary statement. This matter has been referred to the Delegate.

## Risk-benefit analysis

### Delegate's considerations

#### *Efficacy*

Efficacy was based on a 21162 patient, randomised, double-blind, placebo-controlled, parallel group study of two doses of ticagrelor (60 mg or 90 mg) taken BD with 75 to 150 mg aspirin daily compared to aspirin alone in patients with a history of MI in a single study that was adequately designed to test the efficacy objectives. The choice of aspirin as the active comparator is reasonable as it is recommended for secondary prevention for antithrombotic therapy one year or more after an index cardiovascular event.

The composite primary endpoint was the first occurrence of CV death, non-fatal MI and non-fatal stroke. CV death and all-cause mortality were secondary endpoints.

The composite endpoints were similar for both ticagrelor groups versus placebo suggesting no clear dose-response relationship for efficacy. Most of the first events were MIs, followed by CV deaths then stroke. 80 to 90 % of the strokes were ischaemic across the 3 groups but the most common event was MI. The analyses for the primary and secondary end points and the sensitivity analyses and exploratory analyses consistently showed little difference in efficacy between the 90 mg and 60 mg BD doses. The RRR for ticagrelor 90 mg BD versus placebo was 15%, HR 0.85 [95% CI: 0.75, 0.96],  $p=0.008$ , and for ticagrelor 60 mg BD versus placebo the RRR was 16%, HR 0.84 [95% CI: 0.74, 0.95],  $p=0.0043$ . The ARR for the 60 mg BD ticagrelor group and aspirin versus aspirin alone was 1.27%, giving a number needed to treat (NNT) of 79. The KM plots show the survival curves diverging early in treatment for the ticagrelor groups compared to placebo with little difference between the two ticagrelor groups throughout the study period. The sponsor has only requested approval of a 60 mg BD dosage regimen for the new indication and this is well supported by the efficacy data. The confirmatory (hierarchical) analysis of the primary and secondary endpoints failed to show statistical significance for the observed differences between each of the two ticagrelor doses and placebo. Exploratory efficacy endpoint analysis showed numerical differences between the ticagrelor doses and placebo.

The benefit of dual therapy with ticagrelor and aspirin was driven by predominantly non-fatal MI. For the components of the primary and key secondary endpoints dual therapy with ticagrelor in the proposed dose was not clearly worse than aspirin.

The study protocol was changed early to exclude patients with previous stroke, due to factors external to the study. Patients with myocardial infarction may also have widespread atherosclerotic disease. It is unknown whether the 60 mg BD dose is efficacious in patients with previous stroke, or poses a greater risk of intracranial haemorrhage than aspirin alone. The consequences of a patient resuming therapy sometime after a stroke were not tested in this study.

### ***Safety and RMP***

Adequate numbers of patients were studied with the 60 mg BD dose to detect common and uncommon adverse events for the sample as a whole although may have been inadequate to detect rare events, and events in small sub-groups. The median duration of exposure of about 30 months, although not very long compared with life-long use, is adequate. Bleeding events and dyspnoea are known adverse effects of ticagrelor. The risk of TIMI major bleeding was about 2.3 fold that of aspirin for the 60 mg BD dose and 2.7 fold for the 90 mg BD dose, bleeding SAEs occurred in about 1.7 fold more patients than the aspirin only group although bleeding deaths were infrequent and occurred in similar proportions of each of the studied dosage regimens. From the KM curves, the bleeding risk is ongoing with time, rather than a phenomenon of therapy initiation. The safety data supports the sponsors request for the 60 mg BD dose and not the 90 mg BD dose.

There appeared to be a dose-response relationship between ticagrelor and dyspnoea, and resulted in the discontinuations of 4.3% of the ticagrelor 60 mg BD group, with over 40% of the discontinuations due to dyspnoea. This is of concern as tolerability of this long-term medication is important for compliance.

### ***Amendments to the warnings and precautions in the PI***

The sponsor has provided an inadequate justification to remove the precautionary statement about increased uric acid and gout risk and replace it with a report in the adverse effects section. Increased uric acid in the ticagrelor groups compared to aspirin alone was seen in the PEGASUS study. Patients in the Indicated population are also at risk of gout and the warning remains relevant. The Delegate concurs with the conclusions of the clinical evaluator and the proposal to remove this precaution is not accepted.

The sponsor has provided a justification for moving the reference to increased serum creatinine from the Precautions section to the Adverse Effects section. The sponsor's argument is that there are few increases in creatinine to >50% or >100% of baseline and no permanent renal injury however, this would seem a blunt measure of clinically significant deterioration of renal function. These patients are likely to take multiple medications, some of which may be dependent on renal clearance, and a warning statement about possible creatinine elevation is relevant for the safe use of ticagrelor. The Delegate is of the view that there is insufficient evidence to support the removal of the Precautionary statement, at this time however, the advisory committee will be requested to provide advice on this matter.

The sponsor has proposed the removal of moderate hepatic impairment as a contraindication. Although patients with moderate hepatic impairment were included in the PEGASUS study they were relatively small in number. Removal of the contraindication applies to all patients covered by the Indication, and the different dosage regimens included the loading dose for ticagrelor. The sponsor has provided insufficient evidence to support its change at this time. The sponsor may wish to provide a full justification for its proposal presenting all the evidence from clinical trials, post-market surveillance and literature to support this amendment for a full evaluation in a future submission. At this time the Contraindication should remain.

### **Indication**

In general, the wording of the indication is consistent with the clinical study upon which it is based. If approved, some refinement of the wording of the Indication may be required to the effect that ticagrelor is indicated for the prevention in atherothrombotic events in patients with a history of myocardial infarction (at least one year previously) and a high risk of developing an atherothrombotic event.

