



Australian Government

Department of Health and Ageing  
Therapeutic Goods Administration

# Australian Public Assessment Report for Ticagrelor

Proprietary Product Name: Brilinta

Sponsor: AstraZeneca Pty Ltd

July 2011

**TGA** Health Safety  
Regulation

## About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

## About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

### Copyright

© Commonwealth of Australia 2011

This work is copyright. Apart from any use as permitted under the Copyright Act 1968, no part may be reproduced by any process without prior written permission from the Commonwealth. Requests and inquiries concerning reproduction and rights should be addressed to the Commonwealth Copyright Administration, Attorney General's Department, National Circuit, Barton ACT 2600 or posted at <http://www.ag.gov.au/cca>

# Contents

<b>I. Introduction to Product Submission</b>	<b>4</b>
Submission Details	4
Product Background	4
Regulatory Status	5
Product Information	6
<b>II. Quality Findings</b>	<b>6</b>
Drug Substance (active ingredient)	6
Drug Product	7
Bioavailability	7
Advisory Committee Considerations	8
Quality Summary and Conclusions	8
<b>III. Nonclinical Findings</b>	<b>9</b>
Introduction	9
Pharmacology	9
Pharmacokinetics	11
Toxicology	12
Nonclinical Summary and Conclusions	19
<b>IV. Clinical Findings</b>	<b>21</b>
Introduction	21
Pharmacodynamics	21
Pharmacokinetics	32
Efficacy	51
Safety	61
List of Questions	83
Clinical Summary and Conclusions	83
<b>V. Pharmacovigilance Findings</b>	<b>88</b>
Risk Management Plan	88
<b>VI. Overall Conclusion and Risk/Benefit Assessment</b>	<b>90</b>
Quality	90
Nonclinical	90
Clinical	90
Risk Management Plan	95
Risk-Benefit Analysis	95
Outcome	105
<b>Attachment 1. Product Information</b>	<b>106</b>

# I. Introduction to Product Submission

## Submission Details

<i>Type of Submission</i>	New Chemical Entity
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	9 June 2011
<i>Active ingredient(s):</i>	Ticagrelor
<i>Product Name(s):</i>	Brilinta
<i>Sponsor's Name and Address:</i>	AstraZeneca Pty Ltd Alma Road North Ryde NSW 2113
<i>Dose form(s):</i>	Film coated tablets
<i>Strength(s):</i>	90 mg
<i>Container(s):</i>	Blister pack
<i>Pack size(s):</i>	14 or 56 tablets
<i>Approved Therapeutic use:</i>	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).
<i>Route(s) of administration:</i>	Oral
<i>Dosage:</i>	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.
<i>ARTG Number:</i>	167237

## Product Background

Cardiovascular disease (CVD) is the single largest cause of mortality, morbidity and hospitalisation in the developed world. When atherosclerotic plaques erode or rupture in CVD, the plaque contents activate platelets and the coagulation cascade, with aggregation of platelets and rapid thrombus formation causing partial or total vessel occlusion and acute ischaemic syndrome. Thrombus formation in the coronary arteries can thus result in acute coronary syndrome (ACS) (unstable angina [UA] or myocardial infarction [MI]). A high proportion of patients will die, have recurrent MI, or be rehospitalised, in the months following ACS.

Antiplatelet drugs act on the pathophysiological process by decreasing platelet aggregation. Current treatment guidelines require dual antiplatelet therapy (with acetylsalicylic acid [ASA] [which prevents thromboxane production] and an adenosine diphosphate [ADP] receptor antagonist [which binds irreversibly to P2Y<sub>12</sub> receptors]) as soon as possible regardless of choice of other treatments, for up to 12 months post ACS or post implantation of a drug eluting stent. Despite such treatment, serious CV events still occur in ~11% of patients in the months following ACS. Better antiplatelet therapy may prevent more of these events.

Ticagrelor is the first agent of a new cyclopentyltriazolopyrimidine class that binds reversibly to P2Y<sub>12</sub> preventing signal transduction and thereby markedly decreasing platelet aggregation. According to the sponsor, advantages of ticagrelor over clopidogrel appear to be: quicker onset of action (ticagrelor active on absorption and major metabolite is also active, whereas inactive prodrug clopidogrel requires transformation to active metabolite); quicker offset of action in case of need for surgery (ticagrelor binds reversibly to P2Y<sub>12</sub> so platelet aggregation returns on cessation of therapy, clopidogrel binds irreversibly to P2Y<sub>12</sub> so platelet aggregation returns on generation or transfusion of new platelets); lower interpatient variability (ticagrelor is active on absorption in all patients, clopidogrel shows inconsistent transformation of inactive prodrug to active metabolite); and greater inhibition of platelet aggregation (IPA) and greater clinical efficacy without an increase in bleeding risk.

No previous study has shown a mortality benefit for non ST elevation MI (NSTEMI) and only one study has shown a mortality benefit for ST elevation MI (STEMI). The PLATO study comparing ticagrelor to clopidogrel in patients with ACS (UA, NSTEMI and STEMI; whether intended for percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG] or medical management) was planned based on results from 41 clinical pharmacology studies in healthy volunteers, 4 Phase II studies in patients with atherosclerosis/stable coronary artery disease (CAD), and discussions with the FDA and Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) among others.<sup>1</sup>

This AusPAR describes the evaluation of a submission by the sponsor, AstraZeneca Pty Ltd, to register ticagrelor (Brilinta). The proposed indication is:

*the prevention of thrombotic events (cardiovascular [CV] death, myocardial infarction [MI] and stroke) in patients with Acute Coronary Syndromes (ACS) (unstable angina [UA], non ST elevation MI [NSTEMI] or ST elevation MI [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) (with or without stent) or coronary artery-bypass grafting (CABG).*

## **Regulatory Status**

A similar application was approved in the European Union (EU) on 3 December 2010 and in Canada on 30 May 2011. A similar application was submitted to the US on 16 November 2009. The approved indication in the EU is:

*co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with Acute Coronary Syndromes (unstable angina, 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).*

<sup>1</sup> Wallentin L, Becker RC, Budaj A et al. Ticagrelor versus clopidogrel in acute coronary syndromes. *N Engl J Med* 2009; 361: 1045-57.

## Product Information

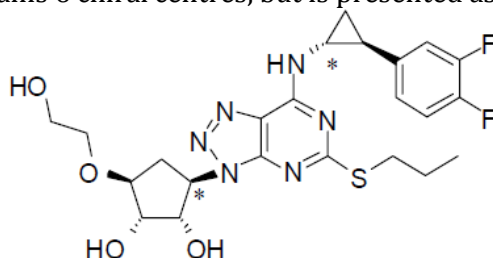
The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

## II. Quality Findings

### Drug Substance (active ingredient)

Ticagrelor is a new chemical entity that is an anti-platelet agent not related to the registered anti-platelet agents (ticlopidine and clopidogrel). There are no compendial monographs for the drug substance or for finished products containing this drug substance.

The drug substance contains 6 chiral centres, but is presented as a single diastereoisomer.



(1S,2S,3R,5S)-3-[7-[[[(1R,2S)-2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol.

$C_{23}H_{28}F_2N_6O_4S$

Molecular mass = 522.57

CAS # = [274693-27-5]

$pK_a = \text{none}$

Aqueous solubility = 16  $\mu\text{g/mL}$  (0.0016 %w/v, practically insoluble) independent of pH

Biopharmaceutical Classification System (BCS) Class 4.

Ticagrelor is prepared completely by chemical synthesis in a 5 step process which ensures the chirality of each chiral centre.

The route of synthesis leads to a single polymorphic form of the anhydrous, non-solvated material. Other polymorphs have been generated but are not formed in the proposed process. The final material precipitates as fine crystals and further micronisation is not necessary.

The specification for ticagrelor drug substance includes satisfactory limits for assay and particle size distribution. Three of the synthetic impurities have proposed limits above the International Conference on Harmonisation (ICH) qualification threshold of 0.15%. Toxicological data was provided to support the limits for UL127 and UL133 and UL134 was considered qualified as it is a metabolite (*inactive*).<sup>2</sup> One of the residual solvents (isooctane) was not listed in ICH guidance. However, the proposed limit was considered qualified by the Medicines Toxicology Evaluation Section of the TGA. The other residual solvent (ethyl acetate) was limited to the limit allowed by ICH guidance.

<sup>2</sup> Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

## **Drug Product**

The tablets are to be manufactured by a single site. The process is typical and involves dry mixing, wet granulation with water, drying, milling, lubrication, compression, coating and packaging. The bulk tablets may be stored in foil bags and shipped to other sites for primary packaging.

The specifications have acceptable expiry limits and identical release limits. This is acceptable as no changes occur on storage

Stability data were provided to support an unopened shelf life of 2 years when stored below 30°C. No other conditions are required.

## **Bioavailability**

### **Clinical Background**

The product used in the Phase III clinical efficacy studies is of the same formulation as that proposed for registration.

### **Studies submitted**

The submission included:

- An absolute bioavailability study (Study D5130C00038).
- A study comparing tablets manufactured with micronised and non-micronised drug substance (Study D5130C00031).
- A study comparing the commercial scale tablets to the pilot scale tablets used in the Phase III clinical efficacy studies (Study D5130C00047).
- A study comparing the proposed tablets to an oral solution (Study D5130C00055). and
- A study on the effect of food on bioavailability (Study D5130C00033).

The levels of ticagrelor (AZD6140) and its active metabolite des-hydroxyethyl ticagrelor (AR-C124910XX) in plasma were determined using a number of related methods with HPLC-MS/MS determination after protein precipitation with acetonitrile. Adequate validation data for these methods were provided.

### ***Study D5130C00038***

This was a two way crossover study in 12 healthy subjects. The study was of an appropriate design using the proposed commercial tablet formulation.

The results indicated that the absolute bioavailability of ticagrelor is 36% with a range of 25-64%. The mean systemic clearance was 14.2 L/h and the geometric mean volume of distribution was 87.5 L.

### ***Study D5130C00031***

This was a three way crossover study in 30 subjects. The study was of an appropriate design using earlier tablet formulations: formulation 318 used non-micronised ticagrelor; and formulations 319 and 307 used micronised ticagrelor. Other than the particle size distribution of the ticagrelor, formulations 318 and 319 were identical. Formulation 307 was used in Phase IIb clinical studies. Formulation 318 was similar to the proposed formulation 334 and it was accepted that the study was relevant.

The results indicated that tablets manufactured with non-micronised ticagrelor are bioequivalent to tablets micronised with micronised ticagrelor. For ticagrelor the 90% confidence intervals (CIs) were 0.91-1.02 for the area under the plasma concentration time curve (AUC) and 0.82-1.00 for the maximal plasma concentration ( $C_{max}$ ). For AR-C124910XX the 90% CIs were 0.93-1.01 for AUC and 0.85-1.02 for  $C_{max}$ . Formulation 307 was also bioequivalent to both formulations 318 and 319.

#### **Study D5130C00047**

This was a two way crossover study in 42 subjects. The study was of an appropriate design using the proposed commercial tablet formulation, manufactured at either the proposed site in Sweden or a pilot scale site.

The results indicated that tablets manufactured at the two sites are bioequivalent. For ticagrelor the 90% CIs were 0.97-1.05 for AUC and 0.89-1.02 for  $C_{max}$ . For AR-C124910XX the 90% CIs were 0.95-1.00 for AUC and 0.85-0.96 for  $C_{max}$ .

#### **Study D5130C00055 (summarised only)**

This was a five way crossover study in 24 subjects. It compared the proposed tablets (B) to an oral solution (A), a tablet compressed to 200% of normal hardness (C), a tablet compressed from only granules > 1 mm (D), and a tablet with no disintegrant and double the binder content (E).

This study was used to justify the chosen dissolution test method. Tablets B and C had similar dissolution profiles. However tablets D and E were much slower to dissolve. The results showed that tablets B, C and D all had similar  $C_{max}$  and AUC results (but slightly lower AUC than the oral solution). However tablet E had a similar AUC, but lower  $C_{max}$ . Thus tablets will fail the dissolution test before bioequivalence is observed.

#### **Study D5130C00033**

This was a two way crossover study in 52 subjects. The study used two cohorts each of 26 subjects. Cohort A received formulation 318 after an overnight fast or with a high fat meal and cohort B received formulation 319 after an overnight fast or with a high fat meal. The study was considered relevant.

The results were similar for each cohort and indicated that food increases AUC for ticagrelor by 20% and the time to maximal plasma concentration ( $T_{max}$ ) by 45 minutes (but not  $C_{max}$ ) and decreases  $C_{max}$  for metabolite AR 124910XX by 25% (but not AUC) and increases  $T_{max}$  by 2 hours. These results were brought to the attention of the Delegate.

### **Advisory Committee Considerations**

Details of this submission were presented at the 134th meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) in September 2010. The PSC endorsed all questions raised by the quality evaluator and had no need to review the submission again if all outstanding issues were resolved to the satisfaction of the TGA.

### **Quality Summary and Conclusions**

Approval of the sponsor's application was recommended with respect to chemistry and quality control.

In relation to bioavailability it was brought to the attention of the Delegate that:

- The absolute bioavailability of ticagrelor from the tablets is 36%.



Food increased the AUC of ticagrelor by 21% and the  $T_{max}$  by 45 minutes, but did not affect  $C_{max}$ . Also food did not affect the AUC of the active metabolite of ticagrelor, but reduced the  $C_{max}$  by 20% and increased  $T_{max}$  by 2 hours. The sponsor claimed that these differences were of minimal clinical significance and the product information (PI) recommends dosing both with and without food.

### III. Nonclinical Findings

#### Introduction

##### Overall quality of the nonclinical dossier

The nonclinical data submitted in support of the safety and efficacy of ticagrelor were extensive and of high quality. Most studies were performed according to Good Laboratory Practice (GLP) standards.

##### Rationale

Ticagrelor is indicated for the prevention of thrombotic events (cardiovascular death, myocardial infarction, and stroke) in patients with ACS, unstable angina, and myocardial infarction. The development of ticagrelor was predicated on several perceived shortcomings of current antithrombotic prophylaxis. These shortcomings include: significant risk of recurrence of serious cardiovascular events; slow onset of maximal drug action; incomplete inhibition of platelet activity; slower conversion of prodrug to active metabolite in a significant fraction of the population; slow recovery of coagulation response after drug treatment; and increase in major bleeding events.

##### Pharmacology

##### Primary pharmacodynamics

Ticagrelor is an antagonist of the  $P2Y_{12}$  purinergic receptor, which is a member of the  $P2Y$  family of G protein coupled receptors that are activated by extracellular nucleotides. Stimulation of the  $P2Y_{12}$  receptor is a part of the mechanism leading to the activation of fibrinogen receptors and platelet aggregation during the response to vascular injury. Drug properties were demonstrated in *in vitro* ligand receptor binding studies using human washed platelet membranes. It was shown that ticagrelor binds to receptors reversibly with a  $K_i$  value of 2 nM (indicating high affinity), does not require metabolic activation and does not interact with the receptor's ADP binding site. These properties distinguish ticagrelor from thienopyridine type  $P2Y_{12}$  inhibitors (for example, clopidogrel and prasugrel).

AR-C124910 (the O-de-ethylated and major circulating metabolite of ticagrelor in man) was shown to have similar properties to the parent compound. Both ticagrelor and AR-C124910 showed potent, concentration dependent inhibition of ADP induced platelet aggregation when tested *in vitro* in blood or platelet rich plasma from various mammalian species (including man). *Ex vivo* experiments, measuring ADP induced platelet aggregation in blood from ticagrelor dosed animals, demonstrated a close correlation between the pharmacodynamic and pharmacokinetic profiles of the drug. Ticagrelor was markedly more effective at inhibiting arterial thrombosis than haemostasis when tested *in vivo* in the cyclic flow reduction model in anaesthetised dogs.

Overall, the submitted primary pharmacodynamic studies showed that ticagrelor inhibits platelet aggregation by inhibiting  $P2Y_{12}$  purinergic receptor activation and thus support the use of ticagrelor in the prevention of secondary cardiovascular events in patients with ACS.

## Secondary pharmacodynamics

The activity of ticagrelor (and in some cases its metabolites AR-C124910 and AR-C133913) was tested against a wide variety of receptors and enzymes, generally using cell lines transfected with the human gene of interest. The drug showed no significant activity against various receptors and enzymes including other P2Y family members, P2X receptors, chemokine receptors, glucocorticoid receptors and oestrogen receptors. Moreover, it was shown that ticagrelor did not significantly inhibit ADP independent platelet aggregation.

Ticagrelor showed weak to moderate inhibition (median inhibitory concentrations [IC<sub>50</sub>] values about 1-10 µM) of adenosine A<sub>3</sub> receptor, adenosine transporter, the urate transporter Organic Anion Transporter (OAT) 3, phosphodiesterases PDE3, PDE4, and PDE5, phospholipase C, platelet activating factor, and human ether-a-go-go related gene (hERG) potassium channel.

Ticagrelor inhibited the human erythrocyte adenosine transporter system *in vitro* (IC<sub>50</sub> value of 100 nM) and augmented the increase in coronary blood flow induced by either endogenous or exogenous adenosine in a beagle dog study.

Ticagrelor was a potent antagonist of GPR17 activation induced by both uracil nucleotide and cysteinyl leukotriene ligands (IC<sub>50</sub> values of about 1-10 nM). Antagonism of GPR17 receptor by ticagrelor may be beneficial as this receptor is highly expressed in brain, heart and kidney, and may be an important mediator of ischaemia induced tissue damage.

## Safety pharmacology

A number of safety pharmacology studies used adult male rats given single oral doses of ticagrelor up to 100 mg/kg, corresponding to a plasma C<sub>max</sub> about ten times that anticipated at the maximum human therapeutic dose of 90 mg. These studies showed no effect of ticagrelor dosing on motor coordination, thermal nociception, memory, response to anaesthesia, or response to chemically or electrically induced convulsions. However, rats dosed at 100 mg/kg did show a significant decrease (-29%) in intestinal transit and changes in renal function (increases in sodium and chloride excretion).

Ticagrelor has low potential for QT interval prolongation: it caused only weak inhibition of hERG (IC<sub>50</sub> 1.72 µM), had no significant change on action potential parameters in isolated canine Purkinje fibre preparations in protein free buffer up to 5 µM, and had no significant effect on electrocardiogram (ECG) or arterial parameters in anaesthetised dogs at single doses up to 100 mg/kg.

The possible respiratory effects of ticagrelor were extensively examined in rats and were of particular interest given the increased incidence of dyspnoea observed in clinical trials. Although initial nonclinical studies suggested that ticagrelor stimulates respiration, perhaps via an effect on adenosine receptors, follow up studies failed to show consistent effects.

## Pharmacodynamic interactions

Possible interactions were examined for several drugs that might be used clinically in combination with ticagrelor using either dog or rat models. Ticagrelor was shown to retain a greater effectiveness at inhibiting arterial thrombosis than haemostasis when combined with the anticoagulants acetylsalicylic acid or melagatran. The combination of ticagrelor with other P2Y<sub>12</sub> receptor inhibitors did not significantly alter the anticoagulant efficacy of either drug (that is, additive results were obtained). Furthermore, the ability of ticagrelor to decrease thrombus mass and prolong bleeding time was not affected when it

was combined with agents that decrease blood loss by enhancing thrombus formation (deamino-Cys1,D-Arg8-vasopressin, aprotinin or tranexamic acid).

## **Pharmacokinetics**

### **Absorption and plasma pharmacokinetics**

Studies were performed in multiple species (including mouse, rat, rabbit, dog and marmoset) and standard plasma pharmacokinetic parameters for ticagrelor and its active metabolite AR-C124190 were derived based on measurements obtained using validated protocols.

The oral bioavailability of ticagrelor was 88% in rat and 37% in marmoset. Absorption was moderate with  $T_{max}$  typically around 2-4 hours. Plasma exposure to ticagrelor was approximately dose proportional at low doses but greater than dose proportional at the higher doses used in the toxicology studies. AR-C124910 exposure was typically around 30-40% of ticagrelor exposure. Gender differences were only observed in the rat, where females showed higher exposure to ticagrelor and lower exposure to active metabolite than male rats, a result suggesting more rapid metabolism of ticagrelor in male rats. Ticagrelor exposure increased during repetitive dosing but at lower doses this increase was modest (<2 fold) even after a year of dosing.

*In vitro* studies of the movement of ticagrelor and its active metabolite AR-C124910 across cell monolayers indicated that both compounds show high permeability and are subject to rapid efflux. Both compounds are P-glycoprotein (P-gp) substrates as well as weak P-gp inhibitors.

### **Distribution**

Binding of ticagrelor to blood cells from various species was relatively low, ranging from 15-20% in humans to 39-54% in rabbits. Plasma protein binding was very high (>98%) for both ticagrelor and AR-C124910 in all species tested.

Following oral administration of radiolabelled ticagrelor to the rat, radioactivity was widely distributed, with the highest concentrations in liver, kidney and adrenal glands. Radioactivity was rapidly eliminated and by 24 hours post dose levels in the majority of tissues were close to background. Comparison between albino and pigmented rats indicated similar distributions of radioactivity with no significant level of binding by melanin. Pregnant rats showed a similar distribution pattern to that found in male animals. Placenta showed the highest levels of radioactivity of the reproductive tissues and was above the blood concentration.

### **Metabolism**

The major routes for metabolism of ticagrelor involve loss of the hydroxyethyl side chain to form the active metabolite, AR-C124910, and loss of a difluorophenyl-cyclopropyl group to form AR-C133913. Other minor metabolites derived from hydroxylation or glucuronidation of ticagrelor, AR-C124910 or AR-C133913. A qualitatively similar spectrum of metabolites was produced in the different animal species examined and this was comparable to the metabolic profile obtained in clinical studies. However, metabolites formed via glucuronidation of ticagrelor or oxidized ticagrelor were found at higher levels in human urine relative to other species.

The conversion of ticagrelor to its major metabolites AR-C124910 and AR-C133913 was shown to be catalysed by both cytochrome P450 (CYP) 3A4 and CYP3A5. These enzymes may have comparable activity at near therapeutic concentrations of ticagrelor. *In vitro* studies using human microsomes show that ticagrelor had no inhibitory effect on CYP1A2, CYP2C19, or CYP2E1 activities, it was a very weak inhibitor of CYP2C8 and CYP2B6 and

showed moderate inhibitory activity towards CYP2C9 and CYP2D6. Ticagrelor showed a complex interaction with CYP3A4 that was highly variable (ranging from activation to partial inhibition to potent inhibition), depending on the substrate and pathway examined. Ticagrelor also showed different levels of inhibition of CYP3A5 depending on the pathway examined. Pre-incubation of CYP enzymes with ticagrelor or its metabolites AR-C124910 and AR-C133913 showed that these compounds did not induce time dependent inactivation of CYP3A or CYP2B6 activity. It therefore appears unlikely that ticagrelor and its metabolites will significantly affect the metabolism of coadministered drugs that are metabolised by other than CYP3A enzymes.

The effect of ticagrelor on testosterone metabolism (catalysed by CYP3A4 and CYP3A5) was examined using human liver microsomes from individual female donors. IC<sub>50</sub> values obtained ranged from 10 to 20 µM, which are considerably higher than clinical C<sub>max</sub> values measured after a human therapeutic dose of 90 mg of ticagrelor.

Possible CYP enzyme induction was studied in rats given up to 300 mg/kg/day of ticagrelor for 28 days. Relative to other agents, only modest levels of induction (generally only at the high dose [HD]) occurred, that were unlikely to be of biological significance. Similar studies with human hepatocyte cultures showed that a 3 day exposure to ticagrelor (20 µM) or AR-C124910 (10 µM) produced weak induction of CYP2B6 and CYP2C9, but did not increase levels of CYP1A1, CYP1A2 or CYP3A4 activity.

## **Excretion**

The major route of drug elimination in all species studied, irrespective of dose or route, was via the faeces. Experiments with bile duct cannulated rats, given an intravenous (IV) dose of radioactively tagged ticagrelor, showed that around 70% of the total dose was excreted in bile within 24 hours of dosing, with a further about 10% found in faeces (possibly due to efflux into the alimentary tract). Radioactivity recovery in faeces was >90% and >80% in mice and rats, respectively, with only low levels of renal elimination (<1-3%). The predominant components in faeces were parent compound and AR-C124910. Similar results were obtained from other species, although urine was a more significant excretion route in the marmoset and in humans (50 to 62% of dose in faeces, 22 to 32% of dose in urine).

*In vitro*, ticagrelor and its major metabolites (AR-C124910 and AR-C133913) were found to inhibit various organic anion transporters that are involved in urate secretion (OAT1 and OAT3) and urate reabsorption (URAT-1). Studies of urate flux in human proximal tubule cells showed that these compounds inhibit the net secretion of urate when added basolaterally, a finding which may underlie the increase in plasma urate observed clinically. However, no consistent or sustained increases in plasma urate levels were observed when marmosets were dosed at 100 mg/kg for four weeks at ticagrelor plasma levels 13 to 18 times that anticipated in humans (Table 1).

Following administration of radiolabelled ticagrelor to lactating rats, there were significantly higher levels of total radioactivity in milk than in the dam's plasma. The major compound in milk was unchanged ticagrelor, although significant levels of AR-C124910 and AR-C133913 were also detected.

## **Toxicology**

### **Relative exposure**

Relative exposure calculations were based on total (free + bound) area under the plasma concentration time curves from time zero to 24 hours (AUC<sub>0-24h</sub>) values as ticagrelor and its major active metabolite had similarly high protein binding in all species. Exposure ratios were calculated by dividing animal AUC<sub>0-24h</sub> values by AUC values from the clinical

study D5130C00002. The latter was a multinational study, including male and female ACS patients of 18 years of age or over. In the study, patients were given a 270 mg loading dose of ticagrelor, followed by a twice daily dose of 90 mg of ticagrelor for up to 12 weeks. Acetylsalicylic acid was coadministered at 75-100 mg per day. (Note that ticagrelor is recommended for twice daily (bd) oral administration (that is, 2 x 90 mg of ticagrelor per day)). Mean clinical AUC<sub>0-12h</sub> values (n = 6, 9, or 15) for ticagrelor and for AR-C124910 after 4, 8, and 12 weeks of dosing were averaged and multiplied by two to provide the denominator for exposure ratio calculations (ticagrelor AUC<sub>0-24h</sub> = ((4.76 + 5.40 + 4.83)/3) x 2 = 9.99 µg•h/mL; AR-C124910 AUC<sub>0-24h</sub> = ((1.96 + 1.97 + 1.79)/3) x 2 = 3.82 µg•h/mL).

**Table 1: Exposure to ticagrelor and AR-C124910 during repeat dose toxicology studies, relative to human exposure at 90 mg bd of ticagrelor. NOAEL values are bolded and underlined.\***

Species	Study type (study no.)	Dosing duration (sample time)	Dose (mg/kg/d )	Sex	AUC <sub>0-24h</sub> (µg•h/mL)		Exposure ratio	
					Ticag	AR-C	Ticag	AR-C
Mouse (CD-1)	Toxicity (456925)	13 weeks (D85)	<u>50</u>	♂+♀	12.9	17.5	1.3	4.6
			250	♂+♀	165	168	16.5	44.0
			750	♂+♀	611	870	61.2	228
Mouse (CD-1)	Carcinogenicity (456988)	2 years (Wk52)	50	♂	12.2	17.0	1.2	4.5
			100	♂	47.9	75.0	4.8	19.6
			<u>250</u>	♂	174	240	17.4	62.8
			50	♀	19.4	23.7	1.9	6.2
			100	♀	73.7	73.6	7.4	19.3
			<u>250</u>	♀	224	262	22.4	68.6
Rat (SD)	Toxicity (99302)	4 weeks (D28)	<u>20</u>	♂	13.6	-	1.4	-
			80	♂	75.8	-	7.6	-
			300	♂	560	-	56	-
			<u>20</u>	♀	10.5	-	1.1	-
			80	♀	81.9	-	8.2	-
			300	♀	706	-	70.7	-
Rat (SD)	Toxicity (TPR3143)	3 months (D90)	20	♂	17.8	-	1.8	-
			<u>60</u>	♂	79.4	-	7.9	-
			180	♂	297	-	29.7	-
			20	♀	20.2	-	2.0	-
			<u>60</u>	♀	115	-	11.5	-
			180	♀	531	-	53.2	-
Rat (Wistar)	Toxicity (456930)	6 months (D172)	<u>10</u>	♂	3.39	1.93	0.3	0.5
			60	♂	49.7	38.5	5.0	10.1

Species	Study type (study no.)	Dosing duration (sample time)	Dose (mg/kg/d)	Sex	AUC <sub>0-24 h</sub> (µg•h/mL)		Exposure ratio	
					Ticag	AR-C	Ticag	AR-C
			180	♂	167	144	16.7	37.7
			10	♀	3.43	1.08	0.3	0.3
			<b>60</b>	♀	51.8	14.2	5.2	3.7
			180	♀	289	74.1	28.9	19.4
Rat (Wistar)	Carcinogenicity (456993)	2 years (Wk52)	20	♂	12.9	9.56	1.3	2.5
			60	♂	67.4	48.8	6.7	12.8
			<b>120</b>	♂	163	123	16.3	32.2
			20	♀	16.4	4.46	1.6	1.2
			<b>60</b>	♀	85.2	18.8	8.5	4.9
			180	♀	311	93.2	31.1	24.4
Rabbit (NZW)	Toxicity (0035DB)	13 days (D13)	40	♀	33.4	12.0	3.3	3.1
			<b>80</b>	♀	137	53.9	13.7	14.1
Marmoset	Toxicity (99228)	4 weeks (D28)	20	♂+♀	14.0	-	1.4	-
			<b>200</b>	♂+♀	158	-	15.8	-
			2,000	♂+♀	554	-	55.5	-
Marmoset	Toxicity (00019)	13 weeks (D56/57)	20	♂	27.7	-	2.8	-
			<b>100</b>	♂	177	-	17.7	-
			20	♀	20.1	-	2.0	-
			<b>100</b>	♀	126	-	12.6	-
Marmoset	Toxicity (0007PT)	15 weeks (Wk15)	<b>200</b>	♂+♀	181	56.9	18.1	14.9
Marmoset	Toxicity (0008FT)	52 weeks (Wk52)	<b>10</b>	♂	8.47	2.85	0.8	0.7
			50	♂	61.1	15.9	6.1	4.2
			100	♂	93.0	36.4	9.3	9.5
			<b>10</b>	♀	6.27	2.72	0.6	0.7
			50	♀	44.4	24.9	4.4	6.5
			100	♀	86.7	41.4	8.7	10.8

Ticag = ticagrelor; AR-C = AR-C124910; - = not determined, NOAEL = No Observable Adverse Effect Level

The toxicokinetic data showed that the various animal species used in the toxicity testing program received adequate exposure to ticagrelor and its active metabolite, with exposure ratios ranging from about 10 to over 100 at the highest doses.