**Dose**

The proposed dose of 60 mg BD is supported by similar efficacy data to the higher dose of 90 mg BD and a more favourable safety profile.

**Data deficiencies**

The data are limited beyond three years of exposure. There were a high proportion of White male patients limiting the generalisability to women and patients of non-White ethnic groups. There are no paediatric data but this is not of concern given the Indication.

**Conclusion**

The aspirin-compared efficacy for the composite primary endpoint of the 60 mg BD dose (HR 0.84, 95% CI: 0.74, 0.95, ARR% of 1.27%) and increased risk of TIMI major bleeding (HR 2.32 95% CI 1.68, 3.21) giving a net clinical benefit RRR (KM%) of 5% and an ARR of 0.3% shows a tight balance between the benefits and risks, which is numerically in favour of ticagrelor. Fatal bleeding occurred in similar proportions of patients, but increases in other major bleeding with the dual anti-platelet therapy, although to be expected, are of concern when there is a small incremental efficacy benefit over aspirin alone. The clinical meaningfulness of the efficacy gain is unclear and it is also unclear if the increased bleeding risk, in particular the ongoing nature of the risk, is adequately offset by the benefits. The sponsor has been requested to provide a clarification about what it considered was a minimum clinically meaningful difference for the primary composite endpoint and the net clinical benefit in the PEGASUS study. The advisory committee is also requested to provide advice on this issue.

**Conditions of registration**

The following conditions of registration are proposed. The sponsor is invited to provide comment.

1. Implement EU-RMP version 9 dated 27 February 2015 (data lock point 14 February 2015) with the Australian Specific Annex version 3.1 dated 17 February 2016 and any future updates as agreed with the TGA.

**Summary of Issues**

- Whether the cardiovascular outcome evidence for dual antiplatelet therapy with treatment commencing  $\geq$  1 year post myocardial infarction is sufficiently robust to support the indication.
- Whether the small difference in net clinical benefit between ticagrelor 60 mg BD and aspirin compared to aspirin alone is sufficient for approval.
- Whether the results are generalisable to the whole population of patients that are  $\geq$  1 year post myocardial infarction.
- Whether moving hyperuricaemia and increased serum creatinine to the Adverse effects section is adequate to convey the risks or whether the precautionary statement should be returned.

**Proposed action**

The Delegate had not in a position to say, at this time, that the application for ticagrelor should be approved for registration, given the uncertainty around whether the increased bleeding risks of ticagrelor and aspirin dual therapy are offset by the efficacy gains.

**Request for ACPM advice**

The committee is requested to provide advice on the following specific issues:

1. Please comment on whether the demonstrated difference in primary endpoint outcomes for ticagrelor 60 mg BD and aspirin compared to aspirin alone are clinically meaningful?
2. The inclusion criteria required patients over the age of 50 and most patients were male. Are the results generalisable to all patients 1 year post MI?
3. The sponsor has been requested to amend its proposed precautionary statement about the absence of data from a population with previous stroke (resulting from the protocol amendment in the PEGASUS study in the updated draft PI that will be provided in the pre-ACPM response. Please comment on whether the statement is now adequate to convey the risks and uncertainties for this population.
4. Do the benefits of ticagrelor 60 mg BD with aspirin offset the increased risk of bleeding to offer an overall favourable benefit-risk?
5. Has the sponsor provided sufficient evidence to support the removal of precautionary statements about:
  - a. Increased uric acid
  - b. Increased serum creatinine

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

**Questions for the sponsor**

1. What was the minimum clinically meaningful difference for the composite primary endpoint and the net clinical benefit in the PEGASUS study?
2. Please comment on the possible impact of the concomitant use of clopidogrel in the placebo group on the safety results for this group.
3. Based on the findings of the PEGASUS study what is the optimal time post-infarct to commence ticagrelor therapy? Is there a time interval post MI beyond which ticagrelor offers no benefit?
4. Compared with aspirin there was a small increase in reported malignancies with ticagrelor. Please comment on the relationship between ticagrelor and malignancy. Please comment on the potential for ascertainment bias in this group.
5. Please briefly summarise the evidence that supported the protocol change in PEGASUS to exclude patients with a prior history of stroke. Please justify why a precautionary statement about the risks for patients with prior stroke is not warranted for all patients taking ticagrelor.
6. Please explain the reason the immune system events included in the list of adverse reactions in the EU SPC should not be included in the Adverse Effects section of the PI.

**Response from sponsor**

AstraZeneca has provided comments in relation to the specific questions asked of the sponsor. Please note where questions overlap with each other or the summary of issues, the discussion has been consolidated to reduce redundancy.

### ***Clinical benefit***

In PEGASUS, treatment with ticagrelor 60 mg BD in combination with ASA, was superior to aspirin alone in the prevention of atherothrombotic events, with a consistent treatment effect over the entire study period yielding a 16% relative risk reduction [RRR] and 1.27% absolute risk reduction [ARR]. Each of the components contributed to the reduction in the primary composite endpoint (CV death 17% RRR, MI 16% RRR and stroke 25% RRR).

A number of different approaches to evaluating the benefit-risk profile of antithrombotic drugs have been described in the literature. One accepted approach is to compare separately the benefits gained versus the harm caused using events of similar clinical importance, focussing on those that are fatal or cause irreversible harm.<sup>9</sup> This method was used in the main assessment of the benefit-risk profile of ticagrelor described in this application. The sponsor considers this approach, which integrates clinical judgement supported by quantitative analysis, is the most informative and relevant method and thus the best method for investigating and expressing clinically meaningful differences.

To compare benefit with risk and place the data in context versus other treatment options and studies, the control (placebo) risk level is important. The sponsor chose to summarise the Risk Difference (RD) between ticagrelor and placebo as the difference in 36 months KM% estimates, with a 95% confidence intervals (CI) to reflect the variability. To further contextualise, the estimated numbers of events prevented (for RD <0) or caused (for RD >0) for 1000 patients treated for 3 years with ticagrelor instead of placebo was calculated as 10\*RD. This measure has been used previously as an acceptable approach to assess benefit versus risk.<sup>9</sup>

The analysis demonstrated that treating 1000 patients for 3 years with ticagrelor 60 mg BD instead of placebo resulted in prevention of an estimated 12 events of all-cause mortality, MI, or stroke (or 13 events of the primary composite endpoint), with no extra events of fatal bleeding or intracranial haemorrhage. These results demonstrate a clear and clinically meaningful difference exists in benefit versus risk when treating patients with ticagrelor versus placebo.

The efficacy endpoints and safety events reported in PEGASUS encompass a range of event types with varying clinical significance, from fatal events to those that can be managed clinically without needing to discontinue study drug. From this full complement, the endpoints selected for the main benefit-risk analysis were those that represent irreversible harm that is prevention of events of all-cause mortality, MI and stroke, were weighed against the risks of fatal bleeding and intracranial haemorrhage. In addition to Fatal bleeding and intracranial haemorrhage, TIMI Major bleeding includes events referred to in the sponsor's Clinical Overview as 'Other TIMI Major' bleeding. 'Other TIMI Major' bleeding includes serious and clinically important events; however, evaluation of the 'Other TIMI Major' bleeding events reported in PEGASUS shows that although reported at a higher frequency on ticagrelor than placebo, they could be managed from a clinical perspective, and did not lead to irreversible harm. Therefore, the 'Other TIMI Major' bleeding events reported in PEGASUS, along with efficacy events of less severe clinical impact (such as hospitalisation for unstable angina or TIA) cannot be directly compared with the events selected for the main risk-benefit evaluation, even if they originally were included in the protocol defined 'net clinical benefit'. The risk of 'Other TIMI Major' bleeding and potential efficacy benefits should of course be part of any evaluation of risk versus benefit when a physician considers the suitability of ticagrelor for an individual patient.

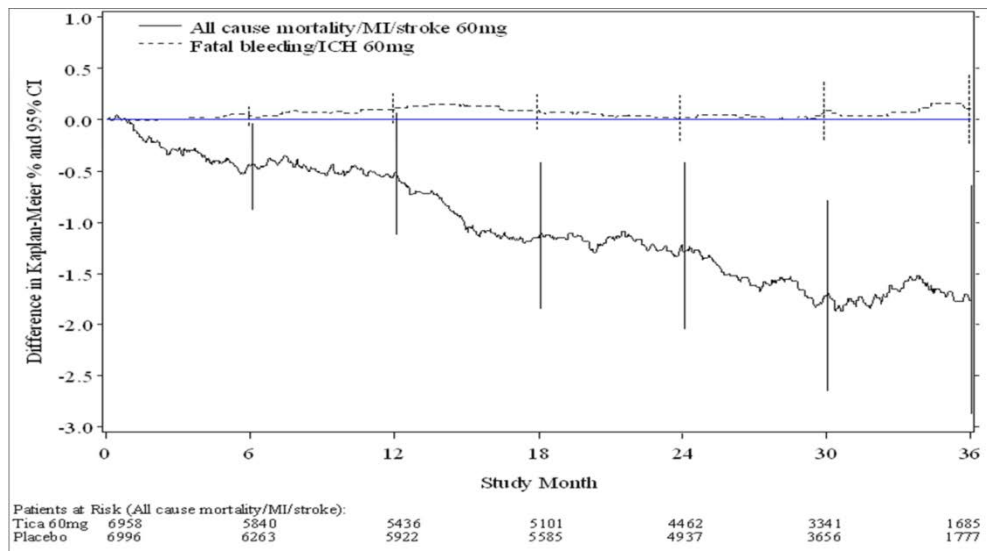
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<sup>9</sup> Ellis F. Unger, M.D. Weighing Benefits and Risks — The FDA's Review of Prasugrel. N Engl J Med 361;10 nejm.org september 3, 2009.



The temporal course of the benefit-risk profile, based on composites of efficacy and safety endpoints together, has been visualised by plotting the risk difference over time. These analyses provide further support that the favourable benefit-risk profile of ticagrelor is maintained over time. The temporal course of the RD for ticagrelor 60 mg versus placebo for the composite endpoints of irreversible harm is presented in Figure 5 for the 'on-treatment' analysis. The magnitude of the benefit versus the risk for ticagrelor 60 mg compared with placebo continued to accumulate over time in the on-treatment analysis.

**Figure 5: Temporal course of risk difference for ticagrelor 60 mg vs placebo, for the benefit composite of all-cause mortality, MI and stroke, and the risk composite of fatal bleeding and intracranial haemorrhage - on treatment (safety analysis set)**



The consistency of the treatment effect was explored for a wide range of pre-defined patient subgroups, based on demographic and important baseline characteristics, including age, weight, sex, race, and medical history. The overall interpretation is that there was a consistent effect on the primary composite endpoint across these subgroups. The profile of bleeding events also appeared consistent across pre-identified patient subgroups, including subgroups based on concomitant medications at baseline, and no other safety concerns were identified in any of the subgroups explored.

This consistency across subgroups indicates that the results are generalisable across all patient populations.

The definition of a minimum clinically meaningful difference for benefit, for risk, and for the balance between the two, in any clinical study is always a matter of considerable debate among clinical experts. However as stated above, using the analysis described in Unger 2009,<sup>9</sup> it is clear that the results of the PEGASUS trial demonstrate a clear and clinically meaningful difference, with the benefits obtained by managing patients with ticagrelor 60 mg BD with aspirin offsetting the potential increased risk of bleeding compared with that observed with aspirin alone.