### **Single dose toxicity**

Ticagrelor was well tolerated by rodents. A single oral dose of 2,000 mg/kg produced no observable effects in male or female mice and only transient bodyweight loss or failure to gain weight in rats of both sexes.

### **Repeat dose toxicity**

Studies were conducted in mice, rats, rabbits and marmosets and involved daily oral dosing with ticagrelor for up to two years. Toxicological findings that occurred in more than one species included irritation of the alimentary tract, adrenal changes and increased haemopoiesis (presumably related to bleeding events).

### ***Gastrointestinal tract***

The gastrointestinal tract was the most common target organ of toxicity, with a variety of changes (mostly reversible) occurring across the different species.

Rodents showed abdominal distension, which was consistent with studies showing that ticagrelor could significantly inhibit transit of material through the intestine. A discolouration of the stomach and small intestine was observed in rats which correlated with histological signs of irritancy, including squamous cell hyperplasia and submucosal inflammation of the forestomach and erosions of the glandular stomach. This irritant effect may have resulted in bleeding as suggested by decreased red blood cell (RBC) counts and increased reticulocyte counts.

Alimentary tract irritation was also a feature of toxicity studies using rabbits and marmosets. Rabbits dosed orally with ticagrelor at 160 or 300 mg/kg/day for 13 days showed body weight reduction and possible stomach irritancy (dark foci) at both dose levels. Marmoset repeat dose studies of one and three months duration showed deaths after dosing at 1,000 or 2,000 mg/kg/day for one to three weeks. Decedents showed reductions in RBC levels and lesions indicative of secondary stress such as lymphoid depletion of germinal centres in mesenteric lymph nodes and thymic cortical atrophy. The deaths were associated with bacterial enteritis. In a twelve month duration study, there were deaths in marmoset groups receiving 200 mg/kg/day of ticagrelor, between Weeks 29 and 36 of treatment. Premature decedents showed low RBC parameters and increased platelet levels, presumably reflecting an exaggerated pharmacological effect. Dead animals also showed distended intestines that had abnormal contents and hepatic adhesions. Histopathology revealed lesions that affected almost the entire length of the alimentary tract and were characterised by mucosal atrophy and chronic inflammation. However, the significance of these lesions was difficult to determine because the incidence and grade of the lesions showed no simple relation to dose and because marmosets are very susceptible to stress induced inflammatory bowel disease.

Overall, it was not entirely clear whether the gastrointestinal effects of ticagrelor observed in animals are secondary to its pharmacological effects on platelet aggregation or due to a primary local irritant effect. Gastrointestinal disorders including abdominal pain, constipation, diarrhoea and gastrointestinal haemorrhage have been noted as common adverse drug reactions in clinical trials (proposed Product Information) and should be monitorable in the postmarket clinical setting.

### ***Bleeding and haemopoietic effects***

The inhibition of platelet aggregation by ticagrelor most likely accounted for several findings that were observed across all species that were suggestive of subclinical bleeding with compensatory haemopoiesis: decreased RBC, increased reticulocytes, increased spleen weights and erythrophagocytosis in mesenteric lymph nodes. The potential for

ticagrelor to increase bleeding is a well recognised risk and is adequately covered by appropriate documentation in the proposed PI.

### **Adrenal effects**

Adrenal changes consisting of reversible increases in adrenal weight along with histological evidence of adrenal cortical inflammatory cell foci, vacuolation and cortical cell hypertrophy were observed in mice and rats but only at high doses and high relative exposure to ticagrelor. Such high doses sometimes produced mortality and clinical signs indicative of stress. An alternative explanation for the adrenal findings came from the observation in rat adrenal cells in vitro that ticagrelor inhibited the basal synthesis and release of corticosterone (an effect that was ameliorated by adrenocorticotrophic hormone [ACTH]).

Overall, the adrenal changes seen in rodents are not of clinical concern as they occurred at high doses/exposures in rodents but not marmosets, and no notable signs of altered adrenal function were noted in the clinical trial data.

### **Other effects**

Rodents that received ticagrelor at high relative exposure levels (60-70 fold based on AUC) showed reversible liver changes indicative of an adaptive response to a high metabolic load: increased liver weights, centrilobular hypertrophy (mice only), increases in alkaline phosphatase (ALP) and aspartate aminotransferase (AST) and slight induction of CYP1A1 and CYP4A. These changes occurred with low incidence and only at high doses and are not considered clinically relevant.

Alveolar histiocytosis and increased lung weight was observed in the 4 week, 3 month and 6 month repeat dose toxicity studies in rats. Both the incidence and severity of alveolar histiocytosis declined during a drug free recovery period. The toxicological significance of these findings was unclear, particularly given that a significant fraction of control group animals also showed these lesions. The incidence and severity of these lesions increased at very high relative exposure levels to ticagrelor (20 to 50 fold) with typical microscopic findings of degenerate foamy macrophages that contained many myelinic whorls. These findings were considered consistent with the induction of phospholipidosis by ticagrelor. While the relationship between drug induced phospholipidosis in animals and adverse clinical effects remains unclear (Anderson and Borlak, 2006), the fact that this only occurred in a single species at very high relative exposure suggests that it is not of clinical concern.<sup>3</sup>

### **Genotoxicity**

Both ticagrelor and AR-C124910 failed to produce a significant increase in the mutation frequency at the histidine locus of *Salmonella typhimurium* or at the thymidine kinase locus of mouse lymphoma cells when tested with or without metabolic activation. Ticagrelor was also shown to produce no significant increase in the frequency of micronucleated bone marrow erythrocytes following oral dosing of rats at 2000 mg/kg.

### **Carcinogenicity**

Lifetime mouse and rat studies showed no statistically significant differences in pre-terminal mortality between control groups and any group receiving ticagrelor.

<sup>3</sup> Anderson N. and Borlak J. Drug-induced phospholipidosis. FEBS Letters 2006; 580: 5533-5540.



CD-1 mice, dosed at up to 250 mg/kg/day (around 20 times expected human therapeutic exposure to ticagrelor, see Table 1) for 2 years, showed no significant effect of ticagrelor dosing on tumour incidence.

Male Wistar rats showed no effect of ticagrelor on tumour incidence when dosed at 120 mg/kg/day (about 16 times expected human therapeutic exposure to ticagrelor) for 2 years. Female rats also showed no effect on tumour incidence when dosed at 60 mg/kg/day (8 times human exposure) for 2 years but showed a statistically significant increase in the incidence of uterine adenocarcinoma at 180 mg/kg/day (about 30 times human exposure). It was suggested that this effect arose from a ticagrelor induced hormonal change (see below). There was also a modest increase in the incidence of benign hepatocellular adenoma in females dosed at 180 mg/kg/day; most likely related to the liver hypertrophy found at this dose (see *Repeat Dose Toxicity* above).

Overall, the tumour findings in female rats were considered a species specific effect restricted to high relative ticagrelor exposure levels and were therefore not considered clinically relevant.

### **Effects on steroidogenesis**

As a possible explanation for the increased incidence of uterine adenocarcinomas following daily administration to rats at 180 mg/kg, the effects of ticagrelor on various aspects of steroidogenesis were examined. Rats dosed at 180 mg/kg/day showed several effects indicating hormonal disturbance, with increases in the incidences of extended oestrus, ovarian interstitial cell vacuolation, and adrenal cortex vacuolation. A time course study showed significant decreases in plasma oestradiol and increases in plasma testosterone values during pro-oestrus of rats dosed at 180 mg/kg/day, as compared with controls. Further mechanistic studies found no direct effect of ticagrelor on oestrogen receptors or aromatase activity but did reveal elevated testosterone and decreased testosterone clearance as well as increases in CYP1A1/2 (at both the mRNA and protein levels) in rat liver and uterus after 13 weeks of dosing at 180 mg/kg/day. As these enzymes catalyse the conversion of oestradiol to 2-hydroxyoestradiol, it was suggested that an increase in metabolism, in combination with increased liver weights, may be responsible for the reduction in plasma oestradiol levels seen in the 180 mg/kg/day group. However, these studies did not provide a simple explanation for the elevation of plasma testosterone levels in 180 mg/kg/day animals.

### **Reproductive toxicity**

#### ***Relative exposure***

Exposure ratios were calculated using animal  $C_{\max}$  and/or  $AUC_{0-24\text{ h}}$  values. This is because some studies did not provide AUC values. These values were divided by  $C_{\max}$  and AUC values from a human study (see details above). The derivation of the human  $AUC_{0-24\text{ h}}$  values for ticagrelor and AR-C124910 is given above (see *Toxicology, Relative exposure*). Human  $C_{\max}$  values for ticagrelor and for AR-C124910 are averages after 4, 8, and 12 weeks of dosing (ticagrelor  $C_{\max} = (0.770 + 0.794 + 0.660)/3 = 0.741 \mu\text{g/mL}$ ; AR-C124910  $C_{\max} = (0.257 + 0.234 + 0.212)/3 = 0.234 \mu\text{g/mL}$ ).

**Table 2: Exposure to ticagrelor and AR-C124910 during repeat dose reproductive and developmental studies, relative to human exposure at 90 mg bd of ticagrelor. NOAEL values are bolded and underlined.**

Species	Study type (study no.)	Dosing duration (sample time)	Dose (mg/kg/d)	Exposure ratio (C <sub>max</sub> )		Exposure ratio (AUC <sub>0-24 h</sub> )	
				Ticag	AR-C	Ticag	AR-C
Rat (Wistar)	♀ fertility, early embryo develpt (0337GR)	14 days before pairing to day 6 post coitum (day 14)	20	1.5	1.5	-	-
			100	10.6	6.8	-	-
			<b><u>200*</u></b>	32.9	29.0	-	-
Rat (Wistar)	embryofetal develpt DR (0274RR)	Day 6 <sup>a</sup> to 16 post coitum (Day 16)	20	1.5	1.4	-	-
			<b><u>100</u></b>	7.5	4.1	-	-
			200	29.8	14.7	-	-
			300	46.8	31.0	-	-
Rabbit (NZW)	embryofetal develpt DR (0038RB)	Day 6 <sup>a</sup> to 19 post coitum (Day 19)	21	2.5	3.0	1.0	1.3
			<b><u>42**</u></b>	3.5	3.5	1.2	1.8
			84	9.0	12.5	6.5	9.1
			99	30.8	39.4	41.4	47.4
Rat (Wistar)	Pre/postnatal DR (AA39254)	GD6 to PND 7 (PND 7)	10	0.22	-	-	-
			<b><u>60</u></b>	5.4	-	-	-
			180	27.0	-	-	-
Rabbit (NZW)	retinal develpt (0073KB)	Day 6 <sup>a</sup> to 19 post coitum (Day 19)	<b><u>63</u></b>	11.1	12.8	6.5	9.0

<sup>a</sup>Day 0 = day of mating; Ticag = ticagrelor; AR-C = AR-C124910; - = not determined; \*fertility NOAEL; \*\* fetal NOAEL

### ***Reproductive and developmental effects***

Oral ticagrelor dosing of male Wistar rats at up to 180 mg/kg/day (exposure ratio about 16) for 10 weeks had no significant effect on male fertility. Dosing of female Wistar rats from 14 days before pairing to day 6 post coitum, at up to 200 mg/kg/day (exposure ratio about 33 based on C<sub>max</sub>), produced an increase in oestrus irregularity but had no adverse effect on female fertility or various embryo parameters.

Embryofetal development studies, in which Wistar rats received oral doses up to 300 mg/kg/day of ticagrelor from Day 6 to Day 16 post coitum, showed a reduction in mean fetal weight at the 300 mg/kg/day level that was associated with decreased food consumption. Litters from animals dosed at 300 mg/kg/day showed statistically significant increases in the incidence of additional liver lobes and of minor abnormalities of skeletal development. These increases were considered consequences of drug induced maternal toxicity. A relative exposure ratio of about 7.5 (based on C<sub>max</sub>) was achieved for ticagrelor at the No Observable Adverse Effect Level (NOAEL) for rat embryofetal development of 100 mg/kg/day.

Embryofetal development studies were also performed using NZW rabbits dosed at up to 63 mg/kg/day of ticagrelor from Day 6 to Day 19 post coitum. Dosing produced no significant increase in the incidence of skeletal abnormalities as compared with controls, although a low incidence of severe retinal folds was found at higher drug doses. A larger follow up study failed to find a significant difference in the incidence of major ocular abnormalities between fetuses from control dams and from dams dosed at 63 mg/kg/day (exposure ratio about 6, based on AUC<sub>0-24h</sub>).

In studies of ticagrelor dosing during the pre/postnatal period in Wistar rats, no significant effect on various delivery and litter endpoints was found. However, an increase in neonatal pup mortality was noted for dams dosed at 180 mg/kg/day, and the suggested NOAEL for exposure during gestation and lactation was  $\geq 60$  mg/kg/day (exposure ratio about 5). Post-weaning development, behaviour, learning, memory, mating performance and fertility were not significantly affected by ticagrelor exposure during the pre/postnatal period.

### **Impurities**

Several synthetic intermediate impurities present in ticagrelor preparations were also tested for mutagenicity and clastogenicity and were qualified with appropriate toxicological data. POK2 and UL111 produced dose dependent, significant increases in the frequency of cultured human lymphocytes containing a chromosomal aberration; but were negative in bacterial mutagenicity and micronucleus assays. C3RO was negative for bacterial mutagenicity but positive for chromosomal aberration *in vitro* and for micronucleus induction *in vivo*. As a clastogenic impurity, C3RO is controlled to a level amounting to no more than 1.5  $\mu\text{g}$ /day intake at the maximum anticipated clinical dose, which is considered acceptable for a potential genotoxic impurity according to ICH guidelines.

### **Local tolerance**

Local tolerance studies with ticagrelor in mouse skin and rat vein failed to show evidence of local irritancy while experiments with human blood showed no potential for erythrocyte clumping, haemolysis, or plasma protein precipitation.

### **Use in children**

The safety and efficacy of ticagrelor has not been established in patients under 18 years of age.

### **Nonclinical Summary and Conclusions**

The nonclinical data presented in support of the use of ticagrelor were extensive and of high quality, with all critical studies performed to GLP standards.

*In vitro* studies confirmed that ticagrelor binds reversibly, and with high affinity, to human P2Y<sub>12</sub> purinergic receptors. Ticagrelor does not require metabolic activation and does not directly interact with the receptor's ADP binding site. ADP induced aggregation of platelets from various mammalian species (including man) was inhibited by ticagrelor in a concentration dependent manner. *Ex vivo* experiments, measuring ADP induced platelet aggregation in blood from ticagrelor dosed animals, demonstrated a close correlation between the pharmacodynamic and pharmacokinetic profiles of the drug. Ticagrelor was significantly more effective at inhibiting arterial thrombosis than haemostasis under *in vivo* conditions. AR-C124910 (the O-de-ethylated and active major circulating metabolite of ticagrelor in man) was shown to have similar properties to the parent compound.

Secondary pharmacodynamic studies showed that ticagrelor inhibited the human erythrocyte adenosine transporter system (IC<sub>50</sub> 100 nM) and augmented the increase in

coronary blood flow induced by either endogenous or exogenous adenosine in beagle dogs. Ticagrelor was also a potent antagonist of GPR17 receptor activation (mediator of ischaemia induced tissue damage) induced by various ligands ( $IC_{50}$  1-10 nM), a property that may be of clinical benefit.

The clinical profile of ticagrelor may be influenced by secondary pharmacological effects including inhibition of the erythrocyte adenosine transporter system, antagonism of GPR17 receptor activation and inhibition of renal organic anion transporters involved in urate secretion.

Ticagrelor and its major metabolites inhibited various Organic Anion Transporters (particularly OAT3) as well as the net secretion of urate flux in human proximal tubule cells *in vitro*, a finding which may underlie the increase in plasma urate observed clinically. However, no consistent or sustained increases in plasma urate levels were observed in marmosets exposed for 4 weeks to ticagrelor plasma levels about 15 times that anticipated in humans.

Safety pharmacology studies on the cardiovascular, respiratory, and central nervous systems did not raise any issues of clinical concern. The dyspnoea seen in clinical trials was not consistently replicated in respiratory studies on rats: the mechanism for this adverse reaction remains unclear.

Pharmacokinetic studies performed in multiple species indicated that exposure to ticagrelor and AR-C124910 was approximately proportional to dose and did not increase markedly after prolonged, repetitive dosing. Both compounds are P-gp substrates as well as weak P-gp inhibitors. Ticagrelor showed wide tissue distribution, qualitatively similar metabolic profiles across species and relatively rapid elimination, primarily via faeces. Ticagrelor was metabolised by, and inhibited, both CYP3A4 and CYP3A5 but showed no significant inhibitory activity towards other CYP enzymes. The modest CYP induction observed at very high exposure to ticagrelor in animal studies was not considered clinically relevant.

Repeat dose toxicology studies were performed in mouse, rat, rabbit and marmoset. Relative exposure ratios (based on AUC) at the highest doses ranged from about 10 to 100 and were generally greater than one at the NOAEL. Common toxicological findings in these studies were stomach irritancy, distended intestines and elevations in haemopoiesis; suggesting irritant effects and/or subclinical bleeding. Adrenal changes, adaptive liver changes and alveolar histiocytosis were only observed in rodents (mice and/or rats) at high relative ticagrelor exposure levels and were not considered clinically relevant.

Exaggerated pharmacological effects may have contributed to the gastrointestinal and haemopoietic changes noted across all species in the repeat dose toxicology studies. Gastrointestinal disorders including abdominal pain, constipation, diarrhoea and gastrointestinal haemorrhage have been noted as common adverse drug reactions in clinical trials and should be monitorable in the postmarket clinical setting. The potential for ticagrelor to increase bleeding is a well recognised risk and is adequately covered by appropriate documentation in the proposed Product Information.

Ticagrelor and its major metabolite were negative in a standard battery of *in vitro* and *in vivo* genotoxicity assays.

There was no increase in tumour incidence in male and female mice or male rats that received oral ticagrelor for 2 years at about 20 times expected human therapeutic exposure. An increased incidence of uterine adenocarcinoma was observed in female rats after dosing at about 30 times expected human therapeutic exposure for 2 years, a finding related to endocrine changes that occurred only at very high doses. This was considered a

species specific effect restricted to high relative ticagrelor exposure levels and was not clinically relevant.

There were no significant effects of ticagrelor on fertility, embryofetal development or pre/post-natal development at about 5 to 20 times expected human therapeutic exposure levels.

There were no objections on nonclinical grounds to the registration of ticagrelor (Brilinta) for the proposed indication.

## IV. Clinical Findings

### Introduction

The clinical data included full reports of 45 pharmacology studies involving 2474 subjects and an abbreviated report of one pharmacology study involving 22 subjects. Also provided was a full report of one efficacy/safety study involving 18624 subjects. This was the PLATO trial which was considered the pivotal trial.<sup>1</sup>

In the submission and in this AusPAR, ticagrelor is abbreviated to TIC and is also referred to as AZD6140 or AR-C126532XX; and P2Y<sub>12</sub> receptors are also referred to as P2T receptors.

A 90 mg immediate release (IR) tablet of TIC, as proposed for marketing, was used in the efficacy study (PLATO) and similar 90 mg IR tablets or variants were used in 28 of the 46 pharmacology studies. Other formulations of TIC used in multiple pharmacology studies included IR tablets of 50 mg (4 studies), 100 mg (9 studies) and 200 mg (4 studies), and oral suspensions of 10 or 30 g containing 0.1, 0.3, 1.0, 3.0, 10, 30, 100, 200 or 300mg (2 studies); while formulations used in single pharmacology studies included an IR tablet of 180 mg, a 200 mg controlled release (CR) tablet, TIC in an "Enterion" capsule, an oral suspension of 100 mg/10.3 g, an oral suspension of 20 mg/g (containing 222.7kBq/g of [<sup>14</sup>C]AZD6140), a 1.0 mg/mL oral solution, and a 0.1 mg/mL IV solution.

The current dose of clopidogrel (CLO) recommended in the treatment of ACS is 75 mg once daily (od) in combination with 75-325 mg ASA long term, after a loading dose of 300 mg, in patients with UA or NSTEMI (in patients with STEMI, the loading dose is optional, and benefit of treatment beyond 4 weeks is unclear). Thus the dose of CLO used in the studies was appropriate and in keeping with Australian approved Product Information (PI).

### Pharmacodynamics

#### Introduction

Pharmacodynamic (PD) data was contained in 30 studies:

- SC-931-9064 and D5130C00020 examined the effect of CLO on platelet function;
- D5130C05261, D5130C00029, D5130C00019, SC-532-5256, SC-532-5169, SC-532-5171, D5130C00049 and SC-532-5239 examined the effect of TIC on platelet function in healthy volunteers;
- D5130C00048 [OFFSET], D5130C00030 [RESPOND], D5130C00008 [DISPERSE] and D5130C00002 [DISPERSE2] examined the effect of TIC on platelet function in patients with atherosclerosis/stable CAD;
- D5130C00037 examined the effect of TIC on the electrocardiogram (ECG) QTcX (QT interval corrected for heart rate [HR] using a study specific factor interval)
- D5130C00050 examined the effect of TIC on serum uric acid levels;

- D5130C00049, D5130C00028 and D5130C00034 examined the effect of TIC on respiratory parameters;
- D5130C00014, D5130C00015, D5130C00016, D5130C05266 and D5130C05267 examined the effects of intrinsic factors;
- D5130C00039, D5130C00024, D5130C00005, D5130C00042, D5130C00006, D5130C00007 and D5130C00026 examined the effects of extrinsic factors (drug interactions).

### **Effect of clopidogrel (CLO) on platelet function**

#### **SC-931-9064**

A open label, single group, Phase I study in 8 healthy male volunteers, 31-54 years (y), who received CLO 75 mg once daily (od) for 11 days.

Objectives were to assess degree of ADP induced inhibition of platelet aggregation (IPA) produced by steady state CLO 75 mg od, using platelet rich plasma (PRP) optical and whole blood impedance (WBI) aggregometry methods; and if *ex vivo* inhibitory effect was incomplete, to determine if addition of P2T antagonists AR-C69931MX (IV agent) or AR-C126532XX (oral agent) would produce complete inhibition using either method.

Both measures of IPA found CLO 75 mg od was a partial P2T receptor blocker (46-53% inhibition of response to 10  $\mu$ M ADP) with slow onset and high variability; while AR-C69931MX and AR-C126532XX showed greater inhibition of response using PRP optical aggregometry (70-80%) and complete inhibition of response using WBI aggregometry (94-97%).

### **Effect of ticagrelor (TIC) on platelet function in healthy volunteers**

#### **D5130C05261**

A randomised, double blind, double dummy, two period crossover Phase I study in 16 healthy male and female volunteers, 18-53 y, who received ASA +TIC and ASA + CLO with 14 days washout between periods.

Objectives were to compare extent of IPA after multiple dose administration, prolongation of bleeding time (BT), and safety and tolerability, of TIC+ASA vs CLO+ASA; to compare extent of IPA and prolongation of BT, of TIC+ASA vs ASA; and to assess the pharmacokinetics (PKs) of TIC and active metabolite AR-C124910 in the presence of ASA.

Both ADP and collagen induced IPA (final and maximum, % individual peak inhibition of platelet aggregation [IPA<sub>max</sub>] and area under the effect curve from zero to infinity [AUEC]) were statistically significantly greater with TIC+ASA than with CLO+ASA; and with TIC+ASA compared to ASA; after both the first and Day 9 doses. For TIC+ASA, ADP induced IPA was rapid and almost complete (97% inhibition at 2 hours (h) after first dose, and 100% inhibition after Day 9 dose) but for CLO+ASA inhibition was slower and less complete (65% inhibition at 4 h after first [loading] dose; 88% at 4 h after Day 9 dose, indicating steady state was not achieved with the loading dose); interindividual variability was greater with CLO+ASA than with TIC+ASA, particularly after the first dose. Mean lancet BTs were slightly increased with CLO+ASA compared to ASA, and clearly increased with TIC+ASA compared to both CLO+ASA and ASA, after both the first and Day 9 doses.

#### **D5130C00029**

A randomised, double blind, three period crossover Phase I study in 24 healthy male and female volunteers, 25-62 y, who received single oral doses of CLO 600 mg, TIC 270 mg and TIC 540 mg with  $\geq$ 14 days washout between periods.

Objectives were to compare ADP induced IPA, single dose PKs of TIC and active metabolite AR-C124910XX and CLO and inactive metabolite SR 26334, and safety and tolerability, after loading doses of TIC (270 and 540 mg) and CLO (600 mg); and to evaluate the PK/PD relationship between TIC and AR-C124910XX plasma concentrations and ADP induced platelet aggregation.

Time to peak IPA (TIPA<sub>max</sub>) was shorter for both doses of TIC (2 h) compared to 600 mg CLO (12 h) with 20 µM ADP, indicating faster onset of platelet inhibitory action with TIC.

Final extent IPA<sub>max</sub> was 98-99% with both doses of TIC compared to 87% with 600 mg CLO, indicating near complete inhibition of P2Y<sub>12</sub> receptor with TIC but only partial inhibition with CLO. AUEC values were greater for both doses of TIC than for CLO and greater for the higher dose of TIC than for the lower dose, reflecting the greater maintained levels of IPA achieved with TIC over CLO and with higher over lower dose of TIC, during each time period. Concentration at which 50% of maximum effect is reached (EC<sub>50</sub>) increased with increasing ADP concentration showing greater TIC and AR-C124910XX concentrations were required to achieve the same effect for a higher ADP.

### **SC-532-5169, SC-532-5171**

Effect of AR-C126532XX (0.1-100 mg, and 30-500 mg) on platelet function after multiple oral doses was examined in SC-532-5169 and SC-532-5171, respectively, using WBI aggregometry, RPC, optical aggregometry, and lancet BT.

Using WBI aggregometry, no differences were seen for AR-C126532XX from placebo (pbo) for doses up to 10 mg. Mean percentage IPA was <50% at 2 h post dose with 30 mg and 51% with 100 mg (using 10 µM ADP). The authors conclude these doses as a suspension would be insufficient for od dosing.

Using RPC, a dose response was evident for C126532XX inhibition, and the response decreased with increasing provoking ADP dose. Four subjects reached >80% inhibition at 2 h and 4 h post dose of 100 mg AR-C126532XX with 3 and 10 µM ADP. Based on visual comparisons, inhibition using impedance aggregometry appeared to require a threefold increase in ADP concentration compared to RPC. BTs appeared to be prolonged for AR-C126532XX doses of 30 and 100 mg. Two 100 mg subjects had at least one BT>30 minutes (min). There was no correlation seen between impedance aggregometry values and BTs.

Using WBI aggregometry, mean percentage IPA were ≥98% and ≥95% at 2 h post dose with 100-400 mg AR-C126532XX (using 3 and 10 µM ADP, respectively) and the response decreased over time. Using RPC, a dose response was evident for C126532XX inhibition (30-400 mg) and the response decreased with increasing provoking ADP dose. Mean percentage IPA were 63-90% and 50-84% (in citrate; and 64-87% and 46-83% in heparin) at 2 h post dose with 100-400 mg AR-C126532XX (using 10 and 30 µM ADP, respectively) and the response decreased over time. Using PRP optical aggregometry, a dose response was evident for C126532XX inhibition (30-400 mg). Mean final extent %IPA were 94-97% and 88-95%, and mean maximal extent %IPA were 77-81% and 67-75%, at 2 h post dose with 100-400 mg AR-C126532XX (using 5 and 20 µM ADP, respectively) and the response decreased over time. BTs appeared to be prolonged for AR-C126532XX doses of 100-400 mg although a dose response was not evident. One 300 mg subject had BT>30 min at 2 h and 4 h post dose. Due to difficulty in interpreting increased BTs, a 500 mg dose of AR-C126532XX was not tested.

### **D5130C00049**

Effect of TIC on platelet function after single ascending doses was examined using BT. BTs were prolonged for AR-C126532XX (median 10.3 min with 900 mg and 20.0 min with 1260 mg at 48 h post dose) compared to pbo (median 4.3 min at 48 h) and a dose

response was evident. BTs returned to baseline for all subjects by 72 h with 900 mg and by 120 h with 1260 mg. A dose of 1620 mg was not tested.

### ***SC-532-5239***

Effects of different schedules of multiple ascending doses of TIC (50-200 mg od, 50-200 mg bd, 50-300 mg bd, 200-600 mg od) on platelet function were compared to CLO (300 mg then 75 mg od) using optical aggregometry and lancet BT.

All doses of TIC caused IPA, with increasing degree and duration of inhibition with increasing dose. TIC 50 mg bd and 200 mg od gave comparable 24 h IPA to steady state CLO 75 mg od at Day 14. Twice daily doses of  $\geq 100$  mg and once daily doses of  $\geq 300$  mg of TIC inhibited platelet aggregation to a greater degree and with less variability compared to CLO. Twice daily regimens gave better maintenance of PAI over 24 h than once daily regimens. The administration of TIC with food did not affect PDs in a clinically relevant manner. All doses of TIC caused a prolongation of BT, but no dose effect was evident, and no clinically relevant difference was seen compared to CLO.

### **Effect of ticagrelor (TIC) on platelet function in patients with atherosclerosis/stable CAD**

#### ***D5130C00048 [OFFSET]***

A multicentre, randomised, double blind, double dummy, parallel group Phase II study in 123 male and female patients, 41-83 y, with documented stable CAD who were taking 75-100 mg ASA od, who received TIC, CLO or pbo, for 6 weeks in addition to the ASA.

Objectives were to determine the onset and offset of the antiplatelet effects of TIC compared to CLO using light transmittance aggregometry (LTA); to investigate if TIC had any clinically significant cardiopulmonary effect compared with CLO and pbo; to assess safety and tolerability of TIC compared with CLO and pbo; and to evaluate the PK/PD relationship of TIC and AR-C124910XX.

The onset of 20  $\mu$ M ADP induced IPA was faster with TIC than with CLO. %IPA was significantly greater with TIC at all time points from 0.5 h to 24 h post dose. At 0.5 h after dose, 40% inhibition was seen with TIC compared to 8% with CLO; at 2 h, 88% inhibition was seen with TIC compared to 38% with CLO. %IPA reached a maximum of 88% at 2 h with TIC, while CLO reached a maximum of 50% at 8 h with CLO.

The offset of 20  $\mu$ M ADP induced IPA occurred earlier and at a faster rate with TIC than with CLO. Although %IPA was higher immediately following the last dose of TIC compared to CLO, rate of offset of effect was greater (as measured by slope of offset of %IPA and platelet aggregation). Thus, %IPA was similar for both treatments by 24 h post dose (so patients missing a single dose of either treatment will have similar antiplatelet effect), and significantly lower from 72 h to 7 days post dose with TIC compared to CLO. The time from last dose for IPA to drop to 10% was 109 h with TIC and 196 h with CLO. Similar findings were seen with 5  $\mu$ M ADP (and collagen for onset, but less consistent for offset) and other markers of platelet activation.