#### ***Concomitant use of clopidogrel in the placebo group and impact on safety results***

If a patient developed an indication for use of an ADP receptor blocker and the blinded modified treatment option was not used, study drug could be discontinued and the patient treated with open label clopidogrel or other agent according to guidelines. The safety analysis was performed with an on-treatment analysis approach including events on or prior to seven days after last dose of study drug. Thus, events occurring thereafter for patients on open label clopidogrel had no impact on the safety analysis.

To assess the impact of use of blinded clopidogrel in the placebo group while on modified study drug, the sponsor performed sensitivity analyses of TIMI Major and TIMI Major or

Minor bleeding with censoring at first dose of modified study drug. The analyses excluded patient time and events occurring after the first dose of modified study treatment and in particular, does not include events occurring whilst on blinded clopidogrel. These analyses did not show marked differences from the main analyses.

In the sensitivity analysis, KM percentages at 36 months for TIMI Major bleeding events were 2.2% versus 1.0% in the ticagrelor 60 mg and placebo groups, respectively, corresponding to HR 2.30 (95% CI 1.65, 3.20) for ticagrelor 60 mg. For the main analysis, KM percentages at 36 months for TIMI Major bleeding events were 2.3% versus 1.1% in the ticagrelor 60 mg and placebo groups, respectively, corresponding to HR 2.32 (95% CI 1.68, 3.21) for ticagrelor 60 mg.

In the sensitivity analysis, KM percentages at 36 months for TIMI Major or Minor bleeding events were 3.2% versus 1.4% in the ticagrelor 60 mg and placebo groups, respectively, corresponding to HR 2.54 (95% CI 1.91, 3.38) for ticagrelor 60 mg. For the main analysis, KM percentages at 36 months for TIMI Major bleeding events were 3.4% versus 1.4% in the ticagrelor 60 mg and placebo groups, respectively, corresponding to HR 2.54 (95% CI 1.93, 3.35) for ticagrelor 60 mg.

Thus, potential concerns that the use of clopidogrel in the placebo group could dilute difference in bleeding event rates could not be substantiated.

#### ***Commencement of ticagrelor 60 mg post-infarct***

In this application, the benefit-risk analysis estimated that treating 1000 patients for 3 years with ticagrelor 60 mg prevents 12 events of all-cause mortality, MI or stroke, with no extra events of fatal bleeding or intracranial haemorrhage compared with placebo (full analysis set). Subgroup analyses were also conducted by time from qualifying MI to start of randomisation to study treatment (< 2 years versus  $\geq$  2 years). The observed effect of ticagrelor did appear slightly less pronounced in patients with longer time from qualifying MI to randomisation. This was considered likely to reflect chance findings due to the large number of subgroups analysed, and consistency across subgroups was concluded. Findings are summarised below:

- KM percentages at 36 months for the primary composite endpoint events in patients randomised to study treatment < 2 years from MI were 7.8% versus 9.7% in the ticagrelor 60 mg and placebo groups, respectively, corresponding to HR 0.77 (95% CI 0.66, 0.90) for ticagrelor 60 mg.
- KM percentages at 36 months for the primary composite endpoint events in patients randomised to study treatment  $\geq$  2 years from MI were 7.8% versus 7.9% in the ticagrelor 60 mg, and placebo groups, respectively, corresponding to HR 0.96 (95% CI 0.79, 1.17) for ticagrelor 60 mg.

The benefit-risk analysis for patients who were randomised to study treatment within < 2 years of qualifying MI, estimates that treating 1000 patients for 3 years with ticagrelor 60 mg prevents 17 events of all-cause mortality, MI, or stroke, with no extra events of fatal bleeding or intracranial haemorrhage. This is within the same order of magnitude as the benefit seen in the overall PEGASUS population.

In summary, a positive benefit-risk profile has been shown for the overall PEGASUS population. The pre-defined subgroup analyses could suggest an improved benefit in the subgroup of patients with qualifying MI occurring < 2 years before randomisation to study treatment. However, it is difficult to draw firm conclusions, and the sponsor does not recommend any restrictions to the target population based on this observation.

#### ***Relationship between ticagrelor and malignancy***

A comprehensive evaluation of fatal and non-fatal malignancy adverse events (AEs) in PEGASUS was conducted following an observed numerical imbalance of adjudicated



malignancy deaths 'on and off treatment', with more events in the ticagrelor 90 mg group than in the 60 mg and placebo groups. For ticagrelor 90 mg over placebo: malignancy AEs HR 1.15 (95% CI 0.99, 1.33), and adjudicated malignancy deaths HR 1.45 (95% CI 1.02, 2.06). The numerical imbalance was less pronounced for ticagrelor 60 mg compared with placebo, with HR 1.03 (95% CI 0.88, 1.19) for malignancy AEs, and HR 1.19 (95% CI 0.82, 1.71) for adjudicated malignancy deaths.

There was no consistency with regard to ticagrelor dose or location of neoplasms for either the reported malignancy AEs or adjudicated malignancy deaths. For patients without a history of malignancy at baseline, no increased risk of AEs of malignancy or adjudicated malignancy death was seen on ticagrelor 60 mg compared with placebo. Since neoplasms may be detected following a bleeding event, those patients who had a bleeding event prior to reported malignancy or classification of death due to malignancy were analysed. The results indicated a potential bias in the detection of malignancy events and in classification of deaths towards malignancy. Review of data from studies with other antiplatelet agents showed a link between increased reports of bleeding and increased reports of malignancy, suggesting that detection bias may play a role in increased reports of malignancy in such studies. A detailed summary and discussion of these findings was provided. It should be noted that the PEGASUS study was not designed to investigate malignancy and patients without symptoms indicative of a potential malignancy, for example a bleeding event, were not specifically investigated for possible malignancy.

In the PLATO study, there was no indication of increased risk of neoplasms; the number of deaths adjudicated as being due to malignancy was similar between ticagrelor and clopidogrel, and post-marketing safety surveillance for ticagrelor has not identified any concerns with regard to neoplasms. Nonclinical studies with ticagrelor do not support a genetic toxicology risk, nor do they support any role in tumour promotion in humans.

Subsequent to the application, in order to further support the evaluation of this topic, additional analysis has been undertaken. Malignancy AEs and adjudicated malignancy deaths are summarised by duration of exposure to study drug in Table 8. The largest number of deaths contributing to the numerical difference between treatment groups occurred in patients with  $\leq 12$  months' exposure, and there was no imbalance between treatment arms in patients with  $> 24$  months of exposure. These findings are not consistent with a drug-related malignancy signal, which would be expected to show an increased incidence of malignancies with longer duration of exposure.

**Table 8: Malignancy adverse events and adjudicated malignancy deaths by duration of exposure to study drug 'on and off treatment' (Safety analysis set)**

Duration of exposure	Ticagrelor 90 mg BD	Ticagrelor 60 mg BD	Placebo
	(N=376)	(N=335)	(N=328)
Malignancy adverse events <sup>a</sup>			
0 to ≤12 months	141	99	68
>12 to ≤24 months	62	71	69
>24 months	173	165	191
Adjudicated malignancy deaths			
0 to ≤12 months	45	35	29
>12 to ≤24 months	17	18	11
>24 months	15	10	13

<sup>a</sup> Adverse events in the SMQ 'Malignant or unspecified tumours'. N=number of patients

The initial observation of a numerical imbalance in the 90 mg ticagrelor treatment group but not in the 60 mg group also brings the biological plausibility of a drug-related response into question. The 2 ticagrelor doses achieve similar exposure, and considerable inter-patient variability translates into overlapping exposure between the 2 doses. Due to similar exposures reached by either dose group, a drug-related cancer signal, if present, would be expected to be seen with both doses of ticagrelor but this is not the case.

Overall, based on a comprehensive evaluation of fatal and non-fatal malignancy AEs in PEGASUS, the sponsor would conclude that there is no causal relationship between malignancy events and long-term treatment with ticagrelor.

#### ***Patients with a prior history of stroke***

The original PEGASUS study protocol allowed patients with a medical history of ischaemic stroke to participate. An amendment to the protocol was implemented as a precautionary measure; emerging data from studies with antiplatelet agents other than ticagrelor suggested that more intensive antiplatelet therapy might pose a high risk of intracranial haemorrhage in patients with history of ischaemic stroke<sup>10,11</sup> and the Executive Committee recommended that these patients be excluded from PEGASUS via a protocol amendment. Note that this protocol amendment did not exclude patients with a history of TIA from PEGASUS.

Adjudicated data from 2 Phase III studies (PLATO and PHILO) in ACS patients treated up to 12 months do not indicate an increased risk of intracranial haemorrhage events in

<sup>10</sup> Morrow, DA, Alberts, MJ, Mohr JP, Ameriso SF, Bonaca MP, Goto S, Hankey GJ, Murphy SA, Scirica BM, Braunwald E Efficacy and Safety of Vorapaxar in Patients With Prior Ischemic Stroke for the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events-TIMI 50 Steering Committee and Investigators Stroke. 2013;44:691-698; originally published online February 8, 2013.

<sup>11</sup> Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15.

patients with a medical history of ischaemic stroke compared to patients without a history of ischaemic stroke. In PEGASUS, there were no adjudicated intracranial haemorrhage events in patients with a history of ischaemic stroke, who were discontinued due to the study protocol amendment. These patients had limited exposure time (median 1 month, range 0 to 27 months). There were few events of adjudicated intracranial haemorrhage events in patients without a history of ischaemic stroke.

Therefore the sponsor considers the following text in the Precautions section of the prescribing information (PI), including an explanatory statement for exclusion of patients with a prior stroke in PEGASUS, to be appropriate:

*ACS patients with prior ischemic stroke can be treated with Brilinta 90 mg for up to 12 months (PLATO). In PEGASUS, patients with a history of MI ( $\geq$  one year) with prior ischemic stroke were excluded because previous studies have shown that combination use of antiplatelet agents (not ticagrelor) is associated with increased risks of intracranial haemorrhage. Therefore, in the absence of data caution is advised for treatment beyond one year.*

#### ***Inclusion of immune system events in the PI***

Table 5 in the proposed Australian PI contains adverse drug reactions (ADRs) observed in PLATO and PEGASUS Phase III clinical studies. Rash and hypersensitivity reactions including angioedema are ADRs identified during post-approval use of ticagrelor. The sponsor considers it to be more appropriate to separate Rash and hypersensitivity reactions including angioedema from the ADRs identified from clinical studies and they are therefore presented under the heading *Postmarketing experience* in the PI. However, for the EU Summary of product Characteristics (SmPC) the sponsor has accepted including Rash and hypersensitivity reactions including angioedema with frequency unknown in the Table of Adverse reactions by frequency and system organ class, following requirements from European medicines Agency (EMA).

#### ***Increased uric acid and serum creatinine in the PI***

As discussed in the separate document regarding amendments to the PI, the sponsor wishes to reiterate that subsequent to the receipt of the clinical evaluation report a revised PI document was provided to the TGA which includes the statement:

*Hyperuricaemia and gout may occur during treatment with ticagrelor (see Adverse Effects). Caution is advised in patients with a history of hyperuricaemia or gout.*

under the subheading of *Uric acid increase* and gout in the Precautions section.