#### ***D5130C00030 [RESPOND]***

A multicentre, randomised, double blind, double dummy, two period crossover Phase II study in 98 male and female patients, 45-85 y, with stable CAD, 41 who were previously identified as CLO nonresponders and 57 who were previously identified as CLO responders (status was confirmed 2-4 weeks prior to the first dose of the study drug, using LTA response to 20  $\mu$ M ADP prior to and 6-8 h after a single 300 mg dose of CLO [difference  $\leq 10\%$ =nonresponder; difference  $>10\%$ =responder]).



All patients randomly received CLO or TIC, in addition to ASA 75-100 mg od for 2 weeks. All nonresponders and half of the responders then received the alternative treatment for 2 weeks with no washout between; while the other half of the responders continued to receive the initial treatment for 2 weeks.

Objectives were to assess the effect on IPA of TIC compared to CLO in patients previously identified as nonresponsive to CLO; to compare IPA, platelet aggregation, and biomarker expression in CLO nonresponsive patients when directly switched from CLO to TIC, as opposed to continuing treatment with CLO without interruption; to compare IPA, platelet aggregation, and biomarker expression in CLO responsive patients when directly switched from TIC to CLO, as opposed to continuing treatment with TIC without interruption; and to assess general tolerability of a direct switch from CLO to TIC without a washout.

More patients achieved >10%, >30%, and >50% final extent %IPA in response to 20 µM ADP 4 h post dose on Days 1 and 14 with TIC than with CLO; however the difference was not statistically significant for the primary variable of >10% 4 h post dose at steady state in CLO nonresponders (p-value 0.157), and the >30% measure was a *post hoc* analysis. The failure to reach the primary endpoint may have been due to a higher than expected response to CLO after 14 days in patients defined as 'CLO nonresponders'.

In nonresponders given TIC, 97% achieved >30% IPA, and 81% achieved >50% IPA. In nonresponders, %IPA increased by 40% at steady state when treatment was changed from CLO to TIC and %IPA decreased by 30% when treatment was changed from TIC to CLO. In responders, %IPA increased by 26% at steady state when treatment was changed from CLO to TIC, and %IPA decreased by 25% when treatment was changed from TIC to CLO. Nonresponders given a loading dose of TIC achieved >70% IPA, and responders achieved >90% IPA, regardless of prior CLO treatment. Thus, no washout period is required for patients changing treatment from CLO to TIC, so antiplatelet effect will be maintained.

#### **D5130C00008 [DISPERSE]**

A randomised, double blind, double dummy, parallel group, multicentre Phase II study in 201 male and female patients, 34-84 y, with documented atherosclerotic disease (ASD), who received ASA 75-100 mg od and either TIC 50 mg bd, 100 mg bd, 200 mg bd or 400 mg od, or CLO 75 mg od, for 28 days.

Objectives were to assess PD effects of TIC at doses of 50 mg bd, 100 mg bd, 200 mg bd and 400 mg od plus ASA compared to CLO 75 mg od plus ASA (by evaluating IPA and BT), in subjects with documented ASD, and to evaluate PKs of TIC and its active metabolite AR-C124910XX when administered over 28 days, in subjects with documented ASD; to compare safety and tolerability of TIC plus ASA with CLO plus ASA; and to evaluate the effect of TIC on CRP.

All doses of TIC+ASA and CLO+ASA inhibited ADP induced platelet aggregation on Days 1, 14 and 28 of treatment. All doses of TIC+ASA inhibited ADP induced platelet aggregation to greater extent than CLO, and dose response evident for TIC.

On Day 1, all doses of TIC gave >50->90% inhibition of mean final extent %PAI in 2 h compared to >15% inhibition in 12 h with CLO. On Days 14 and 28, 50 mg TIC+ASA and 75 mg CLO+ASA gave comparable inhibition of ADP induced platelet aggregation of ~50-80% over 24 h, while 100, 200 and 400 mg TIC+ASA gave comparable inhibition of ADP induced platelet aggregation of ~80-95% over 24 h. Similar effects were seen for final and maximal extent %IPA for ADP induced platelet aggregation and for collagen induced platelet aggregation.

BTs were more prolonged at Day 28 with TIC than with CLO but there was no clear dose response relationship for TIC. There were no clear changes from baseline in CRP with TIC treatment.

### ***D5130C0002 [DISPERSE2]***

A randomised, double blind, double dummy, parallel group, multicentre, multinational Phase II study in 990 male and female patients, 30-93 y, with documented evidence of non-ST segment elevation ACS in the previous 48 h, who received TIC 90 mg bd, TIC 180 mg bd, or CLO 75 mg od, along with ASA 75-100mg od, for 12, 8, or 4 weeks. Half the patients in each TIC group also received a loading dose of 270 mg; while patients in the CLO group received a loading dose of 300 mg unless they were already being treated with CLO or had received an open label loading dose of CLO as part of their initial treatment (they could also be given an additional 300 mg if they had PCI  $\leq$ 48 h post randomisation).

The primary objective was to assess safety and tolerability of different doses of TIC+ASA, compared with CLO+ASA, in patients with non-ST segment elevation ACS, by evaluation of total bleeding events (excluding minimal bleeds) observed within the first 4 weeks of treatment (Day 29).

Secondary objectives were to assess PD effects of TIC+ASA compared to CLO+ASA (in CLO naïve patients); to compare platelet aggregation response to TIC on Day 1 in CLO naïve patients and CLO pretreated patients; to evaluate PK of TIC and its active metabolite AR-C124910XX; to evaluate the relationship between TIC PK and PAI; to evaluate the relationship between TIC and AR-C124910XX exposures and the occurrence of major and minor bleeding; to compare safety and tolerability of TIC+ASA with CLO+ASA by evaluation of adverse events (AEs) including bleeding events and safety laboratory analyses; to assess safety and tolerability of the TIC loading dose by evaluation of AEs including bleeding events; and to evaluate the effect of TIC compared to CLO on inflammatory markers.

Tertiary objectives were to observe the individual and composite incidence of MI (including silent MI), death, stroke and severe recurrent ischaemia; and to test operational procedures for endpoint reporting to aid further development of the Phase III program; to observe the incidence of recurrent ischaemia with TIC+ASA and CLO+ASA on continuous Holter ECG monitoring; to measure the health care resource utilisation (HCRU) associated with clinical endpoints (MI, death, stroke and severe recurrent ischaemia) and compare between treatment groups; to measure the HCRU associated with major bleeding events and compare between treatment groups; and to explore the use of work productivity measurements and work/activity limitations to describe differences in clinical outcome and work status between treatment groups.

In this PK/PD substudy, IPA was evaluated in 46 CLO naïve patients (assessed on Day 1 and weeks 4, 8 and 12) and 44 CLO pretreated patients (assessed on Day 1); and inflammatory risk markers were measured.

In CLO naïve patients: At Week 4 (steady state), inhibition of ADP induced platelet aggregation was greater with TIC 180 mg bd (and 90 mg bd to a lesser degree) compared to CLO 75 mg od, for all time points up to 12 h. Numbers of patients in the substudy at Week 4 and Weeks 8 and 12 were too low to draw firm conclusions. On Day 1 (TIC 90 mg, 180 mg, or loading dose 270 mg; CLO loading dose 300 mg), a larger proportion of TIC patients (44-71%) had an  $IPA > 75\% \leq 2$  h post dose than CLO patients (7%); and patients reached greater final extent  $IPA_{max}$  values with all doses of TIC (81% with 90 mg, 86% with 180 mg, 89% with 270 mg) compared to CLO 300 mg (44%).

On Day 1, pre dose platelet aggregation was less for CLO pretreated patients (35-50%) than for CLO naïve patients (60-70%); and in TIC patients, post dose platelet aggregation was less for CLO pretreated patients than for CLO naïve patients, suggesting TIC gives further IPA than already existing with CLO pretreatment. Inhibition of ADP induced platelet aggregation was greater with TIC 90 mg, and greater again with TIC 180 mg and 270 mg, compared to CLO 300 mg, for both CLO pretreated and CLO naïve patients.

There were no differences between treatment groups for the inflammatory markers, C reactive protein (CRP), interleukin-6 (IL-6), myeloperoxidase (MPO), brain natriuretic peptide (BNP) and CD40L.

### **Effect of ticagrelor (TIC) on ECG QTcX interval**

#### ***D5130C00037***

A randomised, double blind, double dummy, placebo controlled, three period crossover Phase I study in 36 healthy male volunteers, 20-37 y, who received single doses of TIC 900 mg, moxifloxacin (MOXI) 400 mg and pbo with 7-14 days washout between periods.

Objectives were to study the cardiac ventricular repolarisation effect on the heart in the first 24 h after a single 900 mg dose of TIC in healthy volunteers compared to pbo (by measuring maximum change in time matched QT intervals by QTcX, QTcB [QT interval corrected for HR using the Bazett formula] and QTcF [QT interval corrected for HR using the Fridericia correction]); to assess maximum change in time matched QT intervals, and assay sensitivity, after MOXI compared to pbo; to assess PKs of TIC, AR-C124910XX, and AR-C133913XX, and to explore relationship between plasma concentration and cardiac ventricular repolarisation effect on heart after first 24 h, after a single 900 mg dose of TIC in healthy volunteers; and to evaluate safety and tolerability of TIC.

For TIC, all point estimates were <5 milliseconds (ms) and all upper confidence limits (UCL) of 95% CIs were <10 ms, suggesting TIC did not increase the QTcX interval in a clinically significant way. Compared to pbo, active control MOXI caused an increase in the QTcX interval, demonstrating assay sensitivity. Results for QTcF and QTcB were similar.

### **Effect of ticagrelor (TIC) on serum uric acid levels**

#### ***D5130C00050***

A randomised, double blind, placebo controlled, two period, two way crossover Phase I study in 24 healthy male volunteers, 22-45 y, who received TIC 90 mg or pbo bd for 5 days each with no gap between.

Objectives were to examine the effect of TIC administration on serum uric acid levels and urinary uric acid excretion in healthy male volunteers under conditions of diet control, on precursors (hypoxanthine and xanthine) in uric acid catabolism pathway and on 6b-hydroxyl cortisol and cortisol levels in urine; and to examine PKs of TIC and AR-C124910XX; and to evaluate safety and tolerability of TIC.

Serum uric acid levels significantly increased by up to 10% with TIC compared to pbo until 36 h after the final dose, returning to baseline levels 60 h after the final dose; the levels were not considered clinically relevant. Urinary excretion of uric acid was also significantly greater by up to 7.0% with TIC compared to pbo. Serum hypoxanthine and xanthine (precursors in uric acid catabolism pathway) levels increased by 25% and 20%, respectively, with multiple doses of TIC compared to pbo, suggesting the increase in serum uric acid may be due more to increased production than decreased renal clearance (CL<sub>R</sub>). 6b-hydroxyl cortisol/cortisol ratios were not statistically significantly changed on Days 1 or 5, with TIC compared to pbo, suggesting CYP3A4 metabolism was not affected by TIC.

Fractional excretion of sodium and creatinine clearance (CrCL) were unaffected by TIC compared to pbo, suggesting glomerular filtration rate (GFR) was not affected by TIC.

### **Effect of ticagrelor (TIC) on respiratory parameters**

#### ***D5130C00049***

The effect of TIC on respiratory parameters after single ascending doses was examined using pulmonary function tests (PFTs). No clinically relevant changes were seen in respiratory rate (RR), minute ventilation ( $V_E$ ), tidal volume ( $V_T$ ), inspiratory pressure, spirometry values or oxygen saturation with 900 mg or 1260 mg TIC compared to pbo.

#### ***D5130C00028***

The effect of TIC on respiratory parameters in healthy elderly subjects (55-75 y) was examined using PFTs. No clinically relevant changes were seen in RR,  $V_E$ ,  $V_T$ , exercise performance, or pulse oximetry with TIC compared to pbo. TIC did not cause bronchospasm as measured by spirometry, and did not worsen either the 'sensation of breathing' or 'change in perception of breathlessness' as measured by the Modified Borg Scale and Bidirectional Dyspnoea Index.

#### ***D5130C00034***

The effect of TIC on respiratory parameters in patients with mild asthma or mild to moderate chronic obstructive pulmonary disease (COPD) was examined using PFTs. No clinically relevant changes were seen in RR,  $V_E$ ,  $V_T$ , spirometry values, Modified Borg Scale or Bidirectional Dyspnoea Index, or pulse oximetry, in patients with asthma and COPD.

### **Effects of intrinsic factors**

#### ***D5130C00014***

The effect of age and gender on PD effects of TIC on platelet function was examined using optical aggregometry and BT. TIC 200 mg caused IPA >80% at 2 h, and >90% at 4 h and 8 h post dose in all treatment groups. Differences in groups were evident at 12 h when IPA was greatest in young males (96%) and lowest in elderly females (78%) and continued to 24 h when inhibition was 85% in young males, 65% in young females, 56% in elderly males and 44% in elderly females. For all treatment groups, BT was prolonged 5.0 to 5.5-fold at 4 h post dose, but had returned to near baseline by 24 h.

#### ***D5130C00015***

The effect of severe renal impairment on the PD effect of TIC on platelet function was examined using optical aggregometry. There were no statistically significant differences for final and maximum %IPA<sub>max</sub>, area under the effect curve from 0 to 24h (AUEC<sub>0-24</sub>) and area under the effect curve from 0 to 72h (AUEC<sub>0-72</sub>) between subjects with severe renal impairment and healthy matched subjects, although variability was greater with severe renal impairment.

#### ***D5130C00016***

The effect of mild hepatic impairment on the PD effect of TIC on platelet function was examined using optical aggregometry. There were no statistically significant differences for final and maximum %IPA, the area under the effect curve from 0 to 12h (AUEC<sub>0-12</sub>) and AUEC<sub>0-72</sub> between subjects with mild hepatic impairment and healthy matched subjects.

#### ***D5130C05266***

The effect of Japanese race on the PD effect of single ascending doses of TIC (50-400 mg and 100-600 mg) on platelet function was examined using optical aggregometry and BT.

There were no clinically relevant differences between Japanese and Caucasian subjects in ADP induced final and maximum %PAI, although there was a trend towards higher values in Japanese. There were no clinically relevant differences in BTs between Japanese and Caucasian subjects with TIC 50-400 mg, but BTs with 600 mg were greater in Japanese subjects compared to Caucasian (79 min vs 61 min, respectively, at 4.5 h post dose). For 50-100 mg, BTs for all subjects returned to near baseline by 24 h post dose; for 200-600 mg, BTs for all subjects returned to baseline by 48 h post dose.

#### ***D5130C05267***

The effect of Japanese race on the PD effect of single and multiple (bd) oral doses of TIC, 100 mg and 300 mg, on platelet function was examined using optical aggregometry and BT.

For single and multiple bd doses of 100 mg and 300 mg TIC, inhibitions of platelet aggregation was close to 100% in Japanese and Caucasian subjects; and  $IPA_{max}$  and AUEC for final and maximum extents of platelet aggregation were higher in Japanese than in Caucasian subjects, however the differences were only statistically significant for  $IPA_{max}$  and AUEC after the 100 mg single dose and multiple bd doses for final extent of aggregation, and for AUEC after the 100 mg single dose for maximum extent of aggregation. IPA values all returned to baseline, demonstrating reversibility of the IPA effect of TIC at both doses for both Japanese and Caucasian subjects. BTs were prolonged to a greater extent, slower to recover to baseline values, and more variable, in Japanese than Caucasian subjects, after single or multiple bd dosing of TIC. A greater number of Japanese than Caucasians had BT >60 min with both 100 mg and 300 mg.

#### **Effects of extrinsic factors (drug interactions)**

##### ***D5130C00039***

The effect of rifampin on TIC was examined using optical aggregometry. Final and maximum extent  $IPA_{max}$  were similar for TIC 180 mg with and without rifampin 600 mg; however, statistically significant decreases in maximum extent AUEC<sub>(0-12)</sub> and AUEC<sub>(0-24)</sub> possibly reflect decreased exposure to TIC and AR-C124910XX when coadministered with rifampin.

##### ***D5130C00005***

The effect of ASA on low (50 mg bd) and high (200 mg bd) dose TIC was examined using optical aggregometry and BTs.

Inhibition of ADP induced platelet aggregation was  $\geq 95\%$  over 12 h with 200 mg bd TIC and 60-90% over 12 h with 50 mg bd; and was unaffected by ASA. Inhibition of collagen induced platelet aggregation was up to 20% 8 h post dose on Day 10 with 200 mg bd TIC and up to 9% 8 h post dose on Day 5 with 50 mg bd; and increased up to 76% 8 h post dose on Day 10 with 200 mg bd and up to 74% 4h post dose on Day 5 with 50 mg with ASA. BTs were more prolonged for TIC+ASA (median 2.1 fold increase) compared to TIC (median 1.4 fold increase); four individual BTs >30 min all occurred with TIC+ASA.

##### ***D5130C00042***

The effect of TIC on the oral contraceptive (Nordette) was examined using pre dose morning plasma levels of endogenous hormones (progesterone, 17-beta oestradiol, luteinizing hormone (LH), follicle stimulating hormone (FSH), and sex hormone binding globulin [SHBG]) on Days 1, 7, 14 and 21. There were no statistically significant differences in endogenous hormone levels for Nordette with or without concomitant TIC 90 mg bd. Low luteal phase progesterone levels in both treatment groups suggest ovulation did not occur and the contraceptive effect of Nordette was maintained.

### **D5130C00006**

The effects of TIC and heparin on each other were examined using optical aggregometry and analysis of activated partial thromboplastin time (aPTT) and activated coagulation time (ACT). There were no clinically relevant effects on platelet aggregation for TIC with and without concomitant heparin; and there were no clinically relevant effects on the area under the effect curve from 2 to 24 h (AUEC<sub>2-24</sub>) of aPTT and ACT for heparin with and without concomitant TIC.

### **D5130C00007**

The effects of TIC and enoxaparin on each other were examined using optical aggregometry and analysis of anti-factor Xa. There were no clinically relevant effects on platelet aggregation for TIC with and without concomitant enoxaparin; and there was no effect on AUEC of anti-factor Xa for enoxaparin with and without concomitant TIC.

### **D5130C00026**

A randomised, double blind, two period crossover Phase I study in 21 healthy male and female volunteers, 20-43 y, who received TIC oral tablet (180 mg bd on Days 1-5) with and without desmopressin IV 0.3 µg/kg (2 h after a morning dose of TIC on Day 5).

The objectives were to assess the effect of desmopressin on BT prolongation induced by TIC at steady state; to evaluate effects of desmopressin on additional PD measures in the presence of TIC at steady state; to compare PKs of TIC in the presence absence of desmopressin; and to examine safety and tolerability of TIC,

The effects of desmopressin on TIC were examined using BT and optical aggregometry; and assessment of von Willebrand factor antigen (vWFAg), ristocetin cofactor and PFA-100 platelet function. There were no clinically relevant effects on BT for TIC with and without concomitant desmopressin; thus desmopressin is unlikely to be of use in controlling bleeding events in patients treated with TIC. The PFA-100, used to test platelet function in a research capacity only, found closure time was more rapid at all time points, and greatest at 2.5-4 h post dose; and time to platelet aggregation and minimum/baseline time to aggregation ratio were significantly reduced; for TIC with concomitant desmopressin compared to TIC alone. As expected since desmopressin affects platelet adhesion rather than platelet aggregation, there was no effect on platelet aggregation but both vWFAg and ristocetin cofactor increased significantly (peaking in 3-5 h) for TIC+DESMO compared to TIC alone

### **Summary of Pharmacodynamics**

#### **1. Effect of clopidogrel (CLO) on platelet function:**

CLO 75g od only partially blocked the P2T receptor (46-53%) with slow onset and high variability of inhibition. Addition of TIC demonstrated further inhibition using both PRP optical aggregometry (70-80%) and WBI aggregometry (94-97%).

#### **2. Effect of ticagrelor (TIC) on platelet function in healthy volunteers:**

Effect on platelet aggregation:

Multiple dose TIC+ASA inhibited both ADP and collagen induced IPA to a greater degree (faster, more complete, and with less variability) compared to multiple dose CLO+ASA, and compared to ASA.

Loading dose TIC inhibited ADP induced IPA to a greater degree (faster, near complete) compared to loading dose CLO. Greater TIC and AR-C124910XX concentrations were required to achieve same effect with increasing concentration of ADP stimulus.

Single dose TIC 30-400 mg showed a dose related inhibition of ADP induced platelet aggregation using 3 different aggregation methods.

Multiple dose TIC showed a dose related inhibition of ADP induced platelet aggregation. TIC 50 mg bd and 200 mg od gave comparable PAI to CLO 75 mg od. TIC  $\geq$ 100 mg bd and  $\geq$ 300 mg od gave greater PAI with less variability than CLO 75 mg od. Bd regimes maintained better PAI than od regimes.

Effect on BT:

All doses of TIC increased BTs, with no relationship to dose or plasma concentration.

Single dose TIC 900 mg and 1260 mg showed a dose related increase in BT.

3. Effect of TIC on platelet function in patients with atherosclerosis/stable CAD:

Effect on platelet aggregation:

In patients with stable CAD, the effect of TIC 90 mg bd+ASA on IPA showed a more rapid onset (40% at 0.5 h [vs 8% CLO], 88% at 2 h [vs 38% CLO]), a greater maintained maximum effect (max 88% reached at 2 h [vs 50% reached at 8 h with CLO]) and a more rapid offset (equivalent at 24 h and significantly lower 72 h-7 days vs CLO), compared to CLO 75 mg od+ASA. Thus, a patient could miss a dose of TIC and still maintain equivalent IPA effect for 24 h as if taking CLO. These findings were consistent with other markers of platelet activation.

In patients with stable CAD previously identified as CLO nonresponders or responders, TIC 90 mg bd+ASA was superior to CLO (75 mg od)+ASA in achieving  $>10\%$  and  $>50\%$  inhibition of ADP induced platelet aggregation but the effect was not statistically significant for the primary endpoint of  $>10\%$  4 h post dose at steady state in CLO nonresponders. Patients can switch directly from CLO to TIC treatment without a washout period, so antiplatelet effect will be maintained and increase by  $\sim 26\%$ .

In patients with ASD, ASA+TIC doses of 50 mg bd-400 mg daily were superior to CLO 75 mg od+ASA in inhibiting ADP induced platelet aggregation on Day 1 in a dose related manner; while ASA+TIC doses of 100 mg bd, 200 mg bd and 400 mg od were superior to CLO 75 mg od+ASA in inhibiting ADP induced platelet aggregation on Days 14 and 28.

In patients with non-ST segment elevation ACS in the previous 48 h, TIC single doses of 90 mg, 180 mg and 270 mg were superior to CLO 300 mg in inhibiting ADP induced platelet aggregation in CLO pretreated and naïve patients and all TIC doses gave an additional antiplatelet effect in CLO pretreated patients; while TIC 180 mg bd (and 90 mg bd to a lesser degree) was superior to CLO 75 mg od, in inhibiting ADP induced platelet aggregation at Week 4 in CLO naïve patients.

Effect on BT:

In patients with ASD, all doses of TIC increased BTs compared to CLO, with no relationship to dose.

4. Effect of TIC on ECG QTcX interval:

A suprathreshold dose of TIC (900 mg) did not increase the QTcX interval in a clinically significant way compared to pbo.

5. Effect of TIC on serum uric acid levels:

Serum uric acid levels increased approximately 10% in a reversible manner with TIC; CYP3A4 metabolism and GFR rate were not affected.

6. Effect of TIC on respiratory parameters:

No clinically relevant changes in PFTs were seen with TIC in healthy subjects (doses of 900 mg, 1260 mg), elderly subjects (doses of 450 mg, 180 mg bd) or in patients with mild asthma or COPD (doses of 450 mg, 180 mg bd) compared to pbo.

#### 7. Effects of intrinsic factors on TIC PDs:

Near peak 80-90% IPA was maintained from 2-8 h post dose in young and elderly, male and female, healthy volunteers; at 12 h and 24 h post dose, IPA was greatest in young males and lowest in elderly females. BT was reversibly prolonged in all treatment groups.

The effect of TIC on platelet aggregation was not affected to a clinically significant degree in the presence of severe renal impairment.

The effect of TIC on platelet aggregation was not affected to a clinically significant degree in the presence of mild hepatic impairment.

There were no clinically relevant differences in the effects of single and multiple doses of TIC on platelet aggregation (single ascending doses of 50-600 mg; single and multiple bd doses of 100 mg and 300 mg) and BT (single ascending doses of 50-400 mg), between Japanese and Caucasian subjects. BT was more generally more prolonged, slower to recover to baseline, and more variable, in Japanese compared to Caucasian subjects after TIC (single dose 600 mg; single and multiple doses of 100 mg and 300 mg).

#### 8. PD effects in drug interaction studies:

Coadministration of rifampin 600 mg with TIC 180 mg had no effect on I IPA<sub>max</sub> but decreased AUEC<sub>(0-12)</sub> and AUEC<sub>(0-24)</sub>, the faster offset possibly reflecting decreased exposure to TIC and AR-C124910XX.

Inhibition of ADP induced platelet aggregation by low (50 mg bd) and high (200 mg bd) dose TIC was unaffected by ASA 300 mg while inhibition of collagen induced platelet aggregation by low and high dose TIC was increased by coadministration of ASA 300 mg.

Endogenous hormone levels were unaffected when the oral contraceptive Nordette was taken with and without TIC 90 mg bd.

Platelet aggregation effects of TIC were unaffected by concomitant heparin and aPTT and ACT following heparin were unaffected by concomitant TIC.

Platelet aggregation effects of TIC were unaffected by enoxaparin and anti-factor Xa effects of enoxaparin were unaffected by TIC.

Platelet aggregation and BT effects of TIC were unaffected by desmopressin, although decreased haemostasis was recorded by PFA-100; so desmopressin is unlikely to be effective in reversing bleeding due to TICs anti-platelet effect. vWF<sub>Ag</sub> and ristocetin cofactor increased when desmopressin was coadministered with TIC (as expected since desmopressin affects platelet adhesion rather than platelet aggregation.).

## Pharmacokinetics

### Introduction

Pharmacokinetic (PK) data was contained in 45 studies:

- D5130C00038, D5130C00055, D5130C00033, D5130C00019, D5130C00031, D5130C00047, SC-532-5238, SC-532-5256 and D5130C00020 were biopharmaceutic studies;
- D5130C00013 examined absorption, distribution, metabolism, and excretion (ADME) of TIC;



- SC-532-5169, SC-532-5171, D5130C00049 and SC-532-5239 examined single and multiple ascending doses of TIC;
- D5130C05261 compared TIC+ASA and CLO+ASA;
- D5130C00029 compared loading doses of TIC and CLO;
- D5130C00037 examined the effect of TIC on the ECG QTcX interval;
- D5130C00050 examined the effect of TIC on serum uric acid levels;
- D5130C00049, D5130C00028 and D5130C00034 examined the effect of TIC on respiratory parameters;
- D5130C00048 [OFFSET], D5130C00030 [RESPOND], D5130C00008 [DISPERSE] and D5130C00002 [DISPERSE2] examined the PK effects of TIC in patients with atherosclerosis/stable CAD;
- D5130C00014, D5130C00015, D5130C00016, D5130C00054, D5130C05266 and D5130C05267 examined the effects of intrinsic factors;
- D5130C00022, D5130C00040, D5130C00039, D5130C00017, D5130C00032, D5130C00024, D5130C00025, D5130C05255, D5130C00051, D5130C05265, D5130C00005, D5130C00006, D5130C00007, D5130C00042 and D5130C00026 examined the effects of extrinsic factors (drug interactions).

## **Biopharmaceutic studies**

### ***D5130C00038***

An open label, randomised, two period crossover bioavailability (BA) Phase I study in 12 healthy volunteers who received single doses of TIC 90 mg oral tablet and an IV infusion of TIC 15 mg/150 mL 0.1 mg/mL at 300 mL/hr with  $\geq 7$  days washout between. It is summarised in Section II.

Objectives were to determine the absolute BA, examine the safety and tolerability of TIC and to characterise the PKs of TIC and AR-C124910XX following oral and IV administration of TIC.

The absolute BA of TIC was 36%, with individual BAs from 25.4 to 64.0%.

For TIC: After a single oral dose of 90 mg TIC,  $C_{max}$  was 403 ng/mL, AUC was 2233ng.h/mL,  $t_{max}$  was 1.5h and the apparent terminal half-life ( $t_{1/2}$ ) was 8.1 h, consistent with other studies. In this first study of PKs of IV TIC (15 mg),  $C_{max}$  was 449ng/mL, AUC was 1058ng.h/mL,  $t_{max}$  was 0.48 h (corresponding with the end of infusion), and  $t_{1/2}$  was 6.75 h. Differences between values following IV and oral doses reflect the difference in the size of the dose and the impact of first pass metabolism of the oral dose.

For AR-C124910XX: After oral TIC,  $C_{max}$  was 144 ng/mL, AUC was 1182 ng.h/mL,  $t_{max}$  was 2.0 h, and  $t_{1/2}$  was 8.1 h and after IV TIC,  $C_{max}$  was 16.5 ng/mL, AUC was 183 ng.h/mL,  $t_{max}$  was 1.7 h, and  $t_{1/2}$  was 8.3 h. As AR-C124910XX formation largely occurs during absorption and as part of the first pass metabolism, metabolite to parent (met:par) ratios for  $C_{max}$  and AUC are greater with oral vs IV administration.

### ***D5130C00055***

An open label, randomised, five period crossover BA Phase I study in 24 healthy volunteers, who received 5 single doses of TIC 90 mg (1 proposed commercial tablet, 3 tablet variants, 1 oral solution 1.0 mg/mL) with  $\geq 7$  days between. It is briefly summarised in Section II.

The objectives were to determine the relative BA for TIC and AR-C124910XX of 4 TIC tablet variants compared to a TIC oral solution and to examine safety and tolerability of the 5 formulations. A non pre-defined objective was to determine the relative BA of the variant tablets compared to the proposed commercial tablet formulation.

None of the formulations affected extent of absorption of TIC or formation of AR-C124910XX.

#### ***D5130C00033***

An open label, randomised, two cohort, two period crossover, BA Phase I study in 52 healthy volunteers, who received single doses of either micronised or non-micronised TIC tablets in both fed and fasted states with a 7day washout between. It is summarised in Section II.

Objectives were to assess the effect of food on the PKs of TIC and AR-C124910XX after administration of Phase III tablets containing either non-micronised or micronised TIC and to examine safety and tolerability of the Phase III tablets containing either non-micronised or micronized TIC.

For TIC, AUC was 21-23% higher when TIC was taken with a meal, with an UCL of 1.32-1.33; but 95%CIs for  $C_{max}$  were contained within the pre-specified bioequivalence (BE) limits for both formulations. For AR-C124910XX, 95%CIs for AUC were contained within the pre-specified BE limits; but  $C_{max}$  was 22-27% lower when TIC was taken with a meal, with a lower confidence limit (LCL) of 0.67-0.69. The changes were not considered clinically significant due to being comparable to previously seen intrasubject variability.