The precautionary statement regarding serum creatinine has not been re-included in the PI with pending the advisory committee's consideration.

#### **Advisory Committee considerations**

The Advisory Committee on Prescription Medicines (ACPM) resolved to recommend to the TGA Delegate of the Secretary that:

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy agreed with the delegate that Brilinta tablet containing 60 mg of ticagrelor has an overall negative benefit-risk profile for the proposed indication.

In making this recommendation the ACPM;

- Advised that there is a numerically modest benefit in continuing ticagrelor 60 mg twice daily in reducing myocardial infarction, a component of the composite primary endpoint, for Caucasian male patients who are 1 to 2 years following myocardial infarction and have associated very high risk features for further cardiovascular events (and low risk for bleeding) at the expense of a numerically large risk of

bleeding. However, benefit after that time was not demonstrated, as shown on the forest plot of the subgroups, compared with the risk of bleeding.

- Was of the view that the net clinical benefit demonstrated was not clinically meaningful.

### ***Specific advice***

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Please comment on whether the demonstrated difference in primary endpoint outcomes for ticagrelor 60 mg BD and aspirin compared to aspirin alone are clinically meaningful?*

The ACPM noted that for the composite primary endpoint of ticagrelor versus placebo, the clinically meaningful benefit was marginal versus risk of bleeding. The ACPM noted that in the intention to treat (ITT) analysis, for every 1000 patients treated with ticagrelor 60 mg twice daily over 3 years versus placebo only 12 composite events (CV death/MI/stroke) will be prevented. The ACPM was of the view that combined with the increased risk of TIMI major bleeding events in the ticagrelor 60 mg BD group), the overall net clinical benefit was marginal at best.

The ACPM noted that 2988 patients will receive treatment without benefit yet having an increased bleeding risk (4.6% of ticagrelor 90 mg BD with hospitalization in 3.7%, 3.9% of ticagrelor 60 mg BD with hospitalization in 3.1%, and 2.2% of placebo group with hospitalization in 1.6% ) (see also response to question 4), and higher likelihood of AEs such as dyspnoea.

The ACPM also noted that despite the small reduction in CV deaths, death from all-causes was not different between placebo or the 60 mg ticagrelor twice daily groups.

2. *The inclusion criteria required patients over the age of 50 and most patients were male. Are the results generalisable to all patients 1 year post MI?*

The ACPM noted that most participants were male (76%, n=10734) and were overwhelmingly Caucasian (86%, n=12201). The ACPM also noted that amongst subgroups in the PEGASUS full analysis set, efficacy in female participants (24%, n=3378) versus placebo was dubious and in non-Caucasian patients outcomes were worse than placebo. The ACPM was of the view that the heterogeneity in results across sub-groups makes generalising overall findings across the whole population difficult.

3. *The sponsor has been requested to amend its proposed precautionary statement about the absence of data from a population with previous stroke. Please comment on whether the statement is now adequate to convey the risks and uncertainties for this population.*

The ACPM advised that this statement was now adequate.

4. *Do the benefits of ticagrelor 60 mg BD with aspirin offset the increased risk of bleeding to offer an overall favourable benefit-risk?*

The ACPM noted although deaths from bleeding were similar, there was an increased risk of TIMI major bleeding events in the ticagrelor 60 mg BD (twice daily) group.

Bleeding serious adverse events (SAEs) occurred in 3.9% of ticagrelor 60 mg BD patients versus 2.2% in the placebo group, with 3.1% versus 1.6% requiring hospitalisation respectively. The ACPM also noted significantly higher bleeding requiring transfusion in the treatment group (ticagrelor 90 mg: 3.2% /ticagrelor 60 mg: 3.1%/ placebo: 1.7%). The ACPM was of the view that the need for transfusion is a clinically meaningful outcome.

As noted in the response to question 1, the ACPM was of the view with current data the increased bleeding risks did not offset the clinical benefit.

5. *Has the sponsor provided sufficient evidence to support the removal of precautionary statements about:*
- Increased uric acid*
  - Increased serum Creatinine?*

The ACPM noted the sponsor's pre-ACPM response states that it had provided a revised PI which includes the statement

*Hyperuricaemia and gout may occur during treatment with ticagrelor (see Adverse Effects). Caution is advised in patients with a history of hyperuricaemia or gout.*

under the subheading of *Uric Acid Increase and Gout* in the Precautions section. This was considered appropriate.

The ACPM was of the opinion the precautionary statement regarding increased serum creatinine should be re-inserted similar to the US Package Insert or the EU Summary of Product Characteristics.

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

- The ACPM noted that there were a small number of patients with moderate hepatic impairment in the clinical trials. However, the ACPM advised that under *Contraindications*, the PI should state *moderate* to severe hepatic impairment, as moderate hepatic impairment could also increase the risk of bleeding.

## Outcome

Based on a review of quality, safety and efficacy, TGA decided not to register Brilinta 60 mg tablet for the proposed indication on the grounds that the safety and efficacy of the goods have not been satisfactorily established for the purposes for which the therapeutic goods are to be used.

The Delegate considered that the quality of Brilinta 60 mg tablets for the proposed indications has been satisfactorily established.