#### ***D5130C00019***

An open label, randomised, two way crossover, group sequential design, BA Phase I study in 2 stages, in 27 healthy volunteers, who received single doses of 2x100 mg TIC in two formulations with  $\geq 7$ days between.

The objectives were to assess the relative BA of a new formulation of TIC tablets to tablets with the previous formulation, to examine safety and tolerability of the new formulation of TIC tablets, to assess the PDs of TIC by measuring IPA using optical aggregometry and prolongation of BT; and to assess PKs of TIC and active metabolite AR-C124910XX.

For the new formulation compared to the old formulation, BA (AUC) for TIC was 17% higher and for AR-C124910XX it was 15% higher and the 94%CIs were contained within the interval (0.7, 1.43) but  $C_{max}$  for TIC was 42% higher, and for AR-C124910XX it was 30% higher and the 94%CIs were not contained within the interval (0.7, 1.43). The formulations were therefore not BE. However as there was no correlation between increased BA and differences in ADP induced PAI or prolongation of BT, or an increase in bleeding related AEs, the formulation could be further developed.

#### ***D5130C00031***

An open label, randomised, three period crossover, BE Phase I study in 30 healthy volunteers, who received 3 single doses of 270 mg TIC, 3x micronised 90 mg Phase III tablets and 3x micronised 90 mg Phase IIb tablets with  $\geq 7$ days between. It is summarised in Section II.

The objectives were to determine if any one tablets were BE to another, to compare the PKs of AR-C124910XX from three tablets and to examine safety and tolerability of the three tablets.

For all comparisons of  $C_{max}$  and AUC for TIC and AR-C124910XX, point estimates ranged from 0.90 to 1.05 and 90%CIs were all within the pre-determined interval for BE of (0.8, 1.25). All three formulations were therefore BE.

### **D5130C00047**

An open label, randomised, two period crossover BE Phase I study in 42 healthy volunteers, who received 2 single doses of 90 mg TIC from either a pilot scale tablet or a commercial scale tablet with  $\geq 7$  days between.

The objectives were to determine if the proposed commercial tablet formulation, manufactured at either the proposed manufacturing site or a pilot scale site were BE, to compare PKs of AR-C124910XX from the two tablets and to examine safety and tolerability of TIC.

For all comparisons of  $C_{max}$ , the AUC from time zero to the last quantifiable concentration ( $AUC_{(0-t)}$ ) and AUC for TIC and AR-C124910XX, point estimates ranged from 0.90 to 1.01, and 90% CIs were all within the pre-determined interval for BE of (0.8, 1.25). The formulations were therefore BE.

### **ADME of ticagrelor (TIC)**

#### **D5130C00013**

An open label, single dose, non randomised, ADME Phase I study in 6 healthy male subjects, 41-54 y, who received [ $^{14}C$ ]AZD6140 200 mg as a suspension.

The objectives were to determine rates and major excretory routes after oral [ $^{14}C$ ]AZD6140 in humans and to provide metabolic profiles after oral [ $^{14}C$ ]AZD6140 and to determine plasma and whole blood concentrations of total [ $^{14}C$ ]-radioactivity, TIC and AR-C124910XX and blood to plasma ratio of total [ $^{14}C$ ]-radioactivity and to assess extent of renal excretion of TIC and its metabolites.

Plasma concentrations of TIC and AR-C124910XX reached maximum levels at 1.5 h and 3.0 h, respectively and returned to pre dose levels by 48 h;  $t_{1/2}$  was 8.4 h for TIC and 11.5 h for AR-C124910XX. AUC and  $C_{max}$  were 6675ng.h/mL and 923ng/mL, respectively for TIC, and 2538ng.h/mL and 264ng/mL, respectively for AR-C124910XX (which were 38% and 29%, respectively of the TIC values). The total amount of TIC and AR-C124910XX excreted unchanged in urine was 0.02% and 0.04%, respectively, suggesting extensive metabolism of TIC *in vivo*.

Of the [ $^{14}C$ ]MK 200 mg dose given, 84.3% was recovered (26.5% in urine, 57.8% in faeces). This recovery was less than the 90% expected. Maximum concentrations of total radioactivity in plasma and whole blood were 1534ng.equiv/mL (at 2.5 h) and 1129ng.equiv/mL (at 3.0 h), respectively. Concentrations then decreased until they were undetectable at 20 h for [ $^{14}C$ ]plasma and 12 h for [ $^{14}C$ ]whole blood. Most of the radioactivity was in the plasma space rather than in or bound to the blood cells.

### **Single and multiple ascending doses of TIC**

These were four randomised, double (SC-532-5169, SC-532-5171, D5130C00049) or single (SC-532-5239) blind, placebo controlled Phase I studies in healthy subjects who received TIC (or CLO for one treatment group in SC-532-5239) or placebo.

#### **SC-532-5169**

A single ascending dose, group comparative Phase I study in 25 subjects who received three single doses of AR-C126532XX oral suspension (0.1, 0.3, 1.0, 3.0, 10, 30 or 100 mg) in an ascending manner or pbo.

The objectives were to study the safety and tolerability of single oral doses of AR-C126532XX, to fully characterise the aggregation inhibition dose response curves of AR-C126532XX, to identify a single dose which maintained maximal inhibition of platelet ADP response at 12 h and/or 24 h post dose, to determine PKs of a single dose of AR-

C126532XX, to identify (by interpolation if necessary)  $\geq 3$  doses of AR-C126532XX to take forward into multiple dosing and to compare WBI aggregometry with RPC methodology.

Plasma concentrations of AR-C126532XX were below the limit of quantification for the 0.1 and 0.3 mg doses but were measurable for 6-8 h for the 1.0 mg dose, 18-24 h for the 3.0 mg dose, 24-36 h for the 10 and 30 mg doses, and 36 h for the 100mg dose. Maximum plasma concentrations occurred at 1.25-2.00 h for all doses from 1.0-100 mg. Half-life appeared to be 7-8.5 h (lower half-lives at 1.0 and 3.0 mg were likely due to low plasma concentrations not allowing accurate measurements). AUC and  $C_{max}$  increased with increasing dose in a dose proportional manner. Similar apparent oral clearance (CL/F) values (6.6-8.2 mL/min.kg) also suggested dose linear PKs. Variability between and within subjects both appeared to be low.

### **SC-532-5171**

A single ascending dose, group comparative study in 13 subjects who received single doses of AR-C126532XX oral suspension (100, 200, 300, 400, and 500 or 30 mg) or pbo.

The objectives were to study safety and tolerability of single oral doses of 100, 200, 300, 400 and either 500 or 30 mg AR-C126532XX. Note that after the study had started the protocol was amended to replace the 500 mg dose with 30 mg if the maximum tolerated dose was reached prior to 500 mg). Other objectives were to further characterise aggregation inhibition dose response curves of AR-C126532XX using 3 methods of platelet aggregometry (WBI aggregometry, RPC and PRP optical aggregometry) and to determine PKs of a single dose of AR-C126532XX and active metabolite.

Plasma concentrations of AR-C126532XX were below the limit of quantification only for the 30 mg dose at 36 h. For AR-C126532XX, maximum plasma concentrations occurred at 1.5 h for all doses from 30-400 mg, and half-life was 7.3-8.1 h while for AR-C124910XX, maximum plasma concentrations occurred at 1.5-3.0 h and half-life was 8.5-10.1 h. AUC and  $C_{max}$  increased with increasing dose in an approximately dose proportional manner for both parent (1005-18547ng.h/mL and 161-2711ng/mL, respectively) and metabolite (376-6577ng.h/mL and 42.1-713ng/mL, respectively). Variability between subjects was low for AR-C126532XX, and slightly greater for AR-C124910XX.

### **D5130C00049**

A single ascending dose study in 16 volunteers. In Cohort A, 8 subjects were randomised to receive single doses of TIC 900 mg oral tablet or pbo and in the following Cohort B, 8 subjects were randomised to receive single doses of TIC 1260 mg oral tablet or pbo.

The objectives were to assess safety and tolerability of single ascending oral doses of TIC in healthy volunteers and to assess PKs and PDs of TIC, AR-C133913XX and AR-C133913XX after single ascending oral doses of TIC in healthy volunteers.

For Cohort A, after 900 mg TIC, a maximum plasma concentration of 5153ng/mL was reached at median of 1.25 h. For Cohort B, after 1260 mg TIC, a maximum plasma concentration of 5799ng/mL was reached at a median of 2.76 h.  $C_{max}$ , AUC,  $t_{max}$  and  $t_{1/2}$  all showed an increase with dose of TIC; which appeared to be dose proportional for AUC. PK profiles for individual patients showed double peaking absorption patterns, consistent with ingestion of large number of tablets (7x180 mg) as well as vomiting in 3 subjects 1-1.25 h after dosing. There was no dose effect seen for met:par  $C_{max}$  and AUC ratios.

### **SC-532-5239**

A parallel group study in 48 volunteers allocated to one of 3 groups. Group A subjects received TIC 50-200 mg od, TIC 50-200 mg bd or pbo, for 16 days; Group B subjects received TIC 200-600 mg od, TIC 50-300 mg bd or pbo, for 20 days; and Group C subjects

received CLO (300 mg loading dose then 75 mg od) or pbo, for 14 days. Groups A and C ran in parallel, with a safety review of data prior to commencing Group B.

The objectives were to investigate safety and tolerability of multiple oral doses of TIC given daily as different dosing schedules by assessment of AEs and safety parameters, to assess PK properties of TIC administered orally as tablets in different dosing schedules, to assess and compare PD properties of TIC administered orally as tablets in different dosing schedules and CLO administered orally, to compare safety of CLO od to various dosing schedules of TIC and to investigate effect of food on PKs and PDs of TIC.

Based on  $t_{1/2}=7.5$  h, accumulation for TIC was theorised to be 1.1 for od dosing and 1.5 for bd dosing and for AR-C124910XX, 1.2 for od dosing and 1.8 for bd dosing. For TIC, maximum plasma concentrations were reached at a median of 1.5-3.0 h and  $t_{1/2}$  was 6.1-13.1 h with a trend towards increasing with increasing dose. AUC increased approximately 2.2 to 2.4 fold with a 2 fold dose increase; and actual accumulation ratios were 1.2, 1.2, and 1.8 for 50 mg od, 200 mg od and 50 mg bd. For AR-C124910XX, maximum plasma concentrations were reached at a median of 2.0-4.0 h and  $t_{1/2}$  was 6.4-16.6 h with a trend towards increasing with increasing dose. AUCs, which were approximately one third that of parent AUCs, increased approximately 2.2 to 2.4 fold with a 2 fold dose increase and actual accumulation ratios were 1.4, 1.3, and 1.9 for 50 mg od, 200 mg od and 50 mg bd. AUC and  $C_{max}$  were approximately 1.25 fold higher for TIC but unchanged for AR-C124910XX when a single dose of TIC 200 mg was taken following a meal.

### **Comparison of ticagrelor (TIC)+ASA and clopidogrel (CLO)+ASA**

#### ***D5130C05261***

In this study (described under Pharmacodynamics), absorption of TIC and formation of AR-C124910XX were similar after the first dose and at steady state (median  $t_{max}=3.0-3.1$  h). AUC and  $C_{max}$  for AR-C124910XX were 28-40% that of the parent AUC and  $C_{max}$  after both the first dose and at steady state. The mean accumulation ratios were 2.2 for TIC and 2.8 for AR-C124910XX, consistent with an effective half-life of 12 h.

### **Comparison of ticagrelor (TIC) and clopidogrel (CLO) loading doses**

#### ***D5130C00029***

In this study (described under Pharmacodynamics), absorption of TIC and formation of AR-C124910XX were rapid after 270 mg and 540 mg TIC (median  $t_{max}=2.0-3.0$  h).  $C_{max}$  and AUC after 540 mg were 1.7 to 2.3 fold greater than after 270 mg for both TIC and AR-C124910XX (dose proportional) and  $t_{1/2}$  was 11.1-12.6 h. AUC and  $C_{max}$  for AR-C124910XX were 40-43% and 24-27%, respectively that of parent AUC and  $C_{max}$ . These results were consistent with previous studies. Formation of SR 26334 was rapid after 600 mg CLO (median  $t_{max}=1.5$  h). Mean  $C_{max}$  was 27546ng/mL, AUC was 130065ng.h/mL, and  $t_{1/2}$  was 8.8 h.

### **Effect of ticagrelor (TIC) on ECG QTcX interval**

#### ***D5130C00037***

In this study (described under Pharmacodynamics), after TIC 900 mg, maximum plasma concentrations of TIC and metabolites were reached at a median of 3.0-4.0 h and  $t_{1/2}$  was 11.5-12.0 h. AUC for TIC was 42328ng.h/mL and  $C_{max}$  was 4422ng/mL; AUC for AR-C124910XX was 13988ng.h/mL (33.0% of parent) and  $C_{max}$  was 885ng/mL (20.0% of parent) and AUC for AC-C133913XX was 3608ng.h/mL (8.5% of parent) and  $C_{max}$  was 394ng/mL (8.9% of parent). These results were consistent with D5130C00049 for a dose of TIC 900 mg.

## **Effect of ticagrelor (TIC) on serum uric acid levels**

### ***D5130C00050***

In this study (described under Pharmacodynamics), after TIC 90 mg bd for 5 days, maximum plasma concentrations of TIC (736ng/mL) and AR-C124910XX (202ng/mL) were reached at a median of 2.0 h; AUC<sub>(0-12)</sub> was 4763ng.h/mL and 1478ng.h/mL, respectively. These results were consistent with previous studies.

## **Effect of ticagrelor (TIC) on respiratory parameters**

### ***D5130C00028***

A randomised, double blind, pbo controlled, two period crossover Phase I study in 12 healthy elderly volunteers, who received TIC (loading dose of 450 mg then 180 mg bd, for 4 days) or pbo with  $\geq 7$  days between.

The objectives were to assess the effect of TIC on RR, V<sub>E</sub>, V<sub>T</sub>, and other respiratory parameters, to evaluate the PK/PD relationship between TIC/AR-C124910XX concentrations and respiratory parameters, to assess PKs of TIC and AR-C124910XX and to evaluate tolerability of TIC in healthy elderly volunteers

The rate of absorption of TIC and formation of AR-C124910XX were similar after loading dose and at steady state (median t<sub>max</sub>=2.0-2.5 h). C<sub>max</sub> was greatest after the loading dose (2933ng/mL for TIC and 993ng/mL for AR-C124910XX). Steady state was reached by Day 3. AUC and C<sub>max</sub> for AR-C124910XX were 44% and 34% respectively that of parent after the loading dose and were 58% and 44%, respectively that of parent at steady state.

### ***D5130C00034***

A randomised, double blind, pbo controlled, two period crossover Phase I study in 18 volunteers with mild asthma or mild to moderate COPD who received TIC (loading dose of 450 mg then 180 mg bd for 4 days) or pbo with  $\geq 7$  days between.

The objectives were to assess the effect of TIC on RR, V<sub>E</sub>, and other respiratory parameters, to evaluate the PK/PD relationship between TIC/AR-C124910XX concentrations and respiratory parameters in mild asthma patients and mild to moderate COPD patients, to compare respiratory parameters and PKs of TIC and AR-C124910XX between mild asthma patients, mild to moderate COPD patients and healthy elderly (55-75y) volunteers from study D5130C00028 and to evaluate tolerability of TIC in mild asthma and mild to moderate COPD patients.

For the asthma cohort: the rate of absorption of TIC and formation of AR-C124910XX was similar after the loading dose and at steady state (median t<sub>max</sub>=2.0 h). C<sub>max</sub> was greatest after the loading dose (2440ng/mL for TIC and 634ng/mL for AR-C124910XX). AUC and C<sub>max</sub> for AR-C124910XX were 32% and 26% respectively that of parent after the loading dose and were 41% and 34%, respectively that of parent at steady state.

For COPD cohort: the rate of absorption of TIC and formation of AR-C124910XX was similar after the loading dose and at steady state (median t<sub>max</sub>=2.0-3.0 h). C<sub>max</sub> was greatest after the loading dose (3001ng/mL for TIC and 713ng/mL for AR-C124910XX). AUC and C<sub>max</sub> for AR-C124910XX were 29% and 24% respectively that of parent after the loading dose, and were 52% and 45% respectively that of parent at steady state.

Patients with asthma or COPD appear to have lower AUC and C<sub>max</sub> for TIC at steady state, and for AR-C124910XX after loading dose and at steady state, compared to healthy elderly patients from D5130C00028.

## **PK effects of ticagrelor (TIC) in patients with atherosclerosis/stable CAD**

### ***D5130C00048 [OFFSET]***

In this study (described under Pharmacodynamics), absorption of TIC and formation of AR-C124910XX were equally rapid after the loading dose and after the maintenance dose (median  $t_{max}$ =2.0-2.1 h);  $t_{1/2}$  was 9.8-12.4 h. The area under the plasma concentration time curve from time zero to 8 h ( $AUC_{0-8}$ ) and  $C_{max}$  for AR-C124910XX were 23-32% and 20-29% respectively that of parent AUC and  $C_{max}$ , after both the loading dose and the maintenance dose.  $C_{max}$ ,  $t_{max}$ , and  $t_{1/2}$  values were in keeping with previous studies and although  $AUC_{0-8}$  is not a standard measure, the values were as might be expected based on previous studies.

### ***5130C00030 [RESPOND]***

In this study (described under Pharmacodynamics), in patients classified as CLO nonresponders, PKs of TIC and AR-C124910XX on Day 1 and at steady state were consistent with previous studies. The PKs were essentially the same regardless of whether TIC was taken in the first treatment period (CLO naïve) or the second treatment period (CLO pretreated) and was not affected by responsiveness to CLO.

In the group of patients classified as CLO responders, PKs of TIC and AR-C124910XX on Day 1 and at steady state were consistent with previous studies except in the group of responders that received TIC in both periods (when PK values were decreased on Period 2 Day 1). This was due to a design flaw that had patients receive pbo instead of active drug for the first 'crossover' medication of Period 2.

This may have affected the ability to compare Day 1 IPA, platelet aggregation and biomarker expression results in CLO responsive patients when directly switched from TIC to CLO but would have no effect on comparison of steady state results which were comparable and suggestive that a direct change from CLO to TIC did not affect PKs of TIC. It should again be noted that the pre-specified primary PD endpoint was not reached in this study.

Although this study was not designed to compare cohorts, it is interesting to note that  $C_{max}$  and  $AUC_{0-8}$  were similar for responders and nonresponders.

### ***D5130C00008 [DISPERSE]***

In this study (described under Pharmacodynamics), absorption of TIC was rapid (mean  $t_{max}$  2.0-3.7 h) for all dose regimens and formation of AR-C124910XX was also rapid with mean  $t_{max}$  generally 0.5-1.0 h behind that for TIC. Plasma concentrations of TIC and AR-C124910XX were similar on Days 14 and 28, showing steady state was reached.

Both  $C_{max}$  and AUC for TIC and AR-C124910XX increased in a linear and dose proportional manner for TIC doses of 50 mg bd and 100 mg bd and in a greater than dose proportional manner for doses of 200 mg bd and 400 mg bd at steady state. Steady state accumulation ratios for bd regimes were 1.5-2.0.

Met:par ratios were 25-35% across all dose regimens for Day 1 and steady state. No differences were seen between males and females. There was a trend to higher AUC values in older subjects ( $\geq 65$  y) compared to younger subjects ( $< 65$  y).

### ***D5130C00002 [DISPERSE2]***

In this study (described under Pharmacodynamics), for CLO naïve patients, plasma concentrations were higher at Week 4 than on Day 1, showing accumulation of parent drug and metabolite after multiple doses of TIC. Absorption of TIC was rapid ( $t_{max}$ =2 h) and formation of AR-C124910XX was similarly rapid ( $t_{max}$ =2-4 h). For CLO pretreated

patients, absorption of TIC was rapid ( $t_{\max}=2-4$  h) with similar values for the metabolite showing rapid conversion; both were comparable to the values seen in CLO naïve patients.

For TIC 90 mg bd and 180 mg bd at steady state (Week 4; in CLO naïve patients only), greater than dose proportional increases were seen with the TIC area under the serum concentration time curve over one dosing interval (AUCt)(4146 and 12333ng.h/mL, respectively) and with AR-C124910XX AUCt (1669 and 4146ng.h/mL), and approximately dose proportional increases were seen with TIC  $C_{\max}$  (685 and 1339ng/mL) and AR-C124910XX  $C_{\max}$  (215 and 384ng/mL, respectively).

For TIC 90 mg, 180 mg and 270 mg on Day 1, there was no consistent pattern with TIC  $C_{\max}$  between CLO naïve and CLO pretreated patients but AR-C1249XX  $C_{\max}$  was comparable between CLO naïve patients and CLO pretreated patients. Additionally, a marked difference in TIC AUCt between CLO naïve and CLO pretreated patients was greater at lower doses but AR-C1249XX AUCt was comparable between CLO naïve and CLO pretreated patients. As patient numbers across the groups were varied and sometimes quite small (n=2-16) firm conclusions cannot be drawn from the data. However, PKs of AR-C124910XX did not appear to be affected by CLO pretreatment.

### **Effects of intrinsic factors**

#### ***D5130C00014***

An open label, non randomised, parallel group Phase I study in 40 healthy, young and elderly volunteers, who received a single dose of TIC 200 mg.

The objectives were to assess the effects of age and gender on PKs and PDs (and the relationship between them) and safety and tolerability of a single 200 mg oral dose of TIC in healthy volunteers and to explore genetic factors important in the disposition of TIC and response to TIC.

TIC was rapidly absorbed for all four groups ( $t_{\max}=2.5-3.0$  h).  $C_{\max}$  and AUC were lowest in young males (728ng/mL and 6194ng.h/mL) and highest in elderly females (1744ng/mL and 12578ng.h/mL), demonstrating exposure is higher in the elderly compared to the young, and higher in females compared to males. Young and elderly males had similar  $t_{1/2}$  (12.1 h and 11.7 h respectively), which were lower than those seen in young and elderly females (13.5 h and 15.5 h respectively). Results for AR-C124910XX were similar to those for TIC. A  $t_{\max}$  of 3.0-3.5 h demonstrated rapid conversion from TIC to the active metabolite.

#### ***D5130C00015***

A non randomised, open label, parallel group, multicentre Phase I study in two stages. In stage 1 10 healthy volunteers and 10 volunteers with severe renal impairment received a single dose of TIC 180mg; Stage 2 was not required.

The objectives were to compare PKs and PDs and safety and tolerability of TIC and active metabolite, AR-C124910XX, in volunteers with severe renal impairment, in healthy volunteers with normal renal function (Stage 1) and in volunteers with mild and moderate renal impairment (Stage 2 had it been necessary).

TIC and AR-C124910XX values for both  $t_{1/2}$  and  $t_{\max}$  were comparable between volunteers with severe renal impairment and healthy matched volunteers, demonstrating the renal impairment does not significantly affect absorption, formation or elimination of TIC and its active metabolite.

TIC AUC and  $C_{\max}$  were approximately 20% lower and AR-C124910XX AUC was approximately 17% higher with severe renal impairment compared to healthy matched



volunteers. When the severe renal impairment data was also analysed without data from 3 subjects with CrCL<20 mL/min (these subjects showed high coefficient of variation [CV%]), TIC AUC and  $C_{max}$  were approximately 8-14% higher and AR-C124910XX AUC and  $C_{max}$  were approximately 17-52% higher. Due to the high variability (and the higher CV% with severe renal impairment compared to normal renal function volunteers) these differences were not considered clinically relevant.

#### **D5130C00016**

A non randomised, open label, parallel group Phase I study in 10 healthy volunteers and 10 volunteers with mild hepatic impairment who received a single dose of TIC 90mg.

The objectives were to compare PKs and PDs of TIC and active metabolite, AR-C124910XX, and safety and tolerability of TIC in volunteers with mild hepatic impairment to normal healthy volunteers.

Mild hepatic impairment had an effect on the PKs of TIC and AR-C124910XX compared to normal volunteers. Although  $t_{max}$  was not affected,  $t_{1/2}$  was longer by 25% and 56%, respectively, indicating absorption and conversion of TIC to the metabolite were not affected but elimination of both parent and metabolite were increased.

TIC AUC and  $C_{max}$  were 23% and 12% higher respectively and AR-C124910XX AUC and  $C_{max}$  were 66% and 17% higher respectively with mild hepatic impairment compared to healthy matched volunteers. The UCLs of all 90% CIs were outside the pre-specified equivalence interval of (0.80, 1.25). Three volunteers with mild hepatic impairment accounted for a large amount of the difference between impaired subject and matched healthy subject. Overall exposure to TIC and AR-C124910XX was higher in volunteers with mild hepatic impairment than in healthy matched volunteers.

#### **D5130C00054**

A non randomised, two cohort, open label, single and multiple dose PK Phase I study in 26 healthy Chinese volunteers, who received single and multiple (bd) doses of TIC, 90 or 180 mg.

The objectives were to characterise the PKs of TIC and its active metabolite AR-C124910XX and to determine safety and tolerability, after single and multiple (bd) doses of TIC 90 and 180 mg in healthy Chinese volunteers.

The rate of absorption of TIC ( $t_{max}=2.0$  h) and formation of AR-C124910XX ( $t_{max}=2.0-3.0$  h) were similarly rapid after a single dose and at steady state of both doses (90 mg and 180 mg);  $t_{1/2}$  values were independent of dose, single or at steady state. Steady state was reached by Day 2 for TIC and by Day 3 for AR-C124910XX. TIC AUC and  $C_{max}$  values for 180 mg TIC appeared to be approximately double those for 90 mg TIC while AR-C124910XX AUC and  $C_{max}$  values for 180 mg TIC appeared to be slightly less than double those for 90 mg TIC. After 90 mg TIC, AUC and  $C_{max}$  for AR-C124910XX were 47% and 30%, respectively that of parent after the first dose and were 49% and 34% respectively that of parent at steady state. After 180 mg TIC, AUC and  $C_{max}$  for AR-C124910XX were 39% and 29% respectively that of parent after the first dose and were 36% and 26% respectively that of parent at steady state.

#### **D5130C05266**

A randomised, double blind, pbo controlled, single centre Phase I study in 40 healthy Japanese and Caucasian volunteers, who received single ascending doses of TIC (Cohort A: 50, 200, 400 mg; Cohort B: 100, 300, 600 mg) or pbo.

The objectives were to assess safety and tolerability and to assess and compare PKs and PDs after single ascending oral doses of TIC given to healthy Japanese and Caucasian subjects.

PK profiles were similar for Japanese and Caucasians. TIC was absorbed rapidly for all single doses of TIC from 50 mg to 600 mg ( $t_{max}=2.0-3.0$  h); and conversion to metabolite AR-C124910XX was also rapid ( $t_{max}$  2.5-4.0 h). After 600mg TIC, TIC  $C_{max}$  and AUC were 33% and 48% higher, and AR-C124910XX  $C_{max}$  and AUC were 55% and 62% higher respectively in Japanese compared to Caucasian subjects. For all other doses no significant differences were seen for  $C_{max}$  and AUC between Japanese and Caucasians. All  $C_{max}$  and AUC values were greater for Japanese subjects than for Caucasian subjects except after the 400mg dose and increases in exposures were greater than dose proportional over the range 50-600 mg for both races.

#### ***D5130C05267***

A randomised, single blind, pbo controlled Phase I study in 36 Japanese and 36 Caucasian healthy male volunteers who received single and multiple (bd) doses of TIC 100 or 300 mg.

The objectives were to investigate safety and tolerability, PKs, PDs, and PK/PD relationship after multiple oral doses of TIC given to healthy male Japanese and Caucasian volunteers

TIC was absorbed rapidly following both a single dose and at steady state for 100 mg and 300 mg TIC in both Japanese and Caucasian subjects ( $t_{max}=2.0-3.0$  h) and conversion to metabolite AR-C124910XX was also rapid ( $t_{max}=3.0$ h). After a single dose,  $t_{1/2}$  was longer for both Japanese and Caucasians with 300 mg TIC (9.0-12.7 h) compared to 100 mg (7.0-8.9 h) and at steady state,  $t_{1/2}$  was longer for both Japanese and Caucasians with 300 mg TIC (11.0-18.7 h) compared to 100 mg (9.5-11.9 h). TIC  $C_{max}$  and AUC were significantly greater (by 37-44%), and AR-C124910XX  $C_{max}$  and AUC were significantly greater (by 42-62%) for Japanese than for Caucasian subjects for both 100 mg and 300 mg TIC, both after a single dose and at steady state. The differences between Japanese and Caucasians were less pronounced when values were normalised for body weight but not significantly so.

#### **Effects of extrinsic factors (drug interactions)**

##### ***D5130C00022***

A randomised, open label, two period crossover drug interaction Phase I study in 16 healthy volunteers, who received single doses of TIC 90 mg, with and without ketoconazole 200 mg bd.

The objectives were to examine the effect of coadministration of 200 mg bd ketoconazole on PKs of a single oral 90 mg dose of TIC and to assess safety and tolerability of 90 mg TIC when coadministered with 200mg bd ketoconazole.

TIC  $C_{max}$  and AUC were increased by 135% and 632% respectively and AR-C124910XX  $C_{max}$  and AUC were decreased by 89% and 56% respectively with 90% CIs all outside the interval (0.70, 1.43) demonstrating a statistically significant PK interaction. Coadministration of ketoconazole increased  $t_{max}$  for AR-C124910XX (from 2.0 h to 6.0 h) but did not affect  $t_{max}$  for TIC (2.0 h).

##### ***D5130C00040***

A randomised, open label, two way crossover Phase I study in 18 healthy volunteers who received single doses of TIC 90 mg, with and without diltiazem 240 mg od.

Objectives were to examine the effect of coadministration of diltiazem on single oral dose PK of TIC and AR-C124910XX and of TIC on steady state PKs of diltiazem and to examine whether coadministration of diltiazem with TIC was safe and well tolerated.

Coadministration of diltiazem caused increases in  $C_{max}$  and AUC of 69% and 174% respectively for TIC and decreases of 38% and 13% respectively for AR-C124910XX. The 90%CI was only inside the 'no effect' interval of (0.70, 1.43) for AUC of AR-C124910XX. Coadministration of diltiazem did not affect  $t_{max}$  for TIC (2.0 h) or AR-C124910XX (3.0 h). Although coadministration of TIC increased  $t_{max}$  of diltiazem (from 8.0 h to 10.0 h), ratios of  $C_{max}$  and AUC showed little change (1.02 [0.89, 1.17] and 0.96 [0.87, 1.06] respectively).

#### **D5130C00039**

An open label, single arm, drug interaction Phase I study in 18 healthy volunteers who received single doses of TIC 180 mg on Days 1 and 15 and rifampin 600 mg od on Days 4 to 17.

The objectives were to examine the effect of coadministration of rifampin on single oral dose PKs and PDs of TIC and to determine whether coadministration of rifampin with TIC is safe and well tolerated.