For the following reasons which demonstrate the increased risk of bleeding with the use of Brilinta 60 mg for the proposed indication, the Delegate is not satisfied that the sponsor has satisfactorily established the safety of Brilinta 60 mg tablets for this purpose:

- It is recognised that ticagrelor is taken in conjunction with aspirin, and that in the PEGASUS study the bleeding risk of dual anti-platelet therapy (60 mg ticagrelor plus aspirin) is compared with single anti-platelet therapy (aspirin only) in the placebo group, and that more bleeding events are anticipated with dual anti-platelet therapy.
- The sponsor provided analyses using different bleeding event classifications but the classification used in its pre-specified analysis of benefit and risk (net clinical benefit) is TIMI Major bleeding. This is a laboratory endpoint and does not take into account the clinical state of the patient during the bleeding event and the extent of intervention required to manage the bleeding event (including resuscitation, use of blood products and surgical intervention). For an acute fall of haemoglobin of 5 or more grams there has been very significant bleeding, and is likely to have included a degree of cardiovascular compromise. An actively resuscitated patient with an acute, potentially life threatening bleeding may not have a fall of haemoglobin of 5 g or more reported because of resuscitation with packed red blood cells and other interventions to reduce the bleeding such as surgery, or interventional radiology. When TIMI major bleeding was subcategorised into spontaneous, procedural and traumatic, all subcategories of bleeding events were more common in the ticagrelor group. The largest difference was

in spontaneous bleeding events that occurred in (KM%) 1.7% of the ticagrelor 60 mg group and 0.7% of the placebo group. This is of concern since these events can be less easily predicted. The absolute risk increase is similar in magnitude to the absolute risk reduction (ARR) for the composite primary endpoint of the studies and the spontaneous TIMI major bleeding events.

- The sponsor analysed the impact of fatal events and intracranial haemorrhage and 'Other' major bleeding events on the total bleeding events that contributed to the TIMI Major bleeding and found a more than three-fold increased risk of 'Other' bleeding events. These other events included gastrointestinal bleeding. Gastrointestinal bleeding is associated with significant morbidity and mortality, particularly in the elderly.
- TIMI Minor bleeding events were also three times more common in the ticagrelor 60 mg BD group (0.6%) compared to placebo (0.2%).
- When TIMI Major and Minor bleeding events were considered together these occurred in 3.4% of the ticagrelor 60 mg BD patients and 1.4% of the placebo patients, with the largest difference being in the number of spontaneous bleeding events. When PLATO bleeding events were analysed 2.5% of the ticagrelor 60 mg group and 0.9% of the placebo group had PLATO major bleeding events. The Delegate considers this is a more clinically meaningful measure of bleeding outcomes than the TIMI categories because it takes into consideration interventions such as blood transfusion that may influence the laboratory findings.
- The sponsor has described the bleeding events that were not an intracranial haemorrhage or resulting in death as 'manageable' and did not consider these as causing irreversible harm. The use of TIMI bleeding categories may therefore underestimate the seriousness of the bleeding events. TIMI Major and Minor bleeding events considered together, or PLATO Major bleeding are considered more clinically meaningful. For each of these categories the ticagrelor 60 mg BD group had a 2.5 fold increase in risk of bleeding. For this reason the Delegate has not accepted the sponsor's assessment and has taken into consideration bleeding events that the Delegate considers to be of clinical concern.
- An additional concern with significant bleeding events is that patients discontinue all anti-platelet therapy indefinitely or for a period of time following the bleeding event. The cessation of anti-platelet therapy exposes them to their background risks of atherothrombotic events. Resuscitation with blood products may further (albeit temporarily) increase the patient's risk of thromboembolic events by creating a hypercoagulable state. Therefore a bleeding event not only exposes the patient to the risks of the bleeding itself, such as hypovolaemia hypotension and potential loss of function of the bleeding organ, but also to the risks of any intervention to stop the bleeding, and to the risks of either permanently or temporarily discontinuing their antiplatelet therapy. While both the ticagrelor and placebo groups were exposed to these risks associated with bleeding events were more commonly experienced by patients in the ticagrelor group.

A small benefit was demonstrated in the PEGASUS study which was provided by the sponsor in support of their application to register Brilinta 60 mg tablets for the proposed indication. The following points outline the Delegate's consideration of this study:

- The primary efficacy endpoint was the time to first occurrence of any event from the composite of cardiovascular death, non-fatal MI or non-fatal stroke comparing ticagrelor 60 mg BD and placebo (noting that aspirin was taken by all study participants). From a clinical perspective the comparison is between single antiplatelet therapy and dual antiplatelet therapy. The primary analysis was a comparison of *'the time from randomization to the first occurrence of any event in the composite endpoint*

using the Cox proportional hazards model with a factor for treatment group'. Although the primary endpoint was statistically significant the Delegate finds the incremental benefit of ticagrelor 60 mg BD in addition to aspirin (ARR 1.2% in the primary composite endpoint after 3 years of treatment) is very small and of uncertain clinical benefit.

- The subgroup analyses of the primary composite endpoint identifies some patient groups that may not benefit from ticagrelor, including female patients, patients with a BMI > 30 kg/m<sup>2</sup>, patients whose MI was more than 2 years prior to the commencement of ticagrelor, and patients whose ADP inhibitor therapy ceased more than 30 days previously. It is recognised that although these subgroups were pre-specified the study was not specifically powered for these comparisons and some of the findings could have occurred by chance. These findings raise doubt about the generalisability of the study results for all patients covered by the proposed indication.
- The efficacy endpoints were not supported by the secondary endpoints of reduction in cardiovascular death and all-cause mortality, because neither of these endpoints was statistically significant for the ticagrelor 60 mg BD patients compared with the placebo group.
- When considered individually, the components of the primary endpoint (cardiovascular death, non-fatal MI or non-fatal stroke) each contributed to the overall outcome. The reduction in cardiovascular death (ARR 0.5%) as noted above was not statistically significant. A reduction in myocardial infarction (ARR [KM%] 0.7%) and stroke (ARR [KM%] 0.4%) occurred with ticagrelor 60 mg compared with placebo after 3 years of treatment. Considering that the ticagrelor group received dual anti-platelet therapy with both ticagrelor 60 mg and aspirin and the placebo group received only aspirin the small differences for each of these hard clinical outcomes is not persuasive of an overall strong clinical benefit for ticagrelor 60 mg.
- The Delegate has concerns about the generalisability of the results of the clinical trial population to the general Australian population proposed for the indication. In particular, PEGASUS study was only conducted in the participants aged > 50 years. The indication does not include an age restriction. While this appears reasonable, since atherothrombotic events are not confined to patients aged >50 years, limitations of the trial data make it difficult to assess the risks and benefits for these patients. No additional clinical data upon which to draw confirmatory support for this patient group has been provided. Accordingly, while it may be assumed that the risks for younger patients may be lower than older patients taking anti-platelet agents the sponsor has not provided evidence in younger patients with the proposed indication to support this assumption.
- Patients with CABG within the previous 5 years were also excluded. This population is likely to have multiple areas of stenosis or more complex disease and may be prescribed dual anti-platelet therapy. Exclusion of this population adds to the uncertainty about the generalisability of the PEGASUS study for the Australian population for whom the Brilinta 60 mg tablet is likely to be prescribed.
- Although initially permitted in the PEGASUS study patients with stroke prior to enrolment were later excluded because of an increased risk of intracranial haemorrhage found in association with another anti-platelet agent in this patient group. While the sponsor has proposed including a warning in the PI to identify that this population has not been studied, the exclusion of this group potentially poses a potential problem for clinicians transitioning patients from that have been treated with Brilinta 90 mg tablets for the currently approved indication. There is no restriction on the use of ticagrelor for ACS in patients with a previous stroke and treatment for the first year post event with Brilinta 90 mg tablets. Because of the

exclusion of this population from the PEGASUS study, there is uncertainty about the safety of this population that may transition from Brilinta 90 mg tablets to Brilinta 60 mg tablets beyond one year, and, although not demonstrated in the relatively small number of patients with prior stroke enrolled in the study prior to the protocol change, there may be an increased risk of intracranial haemorrhage.

- The sponsor submitted a single study in support of its indication. There are no confirmatory Phase III studies in similar or broader populations that support or reinforce the findings of the PEGASUS study, or resolve some of the uncertainties. Although PEGASUS was large and well conducted, for the reasons outlined above, the Delegate considered that it did not provide compelling evidence of the safety and efficacy of ticagrelor 60 mg BD for the proposed indication.

The Delegate is not convinced from this study that the marginal benefit of Brilinta 60 mg tablets for the proposed indication outweighs the risks. In particular, the Delegate has identified a more than doubled risk of major bleeding and a tripled risk of Other TIMI Major bleeding events which of themselves are a cause of significant morbidity and carries their own risks of irreversible harm that cannot be measured in terms of immediate loss of life. The Delegate has given consideration to the sponsor's argument that the benefits of ticagrelor in terms of the reduction of cardiovascular events should be balanced against the risks of fatal events and intracranial haemorrhage as determined in the PEGASUS study. In weighing up the risks of Brilinta 60 mg tablets for the proposed indication the Delegate has considered that the all bleeding events included in the TIMI Major bleeding events category pose a potential risk of death or irreversible harm to patients in the community, outside the clinical trial setting, although that risk may not have been realised in the PEGASUS study. The Delegate has considered the benefits demonstrated by the PEGASUS study are of overall marginal clinical benefit, and that a large number of patients offered treatment with ticagrelor would not benefit from the therapy. The Delegate has considered that there are limitations to the generalisability of the efficacy results from the PEGASUS study to all patients one year or more post MI.

The EU guideline states that when a single pivotal study is presented the evidence should be compelling. Although there was a statistically significant difference for the composite primary endpoint the Delegate did not find the difference between the absolute numbers of patients in each of the treatment groups, the KM% at three years, and the upper bound of the 95% confidence limit of the hazard ratio that approaches unity to be compelling evidence of the efficacy as is recommended in the EU guideline for a single pivotal study. As the sponsor points out, only 12 of 1000 patients treated will gain an additional benefit in reduction of events from the primary composite endpoint over the use of aspirin alone. Conversely, 988 patients will receive the treatment with no additional benefit.

The sponsor in their pre-ACPM response and in their Post-ACPM response urged that the decision maker should adopt the approach taken by Unger 2009.<sup>9</sup> In this paper Unger described the approach taken by the FDA in its consideration of prasugrel (as described). This post hoc approach selected fatal bleeding events and intracranial haemorrhage as the events that should be balanced against the composite efficacy endpoint. The Delegate has considered that this approach as it applies to this application is exploratory since it was not pre-specified in the PEGASUS trial as an endpoint. The Delegate finds that this approach does not take into account the seriousness of TIMI Major bleeding events. As previously noted in this letter, the net clinical benefit is marginal, and the Delegate has not considered this benefit to be clinically meaningful, when taking into account the seriousness of the bleeding events which result in their classification as TIMI Major.

The Delegate has considered the advice of ACPM, to which the Delegate agrees. As such and for the reasons stated above, the Delegate does not consider the sponsor has satisfactorily established the safety and efficacy of Brilinta 60 mg tablets for the proposed indication.



**Conclusion in relation to application to register Brilinta 60 mg tablets for the proposed indications**

In accordance with section 25 (3) of the Act the Delegate has decided not to register Brilinta 60 mg tablets for the proposed indication because the safety and efficacy of the goods have not been satisfactorily established for the purposes for which they are to be used.

**Attachment 1. Extract from the Clinical Evaluation Report**

## **Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia  
Email: [info@tga.gov.au](mailto:info@tga.gov.au) Phone: 1800 020 653 Fax: 02 6232 8605  
<https://www.tga.gov.au>