As might be expected of an inducer of CYP3A and the P-gp transporter, coadministration of rifampin caused a decrease in  $C_{max}$  and AUC of 73% and 86% respectively for TIC and a decrease in AUC of 46% for AR-C124910XX although  $C_{max}$  for AR-C124910XX was not affected (1.02 (0.86, 1.21)). Coadministration of rifampin slightly decreased median  $t_{max}$  for TIC (from 2.0 h to 1.0 h) but did not affect  $t_{max}$  for AR-C124910XX (2.0 h).

#### **D5130C00017**

A randomised, double blind, pbo controlled, two period crossover Phase I study in 28 healthy volunteers, who received TIC 400 mg or pbo for 6 days and a single dose of midazolam 7.5mg on Day 6.

The objectives were to determine if repeated oral dosing of TIC influences the major pathway of CYP3A4 mediated metabolism of midazolam to 1-OH midazolam or the minor pathway of CYP3A5 mediated metabolism of midazolam to 4-OH midazolam after coadministration of TIC with midazolam, to determine if coadministration of single dose midazolam with TIC alters steady state concentrations of TIC and AR-C124910XX and to assess safety and tolerability of TIC after coadministration of single oral dose of midazolam.

Coadministration of TIC caused decreases in  $C_{max}$  and AUC of 27% and 32% respectively for midazolam, and decreases in  $C_{max}$  and AUC<sub>(0-t)</sub> of 35% and 47% respectively for 4-OH midazolam but no changes for 1-OH midazolam; 90%CIs for midazolam and 4-OH midazolam were outside the pre-specified interval (0.70, 1.43) indicating a PK interaction. Addition of TIC did not affect  $t_{max}$  for midazolam (0.75 h), but increased it for 1-OH midazolam (from 0.63 h to 0.75 h) and 4-OH midazolam (from 0.75 h to 0.88 h).

Coadministration of midazolam did not significantly affect  $C_{max}$  or AUC of TIC (1.11 [0.99, 1.24] and 1.14 [1.09, 1.19] respectively) or AR-C124910XX (1.04 [0.94, 1.16] and 1.12 [1.07, 1.17] respectively) with all 90%CIs inside the pre-specified interval of (0.70, 1.43);  $t_{max}$  remained similar for TIC (3.0-3.5 h) and AR-C124910XX (4.0 h).

#### **D5130C00032**

An open label, randomised, four period, four treatment crossover Phase I study in 28 healthy volunteers who received single doses of midazolam (oral 7.5 mg and IV 2.5mg), alone and on Days 1 (2 h after loading dose of 270 mg) and 7 (with morning dose) of concomitant TIC (180 mg bd).

The objectives were to determine if steady state concentrations or a single loading dose of TIC affect IV and oral midazolam exposures or plasma exposures of major metabolite 1-OH midazolam and minor metabolite 4-OH midazolam, to determine if a single IV and a single oral dose of midazolam affect steady state concentrations of TIC and to evaluate safety and tolerability after single dose of midazolam given alone and coadministered with TIC.

For oral midazolam: midazolam  $C_{max}$  and AUC decreased by 24% and 30% respectively with steady state TIC and the 90% CIs were outside the 'no effects' interval of (0.70, 1.43). With single dose TIC, midazolam  $C_{max}$  and AUC decreased by 14% and 19% respectively; the LCL of 90% CI for  $C_{max}$  was outside the 'no effects' interval of (0.70, 1.43) but other LCLs and UCLs were within. 1-OH midazolam  $C_{max}$  and AUC were largely unaffected by single dose or steady state TIC; while 4-OH-midazolam  $C_{max}$  and AUC decreased by 40% and 42% respectively with steady state TIC and by 31% and 33% respectively with single dose TIC and the 90% CIs were outside the 'no effects' limits of 0.70 and 1.43. For IV midazolam, results were similar although the 90% CIs for midazolam  $C_{max}$  and AUC were within the 'no effects' limits of 0.70 and 1.43. For oral and IV midazolam,  $t_{max}$  remained equally rapid (0.03-1.0 h) if given with single or multiple dose TIC.

Coadministration of oral or IV midazolam did not significantly affect  $C_{max}$  or AUC of TIC or AR-C124910XX, with point estimates 0.96-1.15, and all 90% CIs within bounds of 0.90 and 1.23, which were within the pre-specified 'no effects' limits of 0.70-1.43.

#### **D5130C00024**

An open label, randomised, two way crossover Phase I study in 24 healthy volunteers who received single doses of simvastatin 80 mg alone and on Day 5 of concomitant TIC (180 mg bd).

The objectives were to assess the effect of TIC on single dose PKs of simvastatin and on serum concentrations of active and total 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, to assess the effect of single dose simvastatin on steady state PKs of TIC and AR-C124910XX and to examine safety and tolerability of TIC and simvastatin.

Coadministration of TIC led to an increase in simvastatin  $C_{max}$  and AUC of 81% and 56% respectively and in simvastatin acid  $C_{max}$  and AUC of 64% and 52%; with all 90% CIs outside the pre-specified 'no effect' limits of 0.70 to 1.43. Coadministration of TIC decreased median  $t_{max}$  for simvastatin (from 2.0 h to 1.0 h) and for simvastatin acid (from 4.0 h to 3.5 h). Coadministration of simvastatin led to increases of 9-14% in the maximum plasma drug concentration at steady state ( $C_{ss,max}$ ) and the area under the plasma concentration time curve during one dosing interval at steady state ( $AUC_{ss,t}$ ) for TIC and AR-C124910XX; with all 90% CIs inside the pre-specified 'no effect' limits of 0.70 to 1.43. Coadministration of simvastatin slightly increased the median time to reach maximum steady state in a dosing interval ( $t_{ss,max}$ ) for AR-C124910XX (from 2.5 h to 3.0 h) but did not affect  $t_{ss,max}$  for TIC (2.0 h).

#### **D5130C00025**

A randomised, double blind, two period crossover Phase I study in 24 healthy volunteers who received single doses of atorvastatin calcium 80mg, alone and on Day 5 of concomitant TIC (90 mg bd).

The objectives were to assess PKs of atorvastatin acid, atorvastatin lactone, 2-OH atorvastatin and 4-OH atorvastatin when atorvastatin calcium is given alone and in combination with TIC, to assess PDs of atorvastatin calcium when given alone or in combination with TIC by measuring serum concentrations of active HMG-CoA reductase inhibitors, to assess the effect of atorvastatin calcium on steady state PKs of TIC and AR-

C124910XX and to examine safety and tolerability of TIC when administered alone, and in combination with atorvastatin calcium.

The ratios (95%CI) of TIC+atorvastatin vs atorvastatin for AUC and  $C_{max}$  were 1.36 (1.16, 1.58) and 1.23 (0.96, 1.58) respectively for atorvastatin acid, indicating extent of exposure and peak plasma concentration of atorvastatin acid were significantly increased by 36% and 23% respectively by coadministration of TIC. There were similar findings for the metabolites atorvastatin lactone, 2-OH atorvastatin and 4-OH atorvastatin. The UCL of the 95%CIs for all comparisons (except  $C_{max}$  for 2-OH atorvastatin) lay outside the 'no effect' interval of (0.7, 1.43). Median  $t_{max}$  for atorvastatin and metabolites was generally unaffected by TIC coadministration.

The ratios (95%CI) of TIC+atorvastatin vs TIC for the area under the plasma concentration time curve from time zero to 12 h ( $AUC_{(0-12)}$ ) and  $C_{ss,max}$  were 0.97 (0.93, 1.00) and 0.98 (0.90, 1.06) respectively for TIC and 1.13 (1.09, 1.17) and 1.11 (1.03, 1.20) respectively for AR-C124910XX, indicating extent of exposure and peak plasma concentrations of TIC and its metabolite were not significantly affected by coadministration with atorvastatin. The 90%CIs were all within the 'no effects' limits of (0.80, 1.25). Coadministration of atorvastatin and TIC slightly increased median  $t_{max}$  for TIC (from 1.0 h to 2.0 h) but did not affect  $t_{max}$  for AR-C124910XX (2.0 h).

#### **D5130C00051**

A randomised, double blind (with respect to TIC), two period crossover Phase I study in 23 healthy volunteers who received single doses of tolbutamide 500 mg, alone and on Day 5 of concomitant TIC 180 mg bd.

The objectives were to assess the effect of steady state TIC on single dose PKs of tolbutamide and 4-OH-tolbutamide, to assess the effect of single dose tolbutamide on steady state PKs of TIC and AR-C124910XX and to examine safety and tolerability of TIC and single dose of tolbutamide.

The ratios (90%CI) of TIC+tolbutamide vs tolbutamide for AUC and  $C_{max}$  were 1.03 (0.99, 1.07) and 1.10 (1.07, 1.13) respectively for tolbutamide and 0.94 (0.90, 0.97) and 0.90 (0.84, 0.95) respectively for 4-OH-tolbutamide, indicating extent of exposure and peak plasma concentrations of tolbutamide and its metabolite were not significantly affected by coadministration with steady state TIC. The 90%CIs were all within the 'no effects' limits of (0.80, 1.25).

The ratios (90%CI) of TIC+tolbutamide vs TIC for  $AUC_{ss,t}$  and  $C_{ss,max}$  were 0.99 (0.96, 1.02) and 0.99 (0.91, 1.07) respectively for TIC, and 1.09 (1.06, 1.12) and 1.03 (0.97, 1.10) respectively for AR-C124910XX, indicating extent of exposure and peak plasma concentrations of TIC and its metabolite were not significantly affected by coadministration with tolbutamide. The 90%CIs were all within the 'no effects' limits of (0.80, 1.25).

Coadministration of tolbutamide and TIC slightly increased median  $t_{max}$  for AR-C124910XX (from 2.0 h to 3.0 h) but did not affect  $t_{max}$  for TIC (2.0 h), tolbutamide (4.0 h), or 4-OH-tolbutamide (6.0 h).

#### **D5130C05265**

A randomised, double blind, two period crossover Phase I study in 20 healthy volunteers, who received multiple doses of digoxin 0.25 mg od with and without TIC 400 mg od.

The objectives were to compare PKs of digoxin and TIC when administered alone and in combination and to assess safety and tolerability after coadministration of TIC and digoxin.

The ratios (90%CI) of TIC+ digoxin vs digoxin for  $AUC_t$  and  $C_{ss,max}$  were 1.28 (1.12, 1.46) and 1.75 (1.52, 2.01) respectively for digoxin, 1.22 (0.95, 1.56) and 1.20 (0.90, 1.59) respectively for TIC and 1.20 (1.02, 1.41) and 1.15 (0.98, 1.34) respectively for AR-C124910XX. These results suggest coadministration of TIC with digoxin causes a significant increase in extent of exposure and peak plasma concentrations of digoxin by 28% and 75% respectively as 90%CIs were outside the pre-specified no interaction limits of (0.7, 1.43) and increases of 15-22% in extent of exposure and peak plasma concentrations of TIC and AR-C124910XX, which were not significant as 90%CIs were within the pre-specified no interaction limits of (0.7, 1.43).

#### **D5130C00005**

An open label, randomised, two treatment, two period crossover Phase I study in 16 healthy volunteers, who received TIC (50 mg bd for Days 1-5, 200 mg bd for Days 6-9 and 200 mg od for Day 10) with and without ASA (300 mg od for Days 1-10).

The objectives were to assess PKs, to investigate PK and PD relationship of TIC in the presence and absence of ASA and to compare safety and tolerability in subjects given low (50 mg) and high (200 mg) bd doses of TIC coadministered with ASA (300 mg) od.

The ratios (90%CI) of TIC 50 mg+ASA vs TIC 50 mg for  $C_{max}$  and AUC were 95.6 (79.5, 115.1) and 99.3 (86.3, 114.2) respectively for TIC and 105.6 (91.7, 121.8) and 100.1 (90.1, 111.1) respectively for AR-C124910XX and the ratios (90%CI) of TIC 200 mg+ASA vs TIC 200 mg for  $C_{max}$  and AUC were 96.4 (80.1, 116.0) and 96.6 (84.0, 111.2) respectively for TIC and 101.9 (88.4, 117.4) and 98.4 (88.6, 109.3) respectively for AR-C124910XX, indicating extent of exposure and peak plasma concentrations of TIC and its metabolite were not significantly affected by coadministration with ASA. The 90%CIs were all within the 'no effects' limits of (0.80, 1.25). Coadministration with ASA increased AR-C124910XX  $t_{max}$  (from 3.0 h to 4.0 h) for AZD5140 200 mg but AR-C124910XX  $t_{max}$  for 50 mg and TIC  $t_{max}$  for 50 mg and 200 mg were all unaffected (3.0 h).

#### **D5130C00006**

An open label, randomised, three period crossover Phase I study in 30 healthy volunteers who received single doses of TIC 180 mg oral tablet and unfractionated heparin 100IU/kg IV, separate and coadministered.

The objectives were to examine the safety and tolerability of TIC when coadministered with unfractionated heparin, to show no clinically relevant effect of unfractionated heparin on the PKs and PDs of TIC and to show no clinically relevant effect of TIC on the anticoagulant effects of unfractionated heparin.

The ratios (90%CI) of TIC+heparin vs TIC for  $C_{max}$ ,  $AUC_{0-t}$  and AUC were 1.05 (0.97, 1.14), 0.99 (0.93, 1.05) and 0.99 (0.93, 1.05), respectively for TIC and 1.06 (1.00, 1.13), 1.00 (0.96, 1.05) and 1.00 (0.96, 1.05) respectively for AR-C124910XX, indicating extent of exposure and peak plasma concentrations of TIC and its metabolite were not significantly affected by coadministration with heparin. The 90%CIs were all within the 'no effects' limits of (0.80, 1.25). Coadministration of heparin did not affect  $t_{max}$  for TIC (1.50 h) or AR-C124910XX (2.05 h).

#### **D5130C00007**

An open label, randomised, three period crossover Phase I study in 30 healthy volunteers who received single doses of TIC 180 mg oral tablet and enoxaparin 1mg/kg subcutaneously (SC), separate and coadministered.

The objectives were to examine the safety and tolerability of TIC when coadministered with enoxaparin, to show no clinically relevant effect of enoxaparin on PKs or PDs of TIC and to show no clinically relevant effect of TIC on anticoagulant effects of enoxaparin.

The ratios (90%CI) of TIC+ enoxaparin vs TIC for  $C_{max}$ ,  $AUC_{0-t}$  and AUC were 1.02 (0.94, 1.11), 1.01 (0.95, 1.06) and 1.00 (0.95, 1.06) respectively for TIC and 1.03 (0.94, 1.12), 0.99 (0.95, 1.02) and 0.99 (0.95, 1.02) respectively for AR-C124910XX, indicating extent of exposure and peak plasma concentrations of TIC and its metabolite were not significantly affected by coadministration with enoxaparin. The 90%CIs were all within the 'no effects' limits of (0.80, 1.25). Coadministration of enoxaparin did not affect  $t_{max}$  for TIC (1.50 h) or AR-C124910XX (2.02-2.04 h).

#### **D5130C00042**

A randomised, double blind, pbo controlled, two way crossover Phase I study in 26 healthy volunteers, who received ethinyl oestradiol/levonorgestrel (Nordette) 0.03/0.15 mg for 21 days, with and without TIC 90 mg bd for 21days.

The objectives were to examine the effect of coadministration of TIC and Nordette on the PKs of ethinyl oestradiol, to characterise PKs of levonorgestrel and plasma levels of progesterone, 17-beta oestradiol, LH, FSH, and SHBG and to characterise PKs of TIC and AR-C124910XX after concomitant oral administration of TIC and ethinyl oestradiol/levonorgestrel and to examine safety and tolerability of TIC when coadministered with ethinyl oestradiol/levonorgestrel.

Ratios (90%CI) of Nordette+TIC 90 mg bd vs Nordette od for 21days, for the minimum plasma concentration ( $C_{min}$ ),  $C_{max}$  and  $AUC_{0-t}$  were 1.20 (0.96, 1.50), 1.31 (1.18, 1.44) and 1.20 (1.03, 1.40) respectively for ethinyl oestradiol, and 1.02 (0.94, 1.10), 1.09 (1.02, 1.16) and 1.03 (0.97, 1.10) respectively for levonorgestrel, indicating increases of 20-30% in exposure to ethinyl oestradiol but no significant differences in exposure to levonorgestrel, when TIC was coadministered with Nordette. Median  $t_{max}$  was similar for both treatments. The PK profile of TIC was consistent with previous studies.

#### **D5130C00026**

In this study (described under Pharmacodynamics), the ratios (90%CI) of TIC+desmopressin vs TIC for  $C_{ss,max}$  and  $AUC_{ss}$  were 1.05 (0.93, 1.18) and 0.92 (0.85, 1.01), respectively for TIC and 1.03 (0.94, 1.13) and 0.96 (0.89, 1.04) respectively for AR-C124910XX, indicating extent of exposure and peak plasma concentrations of TIC and its metabolite were not significantly affected by coadministration with desmopressin. The 90%CIs were all within the 'no effects' limits of (0.80, 1.25). Coadministration of desmopressin slightly decreased median  $t_{max}$  for TIC (from 2.5 h to 1.8 h) but did not affect  $t_{max}$  for AR-C124910XX (2.5 h).

### **Summary of Pharmacokinetics**

#### **1. Biopharmaceutic studies**

Absolute BA for TIC was 36%; met:par ratios for  $C_{max}$  and AUC were greater with oral vs IV administration, showing AR-C124910XX formation after oral intake occurs largely during absorption and first pass metabolism.

Food had no clinically relevant effect on the PKs of TIC or AR-C124910XX.

#### **2. ADME of TIC**

The primary route of excretion of TIC was via faeces (57.8%), and urine a minor excretory pathway (26.5%). TIC and AR-C124910XX were the main compounds in plasma and faeces but <1% of either was found unchanged in urine, indicating extensive metabolism of TIC

(and therefore likely little effect on exposure to TIC or metabolite in patients with renal impairment). TIC and metabolite were located in the plasma space rather than bound to or within the erythrocytes.

### **3. Single and multiple ascending dose studies of TIC**

TIC  $C_{max}$  and AUC increased with increasing dose in an approximately dose proportional manner;  $t_{max}$  was 1.25-2.00 h for all doses from 1.0-100 mg,  $t_{1/2}$  was 7-8.5 h for doses 10 mg-100 mg (but lower for 1.0 and 3.0 mg). Inter- and intra-subject variability was low.

TIC and AR-C124910XX  $C_{max}$  and AUC increased with increasing dose in an approximately dose proportional manner; TIC and AR-C124910XX  $t_{max}$  were 1.5 h and 1.5-3.0 h respectively and  $t_{1/2}$  were 7.3-8.1 h and 8.5-10.1 h respectively for all doses from 30-400 mg. Intersubject variability was low for TIC and slightly greater for AR-C124910XX.

$C_{max}$ , AUC,  $t_{max}$  and  $t_{1/2}$  for TIC and metabolites AR-C124910XX and AR-C133913XX, all increased with increasing dose and the increase was approximately dose proportional for AUC.

$C_{max}$  and AUC increased with increasing dose in an approximately dose proportional manner; TIC and AR-C124910XX  $t_{max}$  were 1.5-3.0 h and 2.0-4.0 h respectively and  $t_{1/2}$  were 6.1-13.1 h and 6.4-16.6 h respectively for all doses from 50-600 mg od and 50-300 mg bd.

### **4. Comparison of TIC+ASA and CLO+ASA**

After the first dose of TIC+ASA and at steady state, TIC and AR-C124910XX  $t_{max}$  were similar (3.0-3.1 h) and AR-C124910XX AUC and  $C_{max}$  were 28-40% of parent.

### **5. Comparison of TIC and CLO loading doses**

After 270 and 540 mg TIC, TIC and AR-C124910XX  $t_{max}$  were similar (2.0-3.0 h) and  $t_{1/2}$  was 11.1-12.6 h; TIC and AR-C124910XX  $C_{max}$  and AUC increased with increasing dose in a dose proportional manner and AR-C124910XX AUC and  $C_{max}$  were 24-43% of parent. For comparison, after 600 mg CLO, SR 26334  $t_{max}$  was 1.5 h and  $t_{1/2}$  was 8.8 h.

### **6. Effect of TIC on ECG QTcX interval**

There was no relationship between TIC plasma concentration and increases in QTcX interval on ECG. After 900 mg TIC, TIC and AR-C124910XX  $t_{max}$  were 3.0-4.0 h and  $t_{1/2}$  were 11.5-12.0 h; AR-C124910XX AUC and  $C_{max}$  were 20.0-33.0% of parent, and AR-C133913XX AUC and  $C_{max}$  were 8.5-8.9% of parent.

### **7. Effect of TIC on serum uric acid levels**

There was no relationship between TIC plasma concentration and serum uric acid, xanthine or hypoxanthine levels.

### **8. Effect of TIC on respiratory parameters**

TIC plasma concentrations after single dose 900 mg and 1260 mg had no effect on respiratory parameters.

TIC plasma concentrations after loading dose 450 mg and 180 mg bd had no effect on respiratory parameters in healthy elderly subjects; TIC and AR-C124910XX  $t_{max}$  were 2.0-2.5 h; AR-C124910XX AUC and  $C_{max}$  were 34-44% of parent after loading dose and 44-58% of parent at steady state.

TIC plasma concentrations after loading dose 450 mg and 180 mg bd had no effect on respiratory parameters in patients with mild asthma or mild to moderate COPD.



### **9. PK effects of TIC in patients with atherosclerosis/stable CAD**

In patients with stable CAD, TIC and AR-C124910XX  $t_{max}$  was 2.0-2.1 h and  $t_{1/2}$  was 9.8-12.4 h; AR-C124910XX AUC<sub>0-8</sub> and  $C_{max}$  were 20-32% of parent after loading and maintenance doses.

In patients with stable CAD, the PKs of TIC were similar for CLO responders and nonresponders after a single dose and at steady state and were similar in patients pretreated with CLO and CLO naïve patients.

In patients with ASD, TIC  $t_{max}$  was 2.0-3.7 h and AR-C124910XX  $t_{max}$  was 3.0-4.2 h, for all dose regimens. TIC and AR-C124910XX  $C_{max}$  and AUC increased with increasing dose in a dose proportional manner for TIC 50-100 mg bd and in a greater than dose proportional manner for 200-400 mg bd at steady state; accumulation ratios were 1.5-2.0; and AR-C124910XX AUC and  $C_{max}$  were 25-35% of parent for all dose regimens for Day 1 and at steady state.

In patients with non-ST segment elevation ACS events, accumulation of TIC and its metabolite AR-C124910XX after multiple doses of TIC was demonstrated from Day 1 to 4 weeks. In patients both pretreated with CLO and CLO naïve,  $t_{max}$  was 2-4 h for TIC and AR-C124910XX. Day 1 dose proportionality and similarity of TIC  $C_{max}$  and AUC was not clearly demonstrated after single doses of TIC between CLO naïve and CLO pretreated patients but AR-C124910XX PKs were comparable and did not appear to be affected by CLO pretreatment; however results were inconclusive as patient group numbers were small.

### **10. Effects of intrinsic factors on TIC PKs**

After a single dose 200 mg TIC in healthy adults, exposure to TIC and AR-C124910XX was higher in females compared to males (by 40-50%) and higher in the elderly compared to the young (by 50-60%).

Severe renal impairment had no clinically relevant effect on the PKs of TIC and no dose adjustment is required when using TIC in patients with renal impairment.

Mild hepatic impairment resulted in increased exposure to TIC and AR-C124910XX due to decreased elimination.

In Chinese subjects, TIC  $t_{max}$  was 2.0 h and AR-C124910XX  $t_{max}$  was 2.0-3.0 h for single dose and steady state bd doses of 90 mg and 180 mg; TIC and AR-C124910XX  $C_{max}$  and AUC increased with increasing dose in an approximately dose proportional manner for TIC 90-180 mg and AR-C124910XX AUC and  $C_{max}$  were 30-49% of parent for 90 mg and 26-39% of parent for 180 mg, after first dose and at steady state.

There were no significant differences in exposure to TIC and AR-C124910XX between Japanese and Caucasian subjects for TIC doses of 50-400 mg; exposure to TIC and AR-C124910XX was significantly higher in Japanese compared to Caucasian subjects for TIC 600 mg.

Exposure to TIC and AR-C124910XX was significantly higher in Japanese compared to Caucasian subjects for TIC 100 mg and 300 mg after both single dose and at steady state. Normalisation for body weight accounted for approximately 20% of the difference.

### **11. PK effects in drug interaction studies**

Addition of ketoconazole 200 mg bd (a strong CYP3A4 inhibitor) to TIC 90 mg markedly increased extent of exposure and peak plasma concentration of TIC and decreased the extent of exposure and peak plasma concentration of AR-C124910XX to a clinically significant degree, indicating TIC is a CYP3A4 substrate. Strong CYP3A inhibitors should be avoided with TIC.

Addition of diltiazem 240 mg od (a moderate CYP3A4 inhibitor) to TIC 90 mg increased the extent of exposure and peak plasma concentration of TIC and decreased the extent of exposure and peak plasma concentration of AR-C124910XX to a statistically significant degree while addition of TIC to diltiazem did not affect PKs of diltiazem to a clinically significant degree.

Addition of rifampin 600 mg od (a CYP3A and P-gp inducer) to TIC 180 mg decreased the extent of exposure and peak plasma concentration of TIC and decreased the extent of exposure to AR-C124910XX to a statistically significant degree but peak plasma concentration of AR-C124910XX was not affected.

Addition of TIC 400 mg od to midazolam 7.5 mg (a weak CYP3A5 inhibitor) decreased the extent of exposure and peak plasma concentration of midazolam and 4-OH midazolam (but not 1-OH midazolam) to a statistically significant degree while addition of midazolam 7.5 mg to TIC 400 mg did not affect PKs of TIC or AR-C124910XX to a clinically significant degree.

Addition of TIC (loading dose and steady state) to oral and IV midazolam (a weak CYP3A5 inhibitor) decreased extent of exposure and peak plasma concentration of midazolam (some 90%CI limits significant) and 4-OH midazolam (all 90%CI limits significant) but not of 1-OH midazolam while addition of oral or IV midazolam to TIC did not affect PKs of TIC or AR-C124910XX to a clinically significant degree.

Coadministration of simvastatin 80 mg and TIC 180 mg bd significantly increased extent of exposure and peak plasma concentration of simvastatin and simvastatin acid while PKs of TIC and AR-C124910XX were unaffected.

Coadministration of atorvastatin calcium 80 mg and TIC 90 mg bd significantly increased the extent of exposure and peak plasma concentration of atorvastatin acid, atorvastatin lactone, 2-OH atorvastatin and 4-OH atorvastatin while PKs of TIC and AR-C124910XX were unaffected.

Addition of tolbutamide 500 mg and TIC 180 mg did not significantly affect the PKs of tolbutamide or 4-OH tolbutamide or TIC or AR-C124910XX.

Addition of TIC 400 mg od to digoxin 0.25 mg od significantly increased the extent of exposure and peak plasma concentration of digoxin but did not significantly affect the extent of exposure and peak plasma concentrations of TIC and AR-C124910XX.

Addition of ASA 300 mg od to TIC (50 mg bd and 200 mg bd) did not significantly affect the PKs of TIC or AR-C124910XX.

Coadministration of IV heparin 100IU/kg and oral TIC 180 mg did not significantly affect the PKs of TIC or AR-C124910XX.

Coadministration of SC enoxaparin 1mg/kg and oral TIC 180 mg did not significantly affect the PKs of TIC or AR-C124910XX.

Addition of TIC 90 mg bd to Nordette (ethinyl oestradiol/levonorgestrel) 0.03/0.15 mg significantly increased exposure to ethinyl oestradiol by 20-30% but did not significantly affect levonorgestrel.

Coadministration of TIC 180 mg bd and IV desmopressin 0.3 µg/kg did not significantly affect the PKs of TIC or AR-C124910XX.

### ***In summary***

PKs of TIC were significantly affected by

- ketoconazole (strong CYP3A4 inhibitor)

- diltiazem (moderate CYP3A4 inhibitor)
- rifampin (CYP3A and P-gp inducer)

PKs of TIC were not significantly affected by

- oral and IV midazolam
- simvastatin
- atorvastatin
- tolbutamide
- digoxin
- ASA
- IV heparin
- SC enoxaparin
- desmopressin

TIC significantly affected PKs of

- oral and IV midazolam (weak CYP3A5 inhibitor)
- simvastatin
- atorvastatin
- digoxin
- ethinyl oestradiol (as ethinyl oestradiol/levonorgestrel)

TIC did not significantly affect PKs of

- diltiazem
- tolbutamide
- levonorgestrel (as ethinyl oestradiol/levonorgestrel)

There was no drug interaction study of TIC with warfarin.

## **Efficacy**

There was a single pivotal efficacy study, D5130C05262 (PLATO) and a small amount of efficacy data in the Phase II study, D5130C000002 (DISPERSE2).

### **D5130C05262 [PLATO]**

An international, multicentre, randomised, double blind, double dummy, parallel group Phase III study in 18624 patients hospitalised with non-ST or ST segment elevation ACS (index event) and at high risk of a secondary thrombotic event, who were given TIC or CLO. It has been published.<sup>1</sup>

### **Objectives**

Objectives were to test whether TIC is superior to CLO for prevention of vascular events in patient with non-ST or ST elevation ACS, to compare safety and tolerability of TIC with CLO, to compare efficacy and safety of TIC with CLO, overall and in patients who underwent CABG surgery or PCI during study and in relation to timing of these interventions and to compare occurrence of arrhythmic episodes detected by Holter monitoring with TIC with CLO during initial period after randomisation and at 1 month and the relation of these episodes to clinical outcomes.

### **Inclusion and Exclusion Criteria**

Inclusion criteria were males or females (non pregnant, non lactating, and using adequate contraception), ≥18 y, with an index event of non-ST or ST segment elevation ACS, cardiac ischaemic symptoms lasting ≥10 min at rest and occurring ≤24 h prior to randomisation and who were hospitalised for chest pain. Additionally patients were to have either

persistent ST segment elevation or new left bundle branch block (LBBB) and primary PCI planned, or cardiac ischaemic symptoms lasting  $\geq 10$  min at rest as well as 2 of: ST segment changes indicating ischaemia, positive biomarker evidence of myocardial necrosis and one or more risk factors for vascular events.

Patients were excluded:

- if the index event was an acute complication of PCI or they underwent PCI after the index event and prior to first study drug,
- if they were at increased risk of bradycardic events,
- if they required therapy with anticoagulants, fibrinolytics or drugs known to strongly affect CYP3A
- if they had known clinically important thrombocytopenia or anaemia, or required dialysis,
- or if they had known contraindications to CLO or TIC.

### ***Concurrent Medication***

Oral anticoagulants, other oral antiplatelet therapies and fibrinolytic therapy were not permitted although some approved parenteral anticoagulants and GP-IIb/IIIa (GPIIb/IIIa) receptor antagonists were, and open label CLO was only permitted during periods in which the patient was temporarily or permanently discontinued. Digoxin levels were to be closely monitored after initiating or changing dose of study medication. Strong inhibitors and inducers of CYP3A and substrates of CYP3A with a narrow therapeutic index were not permitted but moderate inhibitors and inducers were allowed. Simvastatin and lovastatin doses  $>40$  mg were to be avoided but pravastatin, rosuvastatin, fluvastatin and atorvastatin were allowed at any dose. Other medications were to be given at the investigators discretion for the safety and well being of the patient.

### ***Treatment Protocol***

Patients were randomised at the first visit to (TIC 90 mg bd+CLO pbo od) or (CLO 75 mg od+TIC pbo bd). Additional TIC doses were given of 180 mg (initial loading dose), 90 mg (prior to PCI occurring  $>24$  h after randomisation) or 180 mg (loading dose if drug treatment was interrupted  $>5$  days for inpatient treatment of an ACS event) while additional CLO doses were given of 300 mg (initial loading dose unless patient already receiving CLO) or 300 mg at investigators discretion (if patient had PCI after randomisation). All patients were to receive concomitant ASA 75-100 mg od. Visits were at randomisation within 24 h of onset of chest pain, and at 1, 3 and 6 months, and 9 and 12 months, depending on length of time in the study. An end of study (EOS) visit occurred 1 month after the last treatment at 6, 9 or 12 months. All patients received the same combination of identically appearing tablets and capsules (active or matching pbo). Patients received double blind, double dummy medications in bottles sufficient for each treatment period and an additional bottle as required. Bottles labelled with randomised numbers could be unblinded in an emergency. Patients were assigned sequentially to centrally generated blocked randomisation lists for each site.

### ***Efficacy Endpoints***

The primary efficacy endpoint was:

- time to first occurrence of any event from the composite of death from vascular causes, MI (excluding silent MIs, as time of occurrence of ECG evident MIs could not be determined), and stroke

Secondary efficacy endpoints were analysed in the following order:

- time to first occurrence of any event from composite of death from vascular causes, MI (excluding silent MI) and stroke for subgroup of patients with intent for invasive management at randomisation (planned coronary angiography with revascularisation if indicated during the index event hospitalisation)
- time to first occurrence of any event from composite of all cause mortality, MI (excluding silent MI) and stroke
- time to first occurrence of any event from composite of death from vascular causes, MI (including silent MI by ECG), stroke, severe recurrent cardiac ischaemia (SRCI), recurrent cardiac ischaemia (RCI), transient ischaemic attack (TIA) and other arterial thrombotic events (ATE)
- time to first occurrence of each component of the primary composite efficacy endpoint individually in the order of MI (excluding silent MI), death from vascular causes and then stroke
- time to occurrence of all cause mortality

Remaining components of secondary composite efficacy endpoints presented descriptively were:

- silent MI
- RCI
- SRCI
- TIA
- other ATE

For the subset of patients undergoing CABG surgery or PCI during the study the primary efficacy endpoints were assessed in relation to the timing of these interventions and the secondary efficacy endpoints were assessed.

For the subset of patients receiving Holter monitoring the primary variable was occurrence of ventricular pauses  $\geq 3$  s with secondary variables ventricular pauses of other lengths, other bradycardic episodes, HR, atrial tachyarrhythmias and ventricular arrhythmias.

An 'other' endpoint was the EuroQol-5D (EQ-5D) questionnaire administered at Visits 1, 4 (6 months) and at the end of the study (EOS).

### ***Safety Data Collection***

The primary safety endpoint was:

- time to first occurrence of any total major bleeding event

Secondary safety endpoints were:

- non-CABG, non-procedure related, coronary procedure related and non-coronary procedure related major bleeding events
- total, non-CABG, non-procedure related, coronary procedure related and non-coronary procedure related minor bleeding events
- combined major and minor bleeding events for each of the categories

For the subset of patients undergoing CABG surgery or PCI during the study the primary safety endpoints were assessed in relation to the timing of these interventions, and the secondary safety endpoints were assessed.

Other safety endpoints were:

- Adverse events (AEs) (particularly dyspnoea and bradycardia events)
- laboratory tests

### ***Statistical Considerations***

Efficacy and safety data were analysed using Cox proportional hazards model, Cox regression model, National Health and Nutrition Examination Survey (NHANES) prediction equations, analysis of covariance (ANCOVA) and descriptive and summary statistics.

Based on previous studies, primary efficacy events (composite of death from vascular causes, MI and stroke) in the CLO group were expected to occur at a rate of 11% over 12 months with half of these occurring in the first month, a quarter in the next 3 months and a quarter in the last 8 months. TIC was expected to show a relative risk reduction (RRR) of 15% (reducing to 13.5% if 20% of TIC patients discontinued study medication over the 12 months). Using 2-sided significance  $\alpha=0.0497$  (adjusted for one interim analysis), this RRR could be detected with 90% power from approximately 1780 events, requiring about 18000 patients for up to 12 months. The figures could be adjusted after a planned interim analysis after approximately 1200 events. The hierarchical primary objectives were designed to test the superiority of TIC to CLO for the prevention of vascular events.

Using  $\alpha=0.0497$ , 13500 patients with intent for invasive management at randomisation were required to detect a 15% RRR (13.5% after 12 months discontinuations) for TIC in time to first occurrence of death from vascular causes, MI or stroke (secondary efficacy endpoint) with 80% power.

Based on a previous study, ventricular pauses were expected to occur in 5% of the CLO group. Two thousand Holter recordings (1000 per treatment group) would show a 5% increase with TIC with a 95%CI 2.7%-7.3%; 2500 patients would allow for 20% not completing the second recording.

At least one abnormality of frequency of 1 in 1000 would have a high probability of being detected from baseline and 1 month safety laboratory tests from a sample size of  $\geq 9000$  patients.

### ***Patient Disposition and Characteristics***

Of 18758 patients, 134 were found to be inappropriately enrolled and 18624 (99.3%) were randomised to double blind treatment (9333 TIC, 9291 CLO). Of these 98.9% in each group received at least one dose of study medication (9235 TIC, 9186 CLO). Slightly more patients discontinued the study drug prematurely from the TIC group (23.7%) than from the CLO group (21.8%), the most common reasons for discontinuation being unwillingness to continue treatment (10.2% TIC, 9.4% CLO) and AEs (7.5% TIC, 6.1% CLO). Small numbers from each group discontinued the study altogether (3.3% TIC, 2.7% CLO). Thus, similar percentages of patients from each group completed the study drug treatment (76.3% TIC, 78.2% CLO) and completed the study (96.7% TIC, 97.3% CLO). Of those that completed the study, similar numbers in either group had a final visit (81.9% TIC, 81.2% CLO) or were followed up and found to be alive despite not completing the final visit (10.4% TIC, 10.5% CLO). Of the 18624 patients randomised to the study drug, 3112 (16.7%; 16.6% TIC, 16.8% CLO) had a final diagnosis of UA; 7955 (42.7%; 42.9% TIC, 42.5% CLO) had a final diagnosis of NSTEMI; and 7026 (37.7%; 37.5% TIC, 38.0%) had a final diagnosis of STEMI.

A total of 9333 patients were randomised to TIC 90 mg bd, and 9291 to CLO. The baseline demographics and characteristics were comparable for the two groups. Overall, the majority of patients were male (72%) and Caucasian (92%) with mean age 62.2 (range 19-97) y; 43% were  $\geq 65$  y and 16% were  $\geq 75$  y. The proportion of Black patients was small

overall (1.2%), but greater amongst USA patients (10%). Most patients were Killip Class I (91.3%) or II (7.4-7.6%) at enrolment.<sup>4</sup> All categories of Thrombolysis in Myocardial Infarction (a cardiology clinical trials study group) (TIMI) scores for the index event (validated prognostic risk score of clinical and ECG factors) were represented, for both UA/NSTEMI (score 0-2: 6.6%; 3-4: 49.6%; 5-7: 43.8%) and STEMI (score 0-2: 55.4%; 3-6: 41.0%; >6: 3.6%). The majority of patients had an index event of NSTEMI (43%) or STEMI (38%) and most of the remainder had UA (17%). The proportions of patients experiencing each index event (NSTEMI, STEMI, UA) reflects clinical practice. Approximately twice as many patients were planned for invasive management at randomisation as for medical management with similar proportions of patients in each treatment group; the majority of STEMI patients were for invasive management as expected from treatment protocols. Similar proportions of patients in each treatment group had coronary procedures (coronary angiography, PCI, CABG) prior to, whilst receiving, and after stopping, the study drug. Medical histories were similar for both treatment groups.

## Results

Table 3 summarises the primary and secondary efficacy endpoints hierarchy.

**Table 3: Summary of primary objective: primary and secondary efficacy endpoints hierarchy, FAS, PLATO**

	TIC 90 mg bd	CLO 75 mg od	RRR/ARR/ NNT**	Comparison: TIC/CLO
	n (%) KM%/y*			HR (95% CI)
N	9333	9291		p-value
<b>PRIMARY ENDPOINT:</b>				
Composite of CV death, MI, stroke	864 (9.3%) 9.8%	1014 (10.9%) 11.7%	16%/1.9%/53***	<b>0.84 (0.77, 0.92)</b> <b>0.0003</b>
<b>SECONDARY ENDPOINTS:</b>				
(i) Composite of CV death/MI (excluding silent MI)/stroke - intent to invasively manage	569 (8.5%) 8.9%	668 (10.0%) 10.6%	16%/1.7%/59	<b>0.84 (0.75, 0.94)</b> <b>0.0025</b>
(ii) Composite of all cause mortality/MI (excluding silent MI)/stroke	901 (9.7%) 10.2%	1065 (11.5%) 12.3%	17%/2.1%/48	<b>0.84 (0.77, 0.92)</b> <b>0.0001</b>
(iii) Composite of CV Death /Total MI/Stroke/SRCI/RCI/TIA /Other ATE	1290 (13.8%) 14.6%	1456 (15.7%) 16.7%	13%/2.1%/48	<b>0.88 (0.81, 0.95)</b> <b>0.0006</b>
(iv) Each component of primary endpoint:				
MI (excluding silent MI)	504 (5.4%) 5.8%	593 (6.4%) 6.9%	16%/1.1%/91	<b>0.84 (0.75, 0.95)</b> <b>0.0045</b>
CV death	353 (3.8%) 4.0%	442 (4.8%) 5.1%	22%/1.1%/91	<b>0.79 (0.69, 0.91)</b> <b>0.0013</b>
Stroke	125 (1.3%) 1.5%	106 (1.1%) 1.3%	-15%/-0.2%/-500	1.17 (0.91, 1.52) 0.2249
(v) All cause mortality	399 (4.3%) 4.5%	506 (5.4%) 5.9%	24%/1.4%/72	0.78 (0.69, 0.89) 0.0003

\*Kaplan-Meier percentage calculated at 12months; \*\*RRR/ARR/NNT estimated by evaluator; \*\*\*NNT figure of 54 provided in study; evaluator calculated NNT as 53 based on ARR of 1.9%

<sup>4</sup> **Killip classification:** The Killip classification is a system used in individuals with an acute myocardial infarction in order to risk stratify them. It is an assessment of functional severity of MI; lower class reflects lower risk for morbidity.

### *Evaluator Comment*

The pre-specified hierarchical approach using a composite endpoint as the primary endpoint is consistent with previous studies of treatment of ACS and with relevant TGA-adopted EU guidelines.<sup>5,6</sup>

Examination of multiple endpoints in a clinical trial increases the likelihood of false positive findings (type I error). Hierarchical analysis in a two arm study like PLATO, allows for testing of multiple endpoints without adjustment of the type I error. The endpoints must be ranked in a pre-specified order of importance, no confirmatory claims can be based on variables equal to or below that of the first variable whose null hypothesis cannot be rejected, and the likelihood of false negative findings (type II error) increases as one moves down the hierarchy<sup>4</sup>. The secondary endpoints give supportive evidence but cannot constitute the main evidence in an application.<sup>6</sup> Similarly, subgroup analysis is also exploratory.

A composite variable is used in this case in the context of survival analysis.<sup>6</sup> Combination of a number of relatively rare events into a composite variable increases the power of the study and allows for a smaller sample size than would otherwise be required. The components should be analysed singly, to provide supportive information. It is a valid concern that an adverse effect by the treatment on one or more components may be masked by the combined endpoint, however there is no agreement on what degree of 'negative' findings indicates an adverse effect.<sup>6</sup> To this end, the clinically 'more important' components should not be affected negatively. Mortality is 'more important' than morbidity, thus CV death would be of greater importance than MI or stroke. The TGA-adopted EU guidelines for treatment of NSTEMI ACS state that the majority of studies will use a combined endpoint as the primary efficacy variable (for example death/new MI/refractory angina); and that at least the 'hardest' objective components of death and/or MI should contribute to the treatment effect.<sup>5</sup>

Thus, the primary composite endpoint can be considered significant, even if the individual components of that endpoint lower in the hierarchical analysis do not reach significance.

Table 4 presents the primary efficacy endpoint (time to first occurrence of any event from composite of CV death, MI [excluding silent MI], and stroke), as well as the secondary endpoints of each individual component (taken from Table 3). For the primary efficacy parameter, TIC was significantly better than CLO in preventing the composite of (CV death/non silent MI/stroke) over a 12 month period in patients with an ACS event (UA, NSTEMI or STEMI); hazard ratio (HR) 0.84, p=0.0003. The RRR was 16%, absolute risk reduction (ARR) was 1.9% and it was required to treat 54 patients with TIC instead of CLO for 12 months in order to prevent one composite 'event'.

<sup>5</sup> EMEA, Committee for Proprietary Medicinal Products (CPMP), 17 February 2000. Points to Consider on the Clinical Investigation of New Medicinal Products for the Treatment of Acute Coronary Syndrome (ACS) without Persistent ST-Segment Elevation (CPMP/EWP/570/98).

<sup>6</sup> EMEA, Committee for Proprietary Medicinal Products (CPMP), 19 September 2002. Points to Consider on Multiplicity Issues in Clinical Trials (CPMP/EWP/908/99).



**Table 4: Summary of primary and secondary efficacy endpoints, PLATO, full analysis set (FAS)**

	TIC 90 mg bd	CLO 75 mg od	RRR/ARR/ NNT**	Comparison: TIC/CLO
	N (%) KM%/y*			HR (95% CI)
N	9333	9291		p-value
<b>PRIMARY ENDPOINT:</b>				
Composite of CV death, MI, stroke	864 (9.3%) 9.8%	1014 (10.9%) 11.7%	16%/1.9%/53***	<b>0.84 (0.77, 0.92)</b> <b>0.0003</b>
<b>SECONDARY ENDPOINTS: (IV) EACH COMPONENT OF PRIMARY EFFICACY ENDPOINT:</b>				
MI (excluding silent MI)	504 (5.4%) 5.8%	593 (6.4%) 6.9%	16%/1.1%/91	<b>0.84 (0.75, 0.95)</b> <b>0.0045</b>
CV death	353 (3.8%) 4.0%	442 (4.8%) 5.1%	22%/1.1%/91	<b>0.79 (0.69, 0.91)</b> <b>0.0013</b>
Stroke	125 (1.3%) 1.5%	106 (1.1%) 1.3%	-15%/-0.2%/-500	1.17 (0.91, 1.52) 0.2249

\*Kaplan-Meier percentage calculated at 12 months; \*\*RRR/ARR/NNT (number needed to treat) estimated by evaluator; \*\*\*NNT figure of 54 provided in study; evaluator calculated NNT as 53 based on ARR of 1.9%

For the individual components of the primary endpoint (all secondary endpoints), TIC was significantly better than CLO in preventing CV death (RRR 22%, ARR 1.1%, number needed to treat [NNT] 91) and MI (excluding silent MI; RRR 16%, ARR 1.1%, NNT 91) over 12 months; and although slightly more patients treated with TIC suffered stroke over 12 months compared to those treated with CLO, the difference was not significant (p=0.2249).

A supportive analysis examined the primary composite endpoint over the time periods Days 1-30 and Days 31-360 in patients previously event free (Table 5). It was found that TIC was significantly better than CLO in preventing the composite endpoint over the first 30 days (RRR 11%, ARR 0.6%, NNT 167); and also over the period from Days 31 to 360 in those patients previously event free (RRR 20%, ARR 1.3%, NNT 77). Thus there is a significant benefit in treating patients in the first month after an ACS event and also in treating patients in the period 1-12 months.

**Table 5: Summary of primary efficacy endpoint consistency of effect over time, PLATO, FAS**

	TIC 90 mg bd	CLO 75 mg od	RRR/ARR/ NNT*	Comparison: TIC/CLO
	n (%) KM%/y			HR (95% CI)
N	9333	9291		p-value
Composite of CV death, MI, and stroke	864 (9.3%) 9.8%	1014 (10.9%) 11.7%	16%/1.9%/53	<b>0.84 (0.77, 0.92)</b> <b>0.0003</b>
1-30days	443 (4.7%) 4.8%	502 (5.4%) 5.4%	11%**/0.6%/167	<b>0.88 (0.77, 1.00)</b> <b>0.0446</b>
31-360days	413 (4.7%) 5.3%	510 (5.9%) 6.6%	20%/1.3%/77	<b>0.80 (0.70, 0.91)</b> <b>0.0008</b>

\*RRR/ARR/NNT estimated by evaluator \*\*RRR figure of 12% provided in the study.

With regard to other secondary efficacy parameters, TIC was significantly better than CLO in preventing the composite (CV death/non silent MI/stroke) in the subgroup of patients intended for invasive management, in preventing the composite of (all cause mortality/non silent MI/stroke), and in preventing the composite of (CV death/total MI/stroke/SRCI/RCI/TIA/other ATE).

Although the nominal p-value of 0.0003 suggests TIC is superior to CLO in prevention of all cause mortality, the result is not significant because the prior endpoint (stroke) in the hierarchical analysis did not reach significance and therefore this result cannot be used as proof of superiority.

An exploratory analysis of the primary efficacy endpoint by 31 pre-specified subgroups was carried out. Subgroup analysis suggested results were very consistent for age group <65 y/≥65 y but less so for <75 y/≥75 y and very consistent for gender male/female. The analysis was difficult to interpret for race groups other than Caucasian due to small numbers and for final diagnosis. It was very consistent for NSTEMI and STEMI but less so for UA although none of these results were significantly different. Analysis of the subgroup region, however, found that while results were consistent for Asia/Australia (HR=0.80 [0.61, 1.04]), Central/South America (HR=0.86 [0.65, 1.13]), and Europe/Middle East/Africa (HR=0.80 [0.72, 0.90]), CLO was favoured over TIC for North America (HR=1.25 [0.93, 1.67]) and this interaction was statistically significant (p=0.0453).

The sponsor further explored the interaction in the special report, *Exploratory analyses of treatment interactions in PLATO* in an effort to identify any causative or associated factor. Within the North American countries they found that USA data contributed most to the anomalous result. As the likelihood of finding a false negative result increases with multiple comparisons, it could be a 'chance' finding; however, systematic drug delivery errors, patient population differences, style of medical care, discontinuations and compliance were eliminated as factors. Exploration by the 31 pre-specified and another 6 *post hoc* factors identified one possibly associated non pre-specified factor: aspirin dose. Most USA patients received aspirin doses of 81 or 325 mg, while most non-USA patients received 75 or 100 mg. The majority of higher doses were given in the USA, but 1.4% of non-USA patients also received the higher dose. A dose comparison found TIC gave greater efficacy for the primary endpoint at lower doses of aspirin, but CLO gave superior efficacy at higher doses (greater than approximately 150 mg).

#### *Evaluator Comment*

TGA guidelines suggest that a strong interaction indicating “an adverse effect of the treatment in one of the subgroups and no convincing explanation for the phenomenon” may be grounds for excluding that subpopulation from the registration license until further information is available. The evaluator considered that the sponsor was very thorough in identifying and examining further a possible association between increasing aspirin dose and decreasing efficacy of TIC on the primary endpoint in PLATO. However, it must be kept in mind that this was a subgroup analysis using small numbers in some of the group comparisons, that analysis by aspirin related factors was *post hoc* and that this was a superiority study and thus lack of proof of superiority does not equate to equivalence or inferiority of treatment to control. The sponsor was undertaking further work to try to determine whether this region effect is a true effect and if so what the mechanism might be. Additionally it was recommended in the Brilinta PI that patients take aspirin at a dose of 75-150 mg whilst taking TIC. Whilst further data should be provided to the TGA when available, the evaluator did not consider the current evidence for this possible interaction to be sufficient reason to advise

against registration when weighed against the much stronger evidence supporting the overall primary efficacy endpoint.

A comparison of the primary efficacy endpoint according to intent to manage invasively or medically indicated that TIC was better than CLO in preventing the composite of (CV death/non silent MI/stroke) in the subgroup of patients intended for medical management and the p-value for the HR was <0.05. Also examined were patients who had invasive procedures during the initial hospitalisation according to their initial planned management. Amongst those planned for invasive procedures, 89.6% had coronary angiography prior to a decision about further management, 71.7% had PCI and 5.5% had CABG surgery and of those planned for medical management, 41.6% had coronary angiography, 20.1% had PCI and 4.7% had CABG surgery; proportions of patients were similar for those treated with TIC and those treated with CLO.

The evaluator was unable to find an analysis of the primary endpoint in those patients who actually received only medical management. However, an exploratory analysis of the primary efficacy endpoint in patients who actually received PCI or CABG was carried out. TIC was better than CLO in preventing the composite (CV death/non silent MI/stroke) in the subgroups of patients who actually received PCI and those who actually received CABG surgery but the p-values for the HRs were >0.05. These results are akin to a per protocol analysis, and although not essential figures they are supportive of the 'intent to treat' results presented in the previous paragraph.

Additional individual components of the composite efficacy endpoints were experienced to a slightly greater degree with CLO compared to TIC (5.4% TIC and 5.8% CLO patients had RCI, 3.2% TIC and 3.7% CLO patients had SRCI) or were experienced by similar proportions of patients in each treatment group (0.1% TIC and 0.1% CLO patients had a silent MI; 0.2% TIC and 0.2% CLO patients had a TIA; 0.2% TIC and 0.3% CLO patients had other ATE).

QoL, as measured on the EQ-5D, was similar for patients receiving TIC and CLO.

## **D5130C00002 [DISPERSE2]**

Efficacy variables were incidence of MI, death, stroke, and severe recurrent ischaemia; total duration of ischaemia during continuous Holter monitoring for 4-7 days after randomisation; and health economic variables and questionnaires regarding work.

There were no clear differences for the individual endpoints between treatment groups, however there were more deaths in the TIC groups and a trend to decreasing MI with TIC dose. There were no clear differences for the composite endpoints although TIC 180 mg had lower incidence compared to both TIC 90 mg and CLO 75 mg for all composite endpoints. Holter monitoring showed 24% of patients to have episodes of ischaemia  $\geq 1.0$  mm ST depression or elevation with no differences between treatment groups. There were no differences between treatment groups for length of hospital stay, or employment status.

### **Summary of Efficacy**

The pivotal efficacy study in hospitalised patients with an index event of non-ST or ST segment elevation ACS and at high risk of a secondary thrombotic event showed:

1. TIC was significantly better than CLO in preventing:
  - an event in the composite of CV death, MI (excluding silent MI) and stroke over a 12 month period (Primary Efficacy Endpoint)
2. TIC was significantly better than CLO in preventing:

- CV death over a 12 month period
  - MI (excluding silent MI) over a 12 month period
3. TIC was not better than CLO in preventing:
    - stroke over a 12 month period
  4. TIC was significantly better than CLO in preventing:
    - an event in the composite of CV death, MI (excluding silent MI) and stroke over a 12 month period in those patients intended for invasive management
    - an event in the composite of all cause mortality, MI (excluding silent MI) and stroke over a 12 month period
    - an event in the composite of CV death, total MI, stroke, SRCI, RCI, TIA and other ATE over a 12 month period
  5. TIC was nominally better than CLO in preventing:
    - all cause mortality,  $p < 0.05$ , however the result was not significant.

Further analysis of the primary efficacy endpoint found:

1. Regarding duration of treatment:
  - TIC was significantly better than CLO in achieving the primary efficacy endpoint over the first 30 days following an ACS event
  - TIC was significantly better than CLO in achieving the primary efficacy endpoint from after the first 30 days and up to 12 months, following an ACS event, in patients who were event free in the first 30 days
2. Regarding age, gender, and race, the primary efficacy endpoint results were:
  - very consistent for age (<65 y/≥65 y) and consistent for age (<75 y/≥75 y)
  - very consistent for gender
  - very consistent for Caucasian race but difficult to draw conclusions for other races due to relatively small numbers
3. Regarding final diagnosis, the primary efficacy endpoint results were:
  - very consistent for NSTEMI and STEMI, and consistent for UA
4. Regarding region, the primary efficacy endpoint results were:
  - very consistent for Asia/Australia, Central/South America, and Europe/Middle East/Africa but not consistent for North America
  - CLO was significantly better than TIC in achieving the primary efficacy endpoint in the USA, a finding possibly related to aspirin dose
5. Regarding intended treatment:
  - TIC was significantly better than CLO in achieving the primary efficacy endpoint in patients intended for invasive management
  - TIC was better than CLO in achieving the primary efficacy endpoint in patients intended for medical management,  $p < 0.05$
6. Regarding actual treatment received:
  - TIC was better than CLO in achieving the primary efficacy endpoint in patients who received PCI, although  $p > 0.05$

- TIC was better than CLO in achieving the primary efficacy endpoint in patients who received CABG surgery, although  $p > 0.05$
- there was no analysis of the primary efficacy endpoint in patients who received medical management.

In the Phase II study, D5130C00002 (DISPERSE2) there was a trend to decreasing MI with increasing TIC dose.

## **Safety**

All subjects receiving treatment with the study medication were assessed for safety, which involved AEs (including serious AEs [SAEs], discontinuations due to AEs [DAEs], other significant AEs [OAEs] and deaths), laboratory parameters, physical examinations, vital signs and ECGs, with some studies also individually assessing AEs relating to bleeding, thrombosis, dyspnoea, uric acid and gout, myalgia and hypotension. In particular, the Phase II study DISPERSE2 looked specifically at bleeding, dyspnoea and arrhythmias and the Phase III study PLATO comprehensively examined bleeding, dyspnoea, cardiac arrhythmias, renal function, hyperuricaemia and gout, hepatic function, abnormal vaginal bleeding and related gynaecological cancers excluding breast, neoplasms and designated medical events.

Safety data were contained in one Phase III study (PLATO), four Phase II studies (OFFSET, RESPOND, DISPERSE, DISPERSE2) and 40 Phase I studies (the study drug in two Phase I studies was only CLO and therefore did not contribute TIC safety data). Safety data is presented individually for the Phase III and four Phase II studies and some pooled results from the Phase II studies. For the 40 pharmacology studies safety data is summarised and presented individually for the two studies in which SAEs occurred and the 14 additional drug interaction studies.

There were 18624 subjects evaluable for safety of the formulation for which registration is being sought (the TIC 90 mg tablet) in the Phase III study PLATO (9333 received TIC, 3138 of these for greater than 360 days) and for additional safety of this and other forms of TIC, 1412 subjects evaluable in the Phase II studies (951 received TIC for 4-12 weeks) and 1021 subjects evaluable in 40 pharmacology studies (960 received TIC).

## **Phase III Study – D5130C05262 (PLATO)**

### ***Exposure***

Table 6 summarises exposure to the study medication. Patients were expected to complete 6, 9 or 12 months treatment. Mean exposure to study medication was similar for both treatment groups (246-250 days) throughout the study; 13677 (73%) of patients received treatment >6 months, 10241 (55%) of patients received treatment for >9 months and 6322 (34%) of patients received treatment for >12 months. Fifteen percent of TIC patients and 13.8% of CLO patients had an interruption of the study drug (median 8-9 days) for bleeding events, non-bleeding AEs, CABG or other surgery, for receiving prohibited medication or other reasons (approximately half were for CABG surgery); only 1.9% had more than one interruption.

**Table 6: Exposure to study medication, PLATO, number of subjects**

Exposure	TIC 90 mg bd	CLO 75 mg od	Total
N	9333	9291	18624
Mn (days)	245.64	250.33	247.98
Range (days)	1-606	1-470	1-606
0 days	98 (1.1%)	105 (1.1%)	203 (1.1%)
1-30 days	1250 (13.4%)	1180 (12.7%)	2430 (13.0%)
31-90 days	515 (5.5%)	459 (4.9%)	974 (5.2%)
91-180 days	708 (7.6%)	632 (6.8%)	1340 (7.2%)
181-279 days	1680 (18.0%)	1756 (18.9%)	3436 (18.4%)
271-360 days	1944 (20.8%)	1975 (21.3%)	3919 (21.0%)
>360 days	3138 (33.6%)	3184 (34.3%)	6322 (33.9%)
None	98 (1.1%)	105 (1.1%)	203 (1.1%)
>0 days	9235 (98.9%)	9186 (98.9%)	18421 (98.9%)
>30 days	7985 (85.6%)	8006 (86.2%)	15991 (85.9%)
>90 days	7470 (80.0%)	7547 (81.2%)	15017 (80.6%)
>180 days	6762 (72.5%)	6915 (74.4%)	13677 (73.4%)
>270 days	5082 (54.5%)	5159 (55.5%)	10241 (55.0%)
>360 days	3138 (33.6%)	3184 (34.3%)	6322 (33.9%)

***Bleeding Events***

PLATO defined bleeding severity categories were developed from the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events trial (CURE) and used in preference to TIMI for the following reasons: the PLATO scale was clinically relevant, had lower thresholds than the TIMI scale, was adjudicated using a single set of pre-defined definitions, included all events regardless of whether haematology testing had been performed, and all CABG patients were adjudicated for bleeding.<sup>7</sup>

The primary safety endpoint, PLATO defined 'total major' bleeding, which consisted of both 'major fatal/life threatening' bleeding (fatal, intracranial, intrapericardial with cardiac tamponade, hypovolaemic shock/hypotension, with decrease in haemoglobin (Hb) >50 g/L or requiring transfusion ≥4 units) and 'major other' bleeding (significantly disabling, with decrease in Hb 30-50 g/L or requiring transfusion 2-3 units), is presented in Table 7 and is subcategorised by severity and clinical context.

<sup>7</sup> Mehta et al Clopidogrel in UA prevent recurrent events trial Eur Heart J 2000; 21: 2033-41.

**Table 7: PLATO defined ‘total major’ bleeding events, primary safety endpoint, and sub-categorisation by severity and clinical context, PLATO, number (%) of subjects, safety set**

		TIC 90 mg bd		CLO 75 mg od	
N		9235		9186	
		No. events	n(%) KM%	No. events	n(%) KM%
<b>PRIMARY SAFETY ENDPOINT</b>					
Total major bleeding		1031	961 (10.4%) 11.6	997	929 (10.1%) 11.2
		HR (95%CI) p-value: 1.04 (0.95, 1.13) 0.4336			
<b>SUBCATEGORIES</b>					
Total major bleeding by severity	Major fatal/life threatening	516	491 (5.3%) 5.8	505	480 (5.2%) 5.8
		HR (95%CI) p-value: 1.03 (0.90, 1.16) 0.6988			
	Fatal	21	20 (0.2%) 0.3	24	23 (0.3%) 0.3
		HR (95%CI) p-value: 0.87 (0.48, 1.59) 0.6553			
	Life threatening	495	471 (5.1%) -	481	459 (5.0%) -
	Major other	515	494 (5.3%) -	492	474 (5.2%) -
Total major bleeding by clinical context	Total Major	1031	961 (10.4%)	997	929 (10.1%)
	Not related to CABG surgery	401	362 ( 3.9%)	335	306 ( 3.3%)
	Not procedure related	251	235 ( 2.5%)	190	180 ( 2.0%)
	Non CABG procedural	151	143 (1.5%)	145	133 (1.4%)
	Procedure related	773	756 ( 8.2%)	804	775 ( 8.4%)
	Non coronary	30	27 ( 0.3%)	46	37 ( 0.4%)
	Coronary	743	732 ( 7.9%)	758	745 ( 8.1%)
	CABG related	623	619 ( 6.7%)	659	654 ( 7.1%)
	PCI related	97	93 ( 1.0%)	70	68 ( 0.7%)
	Coronary angiography related	23	23 ( 0.2%)	29	28 ( 0.3%)

There was no significant difference between TIC and CLO for PLATO defined ‘total major’ bleeding (HR [95%CI] 1.04 [0.95, 1.13], p=0.4336) and the total number of events were also similar. In terms of severity, there was no significant difference between treatment groups in the rate of ‘major fatal/life threatening’ bleeding (HR [95%CI] 1.03 [0.90, 1.16], p=0.6988) nor the rate of ‘fatal’ bleeding (HR [95%CI] 0.87 [0.48, 1.59], p=0.6553).

Sub categorisation of ‘total major’ bleeding by clinical context found no significant differences between treatment groups although ‘non-CABG, non-procedure related’ and ‘PCI related’ bleeding appeared more common with TIC and ‘CABG related’ bleeding appeared more common with CLO. There were no clear differences between treatment groups for severity categories ‘fatal’ and ‘major fatal/life threatening’ bleeding, subcategorised by clinical context.

A comparison of the primary endpoint, PLATO defined ‘total major’ bleeding, and the more familiar TIMI defined ‘major’ and ‘minor’ bleeding events was provided and found no

overall treatment differences using either definition. However when CABG related bleeding was removed, there was significantly more bleeding events seen with TIC than with CLO as measured by PLATO 'total major', TIMI 'major' and TIMI 'major+minor' endpoints but no significant difference for PLATO 'major fatal/life threatening' bleeding.

Exploratory subgroup analysis of bleeding identified no differences for race, age or gender for the primary safety endpoint, however the results should be interpreted with caution due to varying disparate group sizes and multiple analyses. There was no relationship with Major and Major+minor bleeding according to dose of aspirin.

The secondary safety endpoint, PLATO defined 'combined major+minor' bleeding is presented in Table 8 and is subcategorised by severity and clinical context. Significantly more patients had PLATO defined 'major+minor' bleeding events with TIC than with CLO (HR [95%CI] 1.11 [1.03, 1.20], p=0.0084), and when severity was looked at it could be seen that this was due to more patients having 'minor' bleeding with TIC than CLO (4.8% vs 3.8%, respectively). This 'minor bleeding category was considered clinically relevant because it may impact on compliance with medication. When broken down by clinical context, the biggest difference between TIC and CLO in minor bleeding was seen for non-procedural bleeding.

**Table 8: PLATO defined 'combined major+minor' bleeding events, secondary safety endpoint, and subcategorisation by severity, PLATO, number (%) of subjects, safety set**

		TIC 90 mg bd		CLO 75 mg od	
N		9235		9186	
		No. events	n(%) KM%	No. events	n(%) KM%
<b>SECONDARY SAFETY ENDPOINT</b>					
'combined major+minor' bleeding		1507	1339 (16.1%)	1377	1215 (14.6%)
		HR (95%CI) p-value: 1.11 (1.03, 1.20) 0.0084			
<b>SUBCATEGORIES</b>					
Combined major+minor bleeding by severity	Major fatal/life threatening	516	491 (5.3%)	505	480 (5.2%)
	Fatal	21	20 (0.2%)	24	23 (0.3%)
	Life threatening	495	471 (5.1%)	481	459 (5.0%)
	Major other	515	494 (5.3%)	492	474 (5.2%)
	Minor	476	442 (4.8%)	380	349 (3.8%)
Minor bleeding by clinical context	All Minor	476	442 (4.8%)	380	349 (3.8%)
	Not related to CABG surgery	420	387 (4.2%)	316	287 (3.1%)
	Not procedure related	261	237 (2.6%)	181	161 (.8%)
	Non CABG procedural	159	157 (1.7%)	135	128 (1.4%)
	Procedure related	209	206 (2.2%)	194	187 (2.0%)
	Non coronary	28	28 (0.3%)	32	31 (0.3%)
	Coronary	181	180 (1.9%)	162	158 (1.7%)
	CABG related	50	50 (0.5%)	59	59 (0.6%)
	PCI related	102	102 (1.1%)	75	71 (0.8%)
Coronary angiography related	28	28 (0.3%)	28	28 (0.3%)	



Bleeding related to PCI, coronary angiography, and CABG were specifically examined. PCI related 'total major' bleeding was greater with TIC (1.6%) than with CLO (1.2%) (the majority of this difference coming from 'major fatal/life threatening' bleeding [0.8% TIC, 0.5% CLO]) and PCI related 'minor' bleeding was greater with TIC (1.8%) than with CLO (1.3%). There were no differences in angiography related bleeding with TIC compared to CLO.

All CABG related bleeding events were Independent Central Adjudication Committee (ICAC) adjudicated (unlike previous ACS studies) and almost all (96%) were assigned to a bleeding category (therefore bleeding categories including CABG related bleeding will be higher compared to previous studies). Eighty percent of patients in each treatment group had 'Major' bleeding events associated with CABG surgery. There were no differences between treatment groups for time from last study drug dose to 'major/fatal/life threatening' CABG related bleeding, even when drug was stopped  $\leq 24$  h prior to surgery. Fatal CABG related bleeding was uncommon (6 patients in each treatment group), however, all cause mortality post CABG was clearly greater in CLO patients compared to TIC patients (8.6% vs 4.3%). The difference in all cause mortality was particularly marked when CABG was performed 2-4 days after last study dose and thus appears unrelated to CABG related bleeding.

It should be noted that this difference in post CABG all cause mortality is supportive of the non-significant secondary efficacy endpoint finding that suggested TIC was superior to CLO in the prevention of all cause mortality with a nominal p-value of 0.0003.

Intracranial haemorrhage was looked at separately in the special report from the sponsor, *Intracranial haemorrhage report addendum to the CSS*. Intracranial haemorrhage was categorized under 'major fatal/life threatening' bleeding, and occurred in 26 TIC patients (27 events, 11 fatal) and 15 CLO patients (15 events, 2 fatal). One fatal intracranial haemorrhage in a CLO patient was procedural and the remaining bleeds were non-procedural.

Non-procedural bleeding events were summarized by anatomic location (Table 9). Although intracranial events occurred more with TIC than with CLO, total non-procedural 'fatal/life threatening' and 'fatal' bleeds were similar for the two medications (fatal/life threatening events: 109 with TIC, 99 with CLO; fatal: 13 [0.1%] with TIC, 13 [0.1%] with CLO) and overall 'fatal' bleeding events were also similar for the two medications (20 [0.2%] with TIC, 23 [0.3%] with CLO). So TIC was associated with more fatal intracranial haemorrhage, but CLO was associated with more fatal gastrointestinal and other bleeding. Haemorrhagic transformation of an ischaemic stroke was reported or suspected in 5 TIC patients and 1 CLO patient.

An independent, blinded neurologist reviewed the diagnosis of intracranial haemorrhage, and identified possible alternative causes in 19 of the 26 TIC patients and in 11 of the 15 CLO patients. No cases were considered definitely related to the study drug, but 24/26 TIC cases and 14/15 CLO cases were considered probably or possibly related to the study drug. Neither the sponsor nor the independent reviewer was able to identify any specific risk factors (demographic or clinical) for intracranial haemorrhage thus the clinical significance of these findings is unclear. Significantly more patients discontinued the study drug due to non CABG and non-procedural bleeding with TIC than with CLO but the discontinuation rates were low (both 2.3% TIC vs 1.0% CLO,  $p < 0.001$ ).

**Table 9: Summary of ‘major fatal/life threatening’ and ‘fatal’ non procedure bleeding events by primary anatomic location – safety analysis set**

Primary location	Total major		Fatal/life threatening		Fatal	
	TIC 90 mg bd	CLO 75 mg od	TIC 90 mg bd	CLO 75 mg od	TIC 90 mg bd	CLO 75 mg od
N	9235	9186	9235	9186	9235	9186
Total bleeds	251	190	109	99	13 (0.1%)	13 (0.1%)
PRIMARY LOCATION						
Gastrointestinal	124	94	47	47	0	5
Intracranial	27	14	27	14	11 (0.1%)	1 (0.0%)
Urinary	13	14	4	4	0	0
Pericardial	11	11	10	10	1	2
Subcutaneous/dermal	11	4	3	1	0	1
Epistaxis	11	8	0	3	0	0
Haemoptysis	6	3	2	0	1	0
Retroperitoneal	2	3	1	3	0	1
Intraocular	0	2	0	0	0	0
Other	46	37	15	17	0	3

### **Adverse Events**

Table 10 summarises AEs including bleeding events during the study and Table 11 summarises AEs excluding bleeding events during the study.

**Table 10: Summary of safety – AEs including bleeding events, PLATO, safety analysis set, number (%) of subjects**

	TIC 90 mg bd	CLO 75 mg od
N	9235	9186
≥1 AE	6714 (72.7%)	6398 (69.6%)
Mild	5655 (61.2%)	5292 (57.6%)
Moderate	3322 (36.0%)	3073 (33.5%)
Severe	1019 (11.0%)	1061 (11.6%)
Any SAE	1864 (20.2%)	1866 (20.3%)
SAE excluding death	1712 (18.5%)	1685 (18.3%)
Deaths	218 (2.4%)	285 (3.1%)
Discontinuation due to an AE	687 (7.4%)	500 (5.4%)
Discontinuation due to an SAE	259 (2.8%)	218 (2.4%)
Deaths (in FAS)	443 (4.7%)	540 (5.8%)
Adjudicated deaths	418 (4.5%)	520 (5.6%)

**Table 11: Summary of safety – AEs excluding bleeding events, PLATO, safety analysis set, number (%) of subjects**

	<b>TIC 90 mg bd</b>	<b>CLO 75 mg od</b>
N	9235	9186
≥1 AE	6337 (68.6%)	6120 (66.6%)
Mild	5206 (56.4%)	4999 (54.4%)
Moderate	3121 (33.8%)	2909 (31.7%)
Severe	907 (9.8%)	964 (10.5%)
Any SAE	1633 (17.7%)	1694 (18.4%)
SAE excluding death	1485 (16.1%)	1519 (16.5%)
Deaths	198 (2.1%)	266 (2.9%)
Discontinuation due to an AE	486 (5.3%)	411 (4.5%)
Discontinuation due to an SAE	172 (1.9%)	174 (1.9%)

When bleeding events were included, AEs were reported in 72.7% TIC and 69.6% CLO patients, 11.0-11.6% were severe, 33.5-36.0% were moderate and 57.6-61.2% were mild. When bleeding events were excluded, AEs were reported in 68.6% TIC and 66.6% CLO patients, 9.8-10.5% were severe, 31.7-33.8% were moderate and 54.4-56.4% were mild. The most frequent AEs reported were dyspnoea, headache, epistaxis, cough, dizziness, nausea, atrial fibrillation and hypertension (Table 12). Non-bleeding related AEs that occurred more frequently with TIC than with CLO were dyspnoea (12.0% TIC, 6.5% CLO), headache (6.5% TIC, 5.8% CLO), nausea (4.3% TIC, 3.8% CLO) and dizziness (4.5% TIC, 3.9% CLO) while bleeding related AEs that occurred more frequently with TIC than with CLO were epistaxis (6.0% TIC, 3.4% CLO), contusion (3.9% TIC, 2.0% CLO) and haematoma (2.2% TIC, 1.3% CLO). There were no clinically relevant differences in AE profile across age, gender or race.

**Table 12: Most frequent AEs during treatment (≥2% in either group), including bleeding events, PLATO, safety analysis set**

	<b>TIC 90 mg bd</b>	<b>CLO 75 mg od</b>
	N = 9235	N = 9186
≥1 AE	6714 (72.7%)	6398 (69.6%)
Dyspnoea	1104 (12.0%)	598 (6.5%)
Headache	600 (6.5%)	535 (5.8%)
Epistaxis	558 (6.0%)	308 (3.4%)
Cough	452 (4.9%)	427 (4.6%)
Dizziness	418 (4.5%)	355 (3.9%)
Nausea	397 (4.3%)	346 (3.8%)
Atrial fibrillation	390 (4.2%)	418 (4.6%)
Contusion	357 (3.9%)	187 (2.0%)
Hypertension	353 (3.8%)	363 (4.0%)
Non cardiac chest pain	344 (3.7%)	306 (3.3%)
Diarrhoea	342 (3.7%)	304 (3.3%)
Back pain	329 (3.6%)	301 (3.3%)
Hypotension	300 (3.2%)	306 (3.3%)
Fatigue	295 (3.2%)	296 (3.2%)
Chest pain	288 (3.1%)	323 (3.5%)
Bradycardia	269 (2.9%)	270 (2.9%)
Pyrexia	266 (2.9%)	261 (2.8%)
Vomiting	234 (2.5%)	215 (2.3%)
Cardiac failure	214 (2.3%)	236 (2.6%)
Oedema peripheral	211 (2.3%)	228 (2.5%)
Haematoma	203 (2.2%)	122 (1.3%)
Constipation	202 (2.2%)	237 (2.6%)
Anxiety	200 (2.2%)	170 (1.9%)
Pain in extremity	196 (2.1%)	211 (2.3%)
Post procedural haemorrhage	192 (2.1%)	180 (2.0%)
Dyspepsia	185 (2.0%)	168 (1.8%)
Urinary tract infection	184 (2.0%)	161 (1.8%)
Ventricular tachycardia	184 (2.0%)	193 (2.1%)
Asthenia	181 (2.0%)	191 (2.1%)
Abdominal pain upper	174 (1.9%)	184 (2.0%)
Insomnia	153 (1.7%)	181 (2.0%)

### *Specific AEs*

#### *Minimal bleeding*

Minimal (non-adjudicated) bleeding was greater with TIC (17.2%) than with CLO (10.6%) with the most frequent minimal bleeding from epistaxis (4.9% TIC, 2.8% CLO) and contusion (2.8% TIC, 1.4% CLO).

#### *SAEs*

SAEs (including deaths and bleeding) were similar for the two treatment groups (20.2-20.3%), with the most frequent SAEs being cardiac failure (1.1% TIC, 1.0% CLO), non-cardiac chest pain (0.9% TIC, 0.9% CLO) and dyspnoea (0.7% TIC, 0.4% CLO). SAEs (including deaths but excluding bleeding) were lower with TIC (17.7%) than with CLO (18.4%), the most frequent SAEs remaining the same. CVAs (including haemorrhagic strokes) were reported in 0.7% (62/9235) TIC 90 mg bd and 0.5% (42/9186) CLO 75 mg od patients while ischemic strokes were reported in 0.2% (18/9235) TIC 90 mg bd and 0.3% (25/9186) CLO 75 mg od patients. Additional AEs reported more frequently with CLO than with TIC were pneumonia (0.5% TIC, 0.9% CLO), thrombosis in device (0.3% TIC, 0.6% CLO) and pulmonary oedema (0.3% TIC, 0.5% CLO).

#### *Discontinuations Due to AEs*

Discontinuations due to AEs including bleeding occurred in 7.4% TIC and 5.4% CLO patients, the most frequent causes being dyspnoea (0.8% TIC, 0.1% CLO) and epistaxis (0.4% TIC, 0.1% CLO). Discontinuations due to AEs excluding bleeding occurred in 5.3% TIC and 4.5% CLO patients, the most frequent causes being dyspnoea (0.8% TIC, 0.1% CLO) and atrial fibrillation (AF; 0.3% TIC, 0.4% CLO).

#### *Deaths*

More patients died with CLO (5.8%) than with TIC (4.7%). The proportion of bleeding related deaths were similar for both treatment groups (0.2%) but there were more vascular related deaths with CLO (3.5%) than with TIC (2.9%) and slightly more non-vascular deaths with CLO (0.2%) than with TIC (0.1%).

#### *OAEs*

A wide range of specific OAEs were examined.

Dyspnoea AEs occurred in 13.8% TIC and 7.8% CLO patients, most were mild or moderate. SAEs occurred in 0.7% TIC and 0.4% CLO patients and DAEs occurred in 0.9% TIC and 0.1% CLO patients. Most patients had only one episode of dyspnoea, which occurred earlier with TIC but was of similar duration with CLO. Patients with dyspnoea tended to be older and have baseline dyspnoea, CHF, COPD, asthma or a history of dyspnoea. The dyspnoea does not appear to be related to heart failure or lung disease. In the pulmonary function substudy there was no difference in forced expiratory volume in 1s (FEV<sub>1</sub>) or any other pulmonary function variable and no evidence of change in lung function over time, for TIC vs CLO patients.

Cardiac arrhythmia AEs, SAEs and DAEs occurred to a similar degree with TIC and CLO. There were a similar proportion of bradycardia related AEs with both treatments but more tachyarrhythmia related AEs and more fatal AEs with CLO. Many patients displayed brady- and tachy-arrhythmias on Holter monitor with both treatments; ventricular pauses were more frequent with TIC but pauses were generally asymptomatic and there were no correlations with clinically relevant events.

Baseline renal function was balanced for the two treatment groups. Renal related AEs occurred in 4.9% TIC and 3.8% CLO patients. The most frequent renal related AEs were

haematuria (1.9% TIC, 1.6% CLO), renal failure (1.0% TIC, 0.7% CLO), increased blood creatinine (0.5% TIC, 0.3% CLO) and acute renal failure (0.5% TIC, 0.5% CLO). There were more AEs in patients with greater renal impairment in both groups; deaths occurred in 2 TIC and 4 CLO patients; similar numbers in both groups required dialysis; and changes in mean estimated GFR were similar for both groups. There were increased AEs in TIC patients and increased SAEs in both groups, with age. TIC may cause a reversible increase in serum creatinine.

There was a reversible 15% increase in serum uric acid with TIC vs an irreversible 7.5% increase with CLO. There were more uric acid AEs with TIC than with CLO but the incidence of gout was similar for the two treatment groups.

Hepatic related AEs, SAEs, deaths, and DAEs occurred to a similar degree with TIC and CLO. The most frequent hepatic related AEs were increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased hepatic enzyme, hepatic steatosis, increased transaminases and abnormal liver function tests. Abnormalities of ALT, AST, ALP and total bilirubin were similar for TIC and CLO. There was no evidence of drug induced liver injury with TIC or CLO.

Abnormal vaginal bleeding was not increased with TIC and female gynaecological cancers (excluding breast) were rare (endometrial cancer in 1 TIC patient).

Both groups showed a similar proportion of patients with neoplasms and deaths due to cancer.

Designated medical events (DME) included events which are historically rare, of high medical importance, inherently serious, and often considered potentially drug related. DMEs occurred in 3.9% TIC and 3.7% CLO patients. No potential signal was identified.

#### *Laboratory Parameters, Vital Signs, Physical Examinations*

If CABG surgery occurred within one day of stopping the study medication, the net change in haemoglobin and requirement for transfusions trended to being slightly greater with TIC than with CLO, but there was no difference on 'Major fatal/life threatening' bleeding. There were no clinically relevant changes in other haematology and clinical chemistry parameters, vital signs, physical examinations, or weight.

#### *Pregnancy, Overdose, Withdrawal Effect*

One patient had a pregnancy with TIC and a healthy baby was delivered at full term. There were 27 cases of overdose (16 TIC, 11 CLO; 1 AE; 1 intentional) from 1 day to 2 months. There is no known antidote and it is unknown whether TIC is dialyzable. Supportive measures are recommended for bleeding. PLATO patients were followed for 30 days after stopping treatment with no difference in events (0.9%) between treatment groups, thus no withdrawal effect. There were no new or unexpected safety issues.

## **Phase II Studies**

### ***D5130C00048 [OFFSET]***

#### *Exposure*

Table 13 summarises exposure to the study medication. The mean exposure to the study drug was similar for TIC (41.0 days), CLO (42.5 days) and both pbo (42.9 days). The mean total dose of TIC was 7211.1 mg and of CLO was 3734.4 mg and the mean average daily dose of TIC was 173.6 mg and of CLO was 97.0 mg. Overall compliance was 94.9% for TIC and 100% for CLO (and 95-98% for pbo tablets).

**Table 13: Exposure to and compliance to with randomised study medication, D5130C00048**

		TIC (180mg loading dose then 90mg bd) for 6wks		CLO (600mg loading dose then 75mg od) for 6wks		Pbo for 6wks	
N		57, n=57		54, n=53		12, n=12	
		TIC	CLO pbo	CLO	TIC pbo	TIC pbo	CLO pbo
Length of exposure (days)	Mn	41.0	41.0	42.5	42.5	42.9	42.9
	Range	2-53	2-53	1-55	1-55	26-50	26-50
Total dose (mg)	Mn	7211.1	46.9	3734.4	86.1	83.0	49.2
	Range	270-9990	8-60	600-5925	2-144	49-100	31-57
Overall compliance (%)	Mn	94.9	97.3	100.6	99.6	95.4	98.3
	Range	29-128	59-112	71-161	67-169	90-99	94-100
Average daily dose (mg)	Mn	173.56	1.21	97.01	2.03	1.93	1.15
	Range	54.0-232.3	0.9-4.0	67.0-600.0	1.6-3.4	1.8-2.0	1.1-1.2

*Adverse Effects*

Table 14 summarises AE data. Similar proportions of patients reported AEs with each treatment, but more AEs were reported with TIC (125 AEs in 39 [68.4%] patients) than with CLO (60 AEs in 34 [63.0%] patients) or pbo (14 AEs in 7 [58.3%] patients). The most frequent AEs reported with TIC were dyspnoea (35.1%), increased tendency to bruise (15.8%), and contusion (10.5%); the most frequent AE reported with CLO was dyspnoea (11.1%); and no AE occurred in more than 1 pbo patient. Most AEs were mild or moderate. More patients had treatment related AEs with TIC (42 AEs in 22 [38.6%] patients) than with CLO (10 AEs in 8 [14.8%] patients) or pbo (no AEs). The most frequent treatment related AEs were dyspnoea (24.6% TIC, 5.6% CLO, 0% pbo), increased tendency to bruise (10.5% TIC, 1.9% CLO, 0% pbo), and contusion (7.0% TIC, 1.9% CLO, 0% pbo).

**Table 14: Summary of safety, D5130C00048, number (%) of subjects**

		TIC (180 mg loading dose then 90 mg bd) for 6 wks		CLO (600 mg loading dose then 75 mg od) for 6 wks		Pbo for 6 wks	
N		57		54		12	
AEs		39 (68.4)		34 (63.0)		7 (58.3)	
No. of AEs		125		60		14	
Drug related AE		22 (38.6)		8 (14.8)		0	
No. of AEs		42		10			
Bleeding related AEs		16 (28.1)		7 (13.0)		1 (8.3)	
No. of AEs		21		11		1	
Thrombotic AEs		0		0		0	
SAEs		0		0		0	
Discontinued due to AE		4 (7.0)		0		1 (8.3)	
Deaths		0		0		0	
OAEs		17 (29.8)		4 (7.4)		1 (8.3)	
No. of AEs		20		4		1	

### *Specific AEs*

Sixteen TIC patients had 21 bleeding events, 7 CLO patients had 11 bleeding events and 1 pbo patient had 1 bleeding event. Two contusions and 1 epistaxis were moderate and the rest mild. One bleeding event was classified as a minor bleed and the rest as minimal bleeds.

There were no thrombotic events.

There were no SAEs. One patient had an SAE prior to receiving the study drug.

Five patients discontinued due to AEs, 4 (7.0%) with TIC (1 exertional dyspnoea, 2 dyspnoea, 1 sleep disorder) and 1 (8.3%) with pbo (allergic dermatitis).

There were no deaths.

Seventeen TIC patients had 20 OAEs (17 dyspnoea, 2 exertional dyspnoea, 1 gout), 4 CLO patients had OAEs (3 dyspnoea, 1 gout) and 1 pbo patient had an OAE (exertional dyspnoea).

### *Laboratory Parameters, Vital Signs, Physical Examinations, ECGs, Cardiopulmonary Parameters*

In keeping with previous studies, increases were seen in serum uric acid <10%. There were no clinically relevant changes in laboratory parameters, vital signs, physical examinations, or abnormal ECGs. No significant differences between TIC and CLO patients were seen from baseline to 6wks for any cardiopulmonary parameter; including in patients who had dyspnoea.

### **D5130C00030 [RESPOND]**

#### *Exposure*

Exposure was presented separately for each treatment group within each cohort.

For nonresponders, mean exposure to the study drug was similar for TIC (14.1-14.4 days), CLO (15.3-15.4 days) and both pbo (13.5-15.3 days). The mean total dose of TIC was 2138-2270 mg and of CLO was 921-938 mg; and the mean average daily dose of TIC was 142.8-160.2 mg and of CLO was 60.4-63.6 mg. Overall compliance was 79-89% for TIC and 81-85% for CLO (and 80-89% for pbo tablets).

For responders, mean exposure to the study drug was similar for TIC (14.1-15.9 days), CLO (14.1-15.4 days) and both pbo (14.1-16.0 days). The mean total dose of TIC was 2224-2382 mg and of CLO was 975-1045 mg; and the mean average daily dose of TIC was 142.2-162.1 mg and of CLO was 64.8-67.7 mg. Overall compliance was 79-90% for TIC and 86-90% for CLO (and 81-91% for pbo tablets).

#### *Adverse Effects*

Table 15 summarises AE data for the 'non-switching period' (all study duration except switching period) and the 'switching period' (24 h period following first dose of Study Period 2 if patient changed the study drug for Period 2).



**Table 15: Summary of safety, D5130C00030, number (%) of subjects**

	Non-switching period (all study duration except switching period)		Switching period (24h after first dose of study period 2 if change drug)	
	TIC	CLO	TICà CLO	CLOà TIC
Nonresponder				
Number of dosed patients	39	38	18	18
AEs	20 (51.3)	19 (50.0)	1 (5.6)	4 (22.2)
No. of AEs	34	31	2	6
Drug related AE	12 (30.8)	6 (15.8)	0	3 (16.7)
No. of AEs	20	12		4
Bleeding related AE	5 (12.8)	2 (5.3)	0	1 (5.6)
No. of AEs	11	3		1
SAEs	2 (5.1)	0	0	0
Discontinued due to AE	3 (7.7)	2 (5.3)	0	0
Deaths	1 (2.6)	0	0	0
OAEs	10 (25.6)	4 (10.5)	1 (5.6)	2 (11.1)
No. of AEs	10	5	1	2
Responder				
Number of dosed patients	44	42	13	16
AEs	28 (63.6)	19 (45.2)	2 (15.4)	1 (6.3)
No. of AEs	47	38	3	1
Drug related AE	14 (31.8)	8 (19.0)	0	1 (6.3)
No. of AEs	18	11		1
Bleeding related AE	14 (31.8)	7 (16.7)	0	1 (6.3)
No. of AEs	15	9		1
SAEs	2 (4.5)	0	0	0
No. of AEs	3			
Discontinued due to AE	1 (2.3)	0	0	0
Deaths	0	0	0	0
OAEs	7 (15.9)	0	0	0
No. of AEs	7			

There was no clear pattern of trends of AEs during the switching period. During the non-switching period there were more AEs in all categories with TIC than with CLO, in both the nonresponder and responder cohorts. In the nonresponder cohort, 20 (51.3%) patients reported 34 AEs with TIC and 19 (50.0%) patients reported 31 AEs with CLO. The most frequent AEs in nonresponders were dyspnoea (17.9% TIC, 7.9% CLO), increased tendency to bruise (7.7% TIC, 2.6% CLO) and dizziness (2.6% TIC, 7.9% CLO). In the responder cohort, 28 (63.6%) patients reported 47 AEs with TIC and 19 (45.2%) patients reported 38 AEs with CLO. The most frequent AEs in responders were dyspnoea (13.6% TIC, 0% CLO), dyspepsia (2.3% TIC, 9.5% CLO), nausea (0% TIC, 9.5% CLO) and epistaxis (6.8% TIC, 0% CLO). Most AEs were mild or moderate. In the nonresponder cohort, 12

(30.8%) patients reported 20 drug related AEs with TIC and 6 (15.8%) patients reported 12 drug related AEs with CLO; while in the responder cohort, 14 (31.8%) patients reported 18 drug related AEs with TIC and 8 (19.0%) patients reported 11 drug related AEs with CLO.

#### *Specific AEs*

In the nonresponders, 5 (12.8%) TIC patients had 11 bleeding events and 2 (5.3%) CLO patients had 3 bleeding events; 2 events in 1 TIC patient were considered major, 1 event in 1 TIC patient was considered minor and the rest were minimal. In the responders, 14 (31.8%) TIC patients had 15 bleeding events and 7 (16.7%) CLO patients had 9 bleeding events; 2 events in 2 TIC patients were considered minor and the rest minimal. Bleeds occurred across a range of organ classes and there was no clear pattern of events.

Four patients had 5 SAEs, all with TIC. Two nonresponders had MI (not related to the study drug) and hypotension (related to the study drug) and 2 responders had atrial fibrillation (AF) (not related to the study drug) and bradycardia/ventricular extrasystoles (related/not related to the study drug). There was no pattern of SAEs with the study drug.

Six patients discontinued due to an AE. Five nonresponders had gastrointestinal (GI) haemorrhage, hypotension, dyspnoea (these 3 related to the study drug), ECG T-wave inversion, and myalgia (these 2 not related to the study drug); and 1 responder had bradycardia (related to the study drug). There was no pattern of discontinuations due to AEs with the study drug.

There were no deaths during the study. One patient died during follow up period (complications of MI; considered unrelated to study treatment).

In the nonresponder population, 10 TIC patients had 10 OAEs and 4 CLO patients had 5 OAEs and another 3 OAEs occurred during the switching period. In the responder population, 7 TIC patients had 7 AEs. The most common OAE was dyspnoea (mostly mild and occurring in 20 patients). All other OAEs were seen in 1 patient (GI haemorrhage, hypotension, ECG-T-wave inversion, myalgia and bradycardia).

There were no clinically relevant changes in laboratory parameters, vital signs, physical examinations, or abnormal ECGs.

#### ***D5130C00008 [DISPERSE]***

##### *Exposure*

Table 16 summarises compliance with the study medication: 73% of patients had 100% compliance with the study medication (65-78% of patients with TIC, no dose relation; 78% with CLO) and 94% of patients had  $\geq 90\%$  compliance (91-97% of patients with TIC, no dose relation; 94% with CLO).

**Table 16: Compliance with randomised study medication, D5130C00008, number of subjects**

Compliance	TIC				CLO	Total
	50 mg bd	100 mg bd	200 mg bd	400 mg bd	75 mg od	
N	41	39	37	46	37	200
Mn (%)	96.1	93.9	97.2	95.0	99.0	96.2
Range (%)	10.7-105.4	10.7-105.4	16.1-103.6	14.3-105.4	85.7-101.8	10.7-105.4
<50%	2 (5%)	2 (5%)	1 (3%)	2 (4%)	0	7 (4%)
50-<60%	0	1 (3%)	0	1 (2%)	0	2 (1%)
60-<70%	0	0	0	0	0	0
70-<80%	0	0	0	1 (2%)	0	1 (1%)
80-<90%	0	0	0	0	2 (5%)	2 (1%)
90-<100%	9 (22%)	8 (21%)	7 (19%)	12 (26%)	6 (16%)	42 (21%)
≥100%	30 (73%)	28 (72%)	29 (78%)	30 (65%)	29 (78%)	146 (73%)

*Adverse Effects*

AE data is summarised in Table 17. Around 51-81% of TIC patients (not dose related) and 70% of CLO patients reported an AE. The number of AEs reported increased with increasing dose of TIC. The most frequent AEs reported were dyspnoea (dose related with TIC: 10% 50 mg bd, 10% 100 mg bd, 16% 200 mg bd, 20% 400 mg od; CLO: 0%), dizziness (TIC: 10% 50 mg bd, 5% 100 mg bd, 3% 200 mg bd, 9% 400 mg od; CLO: 3%) and headache (TIC: 0% 50 mg bd, 13% 100 mg bd, 3% 200 mg bd, 2% 400 mg od; CLO: 8%).

**Table 17: Summary of safety, D5130C00008, number (%) of subjects**

	TIC				CLO
	50 mg bd	100 mg bd	200 mg bd	400 mg bd	75 mg od
N	41	39	37	46	37
AEs	21 (51%)	26 (67%)	30 (81%)	35 (76%)	26 (70%)
No. of AEs	58	63	73	88	62
Drug related AE	6 (15)	5 (13)	8 (22)	8 (17)	4 (11)
No. of drug related AEs	11	8	9	15	6
Major bleeding events	0	0	0	1 (2%)	0
Minor bleeding events	12 (29%)	17 (44%)	19 (51%)	22 (48%)	12 (32%)
SAEs	0	1 (3%)	1 (3%)	3 (7%)	2 (5%)
Discontinued due to AE	1 (2%)	2 (5%)	2 (5%)	4 (9%)	1 (3%)
Deaths	0	0	0	0	0
OAEs	4 (10%)	3 (8%)	1 (3%)	4 (9%)	3 (8%)
Follow up period					
AEs	2 (5%)	1 (3%)	2 (5%)	3 (7%)	1 (3%)
No. of AEs	2	1	2	4	3
Minor bleeding events	0	1 (3%)	1 (3%)	1 (2%)	1 (3%)

### *Specific AEs*

Dyspnoea had not been reported as an AE in previous studies in healthy subjects. In these patients with ASD, one with COPD and one with congestive cardiac failure, 23 subjects reported 29 events (8 moderate and 21 mild intensity; mostly inspiratory difficulty, transient to >3 wks; no apparent relationship to dose, gender or smoking status, but relationship to age [increased AEs when age>60 y]).

Dizziness was mild or moderate, transient to 29 days in length, supine and standing blood pressure (BP) were unaffected and all patients were also taking concomitant medications known to be associated with dizziness as an AE.

Minor bleeding events occurred in 70 patients with TIC (12 [29%] 50 mg bd, 17 [44%] 100 mg bd, 19 [51%] 200 mg bd, 22 [48%] 400 mg od) and in 12 (32%) patients with CLO 75 mg od. Major bleeding events occurred in 1 (2%) patient with TIC 400 mg od. The most frequent bleeding events were contusions and epistaxis, with both TIC and CLO; epistaxis appeared related to dose of TIC.

Seven subjects had SAEs with treatment, 1 each with TIC 100 mg bd and 200 mg bd, 3 with TIC 400 mg od and 2 with CLO 75 mg od. Three events were considered related to the study drug; 1 subject had an SAE prior to randomisation and discontinued.

Ten subjects discontinued due to AEs (4 of them SAEs), 1 each with TIC 50 mg bd and CLO 75 mg od, 2 each with TIC 100 mg bd and 200 mg bd and 4 with TIC 400 mg od. All 6 AEs and 3 of the SAEs were considered related to the study drug.

There were no deaths.

Fifteen subject experienced OAEs (dizziness, syncope, hypotension, orthostatic hypotension), 1 with TIC 200 mg bd, 2 with TIC 50 mg bd, 3 each with TIC 100 mg bd and CLO 75 mg od and 4 with TIC 400 mg od.

Hb levels decreased significantly in 9 subjects across all treatment groups and were associated with bleeding events in 3 cases (epistaxis/melaena with CLO; haematoma/multiple bruises with TIC 200 mg bd; GI haemorrhage with TIC 400 mg od [classified as major bleeding event]). Increases in serum uric acid of 5-10% were seen with TIC, while a decrease in serum uric acid of about 10% was seen with CLO; and 1 subject had gout with TIC 200 mg bd. Evidence did not support a causal relationship between TIC and increased bilirubin or increased creatinine; ALT, AST and gamma-glutamyl transpeptidase were not affected by treatment. TIC did not affect orthostatic BP and did not appear to increase the QT interval on ECG. There were no clinically relevant changes in physical examinations.

### ***D5130C00002 [DISPERSE2]***

#### *Exposure*

Of 250 patients expecting 4 wks treatment, mean exposure to the study drug was 25.1-25.3 days across three groups (TIC 90 mg bd, TIC 180 mg bd, CLO 75 mg od) and 82% of patients received treatment >21 days. Of 243 patients expecting 8 wks treatment, mean exposure to the study drug was 49.9-50.3 days and 76-86% of patients received treatment >49 days. Of the 491 patients expecting 12 wks treatment, mean exposure to the study drug was 67.3-68.5 days and 68-71% of patients received treatment >77 days.

#### *Bleeding Events*

Primary and secondary ICAC adjudicated bleeding endpoints were examined. For the primary endpoint, total ICAC adjudicated bleeding event rate at Week 4 was similar for all three treatment groups (9.6% TIC 90 mg bd, 7.7% TIC 180 mg bd, 8.0% CLO 75 mg od) but

the UCL for TIC compared to CLO was 5.8, indicating the possibility that the total bleeding rate with TIC could be 5.8 times that with CLO. Most of the total bleeding events occurred during the first 14 days. Results were robust for per protocol set, and were unaffected on subgroup analysis by gender, age, and race.

The only category of bleeding that showed an apparent dose related increase with TIC was minor bleeding (2.7% TIC 90 mg, 3.7% TIC 180 mg, 1.2% CLO). There were no differences seen between TIC and CLO for discontinuations due to bleeding, bleeding events related to PCI and CABG, or number of transfusions required.

#### *Adverse Effects*

Table 18 summarises AE data during the study and Table 19 summarises AE data during the follow up period. During the study more patients reported AEs with TIC compared to CLO and with TIC 180 mg compared to TIC 90 mg. A total of 803 AEs were reported by 233 (70%) TIC 90 mg patients, 840 AEs were reported by 244 (76%) TIC 180 mg patients and 589 AEs were reported by 223 (68%) CLO 75 mg patients. The most frequent non-bleeding related AEs reported were headache (10% TIC 90 mg, 7% TIC 180 mg, 9% CLO 75 mg), dyspnoea (8% TIC 90 mg, 12% TIC 180 mg, 5% CLO 75 mg), and chest pain (7% TIC 90 mg, 7% TIC 180 mg, 9% CLO 75 mg).

**Table 18: Summary of safety during treatment period, D5130C00002, number (%) of subjects**

Exposure	TIC		CLO	Total
	90 mg bd	180 mg bd	75 mg od	
N	334	323	327	984
AEs	233 (70%)	244 (76%)	223 (68%)	700 (71%)
No. of AEs	803	840	589	2232
SAEs	41 (12%)	54 (17%)	51 (16%)	146 (15%)
Discontinued due to AE	21 (6%)	23 (7%)	19 (6%)	63 (6%)
Deaths	6 (2%)	3 (1%)	1 (0%)	10 (1%)
OAEs	15 (4%)	19 (6%)	1 (0%)	35 (4%)
Major fatal/life threatening bleeding AE	4 (1%)	3 (1%)	3 (1%)	10 (1%)
Major other bleeding AE	15 (4%)	13 (4%)	15 (5%)	43 (4%)
Minor bleeding AE	16 (5%)	17 (5%)	10 (3%)	43 (4%)
Minimal bleeding AE	89 (27%)	100 (31%)	70 (21%)	259 (26%)

During the follow up period, 51 AEs were reported by 30 (9%) TIC 90 mg patients, 79 AEs were reported by 30 (9%) TIC 180 mg patients and 46 AEs were reported by 26 (8%) CLO 75 mg patients.

**Table 19: Summary of safety during follow up period, D5130C00002, number (%) of subjects**

Exposure	TIC		CLO	Total
	90 mg bd	180 mg bd	75 mg od	
N	334	323	327	984
AEs	30 (9%)	30 (9%)	26 (8%)	86 (9%)
No. of AEs	51	79	46	176
SAEs	9 (3%)	9(3%)	7 (2%)	25 (3%)
Discontinued due to AE	2 (1%)	2 (1%)	5 (2%)	9 (1%)
Deaths	1 (0%)	3 (1%)	3 (1%)	7 (1%)
OAEs	0	0	1 (0%)	1 (0%)
Major fatal/life threatening bleeding AE	1 (0%)	2 (1%)	0 (0%)	3 (0%)
Major other bleeding AE	4 (1%)	1 (0%)	5 (2%)	10 (1%)
Minor bleeding AE	0	1 (0%)	0	1 (0%)
Minimal bleeding AE	4 (1%)	6 (2%)	2 (1%)	12 (1%)

*Specific AEs*

Bleeding related AEs occurred in 33% TIC 90 mg, 37% TIC 180 mg and 28% CLO 75 mg patients. There was a dose related increase in minor bleeding with TIC: (25% TIC 90 mg, 29% TIC 180 mg, 20% CLO 75 mg) but no clear difference between treatment groups for moderate or severe bleeding.

Dyspnoea related AEs occurred in 10% TIC 90 mg, 16% TIC 180 mg and 6% CLO 75 mg patients. About two thirds of dyspnoea reported was mild and one third moderate with only one severe case (CLO 75 mg) and 24% patients had a history of dyspnoea. No clear risk factors for dyspnoea were identified.

Three TIC 90 mg patients died due to serious ventricular arrhythmias. No clear differences were found between treatment groups regarding any arrhythmia related term. A separate *post hoc* Holter monitor analysis found no differences between treatment groups for occurrence of ventricular fibrillation, sustained or non-sustained ventricular tachycardia, ventricular triplets, AF or atrial flutter but an apparent increase in episodes of pauses, dropped beats, and bradycardia occurred with TIC compared to CLO. There was no correlation with clinical AEs or future events.

During the study SAEs were experienced by 12% TIC 90 mg patients, 17% TIC 180 mg patients, and 16% CLO 75 mg patients. The most common SAEs were cardiac (5% TIC 90 mg, 8% TIC 180 mg, 6% CLO 75 mg), with most of the increase with TIC 180 mg due to increased reporting of UA and angina pectoris (AP). Dyspnoea related SAEs were reported in 1% TIC 180 mg patients and 1% CLO 75 mg patients. During the follow up period SAEs were experienced by 3% TIC 90 mg patients, 3% TIC 180 mg patients, and 2% CLO 75 mg patients.

Discontinuations due to AEs were similar for all groups during the study (6% TIC 90 mg, 7% TIC 180 mg, 6% CLO 75 mg). Bleeding related DAEs occurred in 7 TIC 90 mg patients (including 1 cerebral haemorrhage considered related to the study drug), 6 TIC 180 mg patients, and 5 CLO 75 mg patients. CV related DAEs occurred in 6 TIC 90 mg patients, 3 TIC 180 mg patients, and 4 CLO 75 mg patients. Dyspnoea related DAEs occurred in 2 TIC

180 mg patients, and 2 CLO 75 mg patients. DAEs during the follow up period occurred in 1% TIC 90 mg patients, 1% TIC 180 mg patients and 2% CLO 75 mg patients.

Ten patients died during the study (6 [2%] TIC 90 mg, 3 [1%] TIC 180 mg, 1 [0%] CLO 75 mg) and 7 during the follow up period (1 [0%] TIC 90 mg, 3 [1%] TIC 180 mg, 3 [1%] CLO 75 mg). During the study, 8 deaths were CV including 3 arrhythmias, 1 multi-organ failure, and 1 bleeding related motor vehicle accident. During the follow up period, 5 deaths were CV (1 also bleeding related), 1 ischaemic stroke, and 1 multi-organ failure. None were considered related to treatment.

OAEs occurred in 4% TIC 90 mg patients, and 6% TIC 180 mg patients. The most frequent OAEs were anaemia (7 TIC 90 mg patients, 6 TIC 180 mg patients, 2 CLO 75 mg patients). Also noted were renal OAEs (1 TIC 90 mg, 9 TIC 180 mg, 1 CLO 75 mg), uric acid OAEs (4 TIC 90 mg, 4 TIC 180 mg) and myalgia (2 TIC 90 mg, 4 TIC 180 mg).

Increases in serum uric acid were seen with TIC groups which may lead to an increase in gout. There were no clinically relevant changes in vital signs, cardiopulmonary assessments, procedures and operations required during the study, transfusions of blood products or physical examinations.

### ***Pooled Phase II Studies***

#### *Exposure*

Although the Phase III study provided the main safety data for this submission, pooled data from the four Phase II studies in patients with atherosclerosis (stable CAD/ACS) was supportive. Mean exposure was greatest for TIC 180 mg bd (51.9 days in 360 patients); similar for TIC 90 mg bd (44.4 days in 513 patients), CLO (45.2 days in 498 patients) and pbo (40.7 days in 12 patients) and lowest for TIC 50 mg bd (27.9 days in 41 patients) and TIC 400 mg od (27.5 days in 46 patients). Of the 960 patients exposed to TIC, the majority of patients were exposed >4 wks. The Phase II studies were balanced for baseline demographics and characteristics, but differed where they investigated different diseases.

#### *Specific AE:*

Bleeding related data was pooled for DISPERSE2, OFFSET and RESPOND (Table 20). Bleeding AEs for pooled Phase II studies, DISPERSE2, OFFSET, and RESPOND demonstrated a dose response pattern with TIC. Minor AEs occurred more commonly with TIC 90 mg compared to CLO 75 mg but more serious AEs occurred at a similar or lower rate. There were no safety concerns regarding bleeding in the Phase II studies.

**Table 20: Bleeding related AEs for pooled Phase II studies, DISPERSE2, OFFSET, and RESPOND**

		TIC 50 mg	TIC 90 mg	TIC 180 mg	TIC 400 mg	CLO 75 mg	Pbo
N		41	513	360	46	498	12
Any AEs		12 (29.3%)	162 (31.6%)	140 (38.9%)	22 (47.8%)	117 (23.5%)	1 (8.3%)
Intensity	Mild	11 (26.8%)	146 (28.5%)	127 (35.3%)	17 (37.0%)	94 (18.9%)	1 (8.3%)
	Moderate	1 (2.4%)	24 (4.7%)	22 (6.1%)	5 (10.9%)	20 (4.0%)	0
	Severe	0	4 (0.8%)	6 (1.7%)	0	7 (1.4%)	0
Any SAE		0	9 (1.8%)	11 (3.1%)	2 (4.3%)	12 (2.4%)	0
Death		0	1 (0.2%)	0	0	0	0
SAE excluding death		0	8 (1.6%)	11 (3.1%)	2 (4.3%)	12 (2.4%)	0
Discontinuation due to AE		1 (2.4%)	10 (1.9%)	7 (1.9%)	4 (8.7%)	5 (1.0%)	0
Discontinuation due to SAE		0	5 (1.0%)	5 (1.4%)	2 (4.3%)	3 (0.6%)	0

### *Adverse Effects*

The safety profile from the pooled Phase II studies was very similar to that for PLATO. The most frequent AEs were dyspnoea, epistaxis and headache with a TIC dose response for dyspnoea and epistaxis but no relationship to TIC dose for headache.

Nine deaths occurred in the DISPERSE2 study (7 cardiac; all considered unrelated to treatment).

Most SAEs occurred in the DISPERSE2 study. The type and frequency of SAEs were similar for TIC 90 mg and CLO 75 mg groups and similar to PLATO.

There was an apparent dose response for Discontinuations due to GI disorders but not for any other group of AEs. DAEs (excluding bleeding) occurred to a similar degree between TIC 90 mg and CLO 75 mg groups while bleeding related DAEs occurred in more CLO 75 mg than TIC 90 mg patients.

Dyspnoea was first noted in DISPERSE and examined further in DISPERSE2 although no risk factors were identified. No differences in cardiopulmonary parameters were found between TIC, CLO and pbo patients over 6 wks in OFFSET including for patients with dyspnoea. A pooled Phase II analysis found an apparent TIC dose relationship.

Ventricular pauses were noted on Holter in DISPERSE2 and further investigated in PLATO. Pooled Phase II data did not indicate a dose relationship for brady- or tachy-arrhythmias.

Increased serum creatinine was seen more frequently with TIC than with CLO. There was no clear pattern of renal related AEs and TIC dose in the pooled studies.

Pooled Phase II data suggested mean serum uric acid increases of 5-10% are seen in 1.2-1.9% TIC patients. There was no clear association with gout.

Pooled Phase II data did not indicate a dose relationship for TIC in the few hepatic related AEs.

Vaginal bleeding was of no specific concern in the Phase II studies.



## Pharmacology Studies

The 40 pharmacology studies were conducted in 1001 healthy subjects with D5130C00016 and D5130C00015 also including 10 patients each with mild hepatic insufficiency and severe renal impairment, respectively. Of these, 604 subjects were exposed to various 90 mg TIC tablets and 380 to other TIC doses and formulations. The safety profiles of TIC in the pharmacology studies were generally in keeping with those seen in PLATO and the Phase II studies. There were no deaths and only 2 subjects had SAEs. A total of 29 subjects discontinued due to AEs in 17 of the studies (1-4 per study). Apart from ~10% increase in uric acid which was in keeping with that seen in Phase III and II studies, there were no clinically relevant changes in laboratory parameters, physical examination, ECGs, or vital signs (for doses up to 900 mg TIC).

Safety data was summarised for the two studies in which SAEs occurred and for the 14 additional drug interaction studies but in this AusPAR, only the study which drew a comment from the evaluator is included.

### **D5130C00049**

Sixteen subjects enrolled and all completed the study. Five subjects reported 15 AEs with 900 mg TIC, of which 8 AEs in 2 subjects were considered related to study medication. The most frequent AEs were dermatitis from ECG leads and headache. One headache was severe, one moderate, and remaining AEs were mild.

Six subjects reported 46 AEs with 1260 mg TIC of which 40 AEs in 6 subjects were considered related to study medication. The most frequent AEs were dizziness, dermatitis, hyperhidrosis and nausea. Three moderate GI AEs led to breaking of the blind, and these together with an SAE and an AE of mild dyspnoea, met dose stopping criteria for the study which did not progress to Cohort C.

#### *Evaluator Comment*

This was a dose escalation study designed to assess safety and tolerability of TIC with clear stopping criteria. The proposed dose of TIC was 90 mg bd and previous single doses of 600 mg and 540 mg had been well tolerated. Single doses of 900 mg, 1260 mg and 1620 mg TIC were planned for investigation in a stepwise ascending manner with clear pre-specified stopping criteria. Such criteria were fulfilled at the second dose of 1260 mg TIC. After the second cohort received treatment, multiple GI AEs were noted and the decision was made to break the blind for the entire cohort in order to assess whether GI stopping criteria had been met. Additionally, the SAE and AE of mild dyspnoea were considered indicative of dose limiting AEs.

With TIC, an increase in % neutrophils and decrease in % lymphocytes on Day 2 (within normal limits) which resolved by Day 4, was thought to be associated with physiological stress. One subject had increased total bilirubin to <1.5x the upper limit of normal (ULN) with TIC 1260 mg. Increases in serum uric acid with TIC and which resolved were consistent with previous studies. There were dose related increases in HR and ECG HR with the 1260 mg group, likely related to GI distress. One subject in the 1260 mg group had bifid T-waves and had a 10 s sinus pause 1h post dose. TIC did not appear to affect the QTc parameters. There were no clinically relevant changes in physical examinations. It was concluded that the upper limit of single dose tolerability of TIC was 900 mg.

There was one SAE with TIC 1260 mg (sinus arrest with high grade AV block and ventricular escape and syncope; recovered in <1 min) which was considered related to the study drug.

## Summary of Safety

### *Exposure*

There were 9333 patients exposed to the 90 mg TIC tablet in the Phase III study; 513 patients exposed to 90 mg TIC tablet, and 447 exposed to other doses/formulations of TIC in the Phase II studies; and 604 subjects exposed to various 90 mg TIC tablets, and 380 to other doses/formulations of TIC in the pharmacology studies.

For long term treatment data provided in the Phase III study, PLATO:

- 16325 (87.7%) patients (8190 TIC, 8135 CLO) completed 6 months
- 12938 (69.5%) patients (6487 TIC, 6451 CLO) completed 9 months
- 9487 (50.9%) patients (4768 TIC, 4719 CLO) completed 12 months
- 16254 (87.3%) patients (8171 TIC, 8083 CLO) completed the 1 month follow up visit.

TGA guidelines require safety data in 300-600 patients for 6months or longer. Hence the patient numbers exposed to long term TIC at the dose for registration, 90 mg, more than satisfies this requirement.

### *Adverse Events*

In the pivotal efficacy study (PLATO) patients receiving TIC experienced slightly more AEs compared to patients receiving CLO (73% vs 70%, respectively when bleeding AEs were included and 69% vs 67%, respectively when bleeding AEs were excluded). The AEs reported more commonly with TIC vs CLO were dyspnoea (12.0% TIC, 6.5% CLO), headache (6.5% TIC, 5.8% CLO) and epistaxis (6.0% TIC, 3.4% CLO). SAEs (including deaths and bleeding) were similar for TIC and CLO (20.2-20.3%) but were slightly less with TIC (17.7%) than with CLO (18.4%) when deaths were included but bleeding SAEs were excluded. More deaths occurred with CLO (5.8%) than with TIC (4.7%). More TIC patients discontinued due to AEs than CLO patients both when bleeding AEs were included (7.4% vs 5.4%, respectively) and when they were excluded (5.3% vs 4.5%, respectively).

Thus in the pivotal study up to 12 months, although AEs, SAEs and DAEs were slightly greater with TIC than with CLO, deaths were less common. So the safety profile of TIC is not inferior to that of CLO.

### *Specific AEs*

#### *Bleeding*

There was no significant difference between TIC and CLO for the primary safety endpoint, PLATO defined 'total major' bleeding nor for 'Major fatal/life threatening' bleeding or TIMI defined 'major+minor' or TIMI defined 'major' bleeding. There was significantly more 'combined major+minor' bleeding with TIC compared to CLO as a result of increased 'minor' bleeding with TIC. There was no difference between groups for CABG or angiography related bleeding, however PCI related bleeding was greater with TIC. There were more non-procedural bleeding events with TIC than with CLO but no difference for non-procedural fatal or major life threatening/fatal bleeding. There were more intracranial haemorrhages and fatal intracranial haemorrhages with TIC than with CLO but less overall fatal bleeding. No risk factors for overall bleeding or intracranial haemorrhage were identified.

### *Dyspnoea*

Dyspnoea was more common with TIC than with CLO. It occurred more in older patients and those with baseline dyspnoea, COPD, asthma or CHF but was not associated with heart failure or lung disease.

### *Cardiac arrhythmias*

Ventricular pauses occurred more commonly with TIC than with CLO but were generally asymptomatic and not correlated with clinically relevant events.

### *Renal function*

TIC may cause a reversible increase in serum creatinine. There was a reversible ~15% increase in serum uric acid with TIC compared to a non-reversible 7.5% increase in creatinine with CLO but rate of gout remained the same for both.

### *Hepatic function*

No dose adjustment was required for use of TIC in patients with hepatic impairment.

### *Cancers*

There were no safety concerns regarding neoplasms.

### *Subpopulations*

TIC AEs appeared to increase with age and with female gender.

## **List of Questions**

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated. The clinical evaluator directed the following questions. Note that this does not include a number of questions regarding the PI which are outside the scope of this AusPAR.

1. Regarding the subgroup interaction seen for the region of North America in the PLATO study being possibly associated with aspirin dose, what further work is the sponsor planning, in order to determine whether this interaction is a true or chance finding?
2. In PLATO, was there an analysis of primary endpoint in those patients who actually received only medical management?

The sponsor provided an adequate response to the issues raised by the clinical evaluator.

## **Clinical Summary and Conclusions**

The sponsor provided a program of studies to justify registration of Brilinta (ticagrelor; 90 mg) tablets in the prevention of thrombotic events (CV death, MI and stroke) in patients with ACS (UA, NSTEMI or STEMI) including patients managed medically and those who are managed with PCI (with or without stent) or CABG. The advantages of TIC over CLO are: quicker onset of action, quicker offset of action, lower interpatient variability, and greater inhibition of platelet aggregation and greater clinical efficacy without an increase in bleeding risk. TIC is not currently registered.

In summary,

The PD studies demonstrated:

- TIC or TIC+ASA inhibited (in a dose related manner) ADP and collagen induced IPA to a greater degree (faster, more complete, and with less variability) compared to CLO or CLO+ASA in healthy subjects.

- Therapeutic doses of TIC increased BT with no relationship to dose in healthy subjects and in patients with ASD.
- TIC+ASA inhibited (in a dose related manner) ADP induced IPA to a greater degree (faster onset, greater maintained effect, faster offset) compared to CLO+ASA in patients with stable CAD/ASD.
- A patient could miss a dose of TIC and still maintain equivalent IPA effect for 24 h as if taking CLO.
- A patient could switch directly from CLO to TIC without a washout period and increase antiplatelet effect by ~26%.
- TIC inhibited ADP induced IPA to a greater degree compared to CLO in patients with NSTEMI, whether CLO pretreated (who gained additional antiplatelet effect) or CLO naïve.
- A supra therapeutic dose of TIC did not increase the QTcX interval to a clinically significant degree compared to pbo.
- Serum uric acid levels reversibly increased ~10% with TIC.
- TIC did not affect respiratory parameters in a clinically significant way in healthy subjects and in patients with mild asthma or COPD, compared to pbo.
- TIC was not affected in a clinically significant way by age, gender, race or severe renal or mild hepatic impairment.
- Exposure of TIC was decreased by rifampin.
- Platelet aggregation effects of TIC were not affected by heparin, enoxaparin or aspirin; and TIC did not affect heparin (aPTT, ACT) or enoxaparin (anti-factor Xa).
- TIC did not affect endogenous hormone levels after oral contraceptive Nordette.
- Platelet aggregation effects of TIC were not affected by desmopressin, so desmopressin is unlikely to be of use in reversing bleeding due to TIC.

The PK studies demonstrated:

- For single and multiple dose TIC (up to 540 mg and up to 600 mg od or 300 mg bd, respectively) and AR-C124910XX in healthy subjects, extent of exposure and peak plasma concentrations increased approximately dose proportionally;  $t_{max}$  was rapid for both TIC (1.25-3.00 h) and AR-C124910XX (1.5-4.0 h), and  $t_{1/2}$  was ~7-16 h, appropriate for bd dosing. Intersubject variability was low. Steady state was reached by ~Day 2.
- PKs in patients with atherosclerosis/stable CAD were similar to those in healthy subjects. Extent of exposure and peak plasma concentrations increased approximately dose proportionally at therapeutic doses;  $t_{max}$  was rapid for both TIC and AR-C124910XX (~2.0-4.0 h), and  $t_{1/2}$  was ~10.0-12.5 h.
- PKs of TIC were similar for CLO responders and nonresponders and were similar in CLO pretreated and CLO naïve patients.
- TIC was excreted primarily in the faeces (~58%) and in the urine (~27%).
- Absolute bioavailability of TIC (oral/IV) was 36%; AR-C124910XX formation after oral intake occurs largely during absorption and first pass metabolism.
- TIC was absorbed in a decreasing manner as point of release moved distally in the GIT.

- PKs of TIC were clinically unaffected by food intake.
- CLO tablets used during PLATO were bioequivalent to marketed CLO and TIC tablets used during PLATO were bioequivalent to those for marketing.
- A supra-therapeutic plasma concentration of TIC did not increase the QTcX interval to a clinically significant degree compared to pbo.
- There was no relationship between plasma concentrations of TIC and serum uric acid, xanthine or hypoxanthine levels.
- Plasma concentrations of TIC had no effect on respiratory parameters in healthy elderly subjects or in patients with mild asthma or mild to moderate COPD.
- TIC was not affected in a clinically significant way by age, gender, race, or severe renal or mild hepatic impairment. No dose adjustment is required for any of these factors.
- Drug interaction studies showed:
  - PKs of TIC were significantly affected by ketoconazole (strong CYP3A4 inhibitor), diltiazem (moderate CYP3A4 inhibitor) and rifampin (CYP3A and P-gp inducer)
  - PKs of TIC were not significantly affected by oral and IV midazolam, simvastatin, atorvastatin, tolbutamide, digoxin, ASA, IV heparin, SC enoxaparin or desmopressin
  - TIC significantly affected PKs of oral and IV midazolam (weak CYP3A5 inhibitor), simvastatin, atorvastatin, digoxin and ethinyl oestradiol (as ethinyl oestradiol / levonorgestrel)
  - TIC did not significantly affect PKs of diltiazem, tolbutamide or levonorgestrel (as ethinyl oestradiol / levonorgestrel)
  - There was no drug interaction study with warfarin
- Thus, TIC is metabolised by CYP3A4 to AR-C124910XX so strong CYP3A4 inhibitors should be avoided with TIC but moderate CYP3A inhibitors can be given with TIC, and CYP3A4 inducers can be given with TIC although exposure may be decreased. Clinical significance of the effect of TIC on simvastatin, atorvastatin and digoxin should be considered when coadministered. Digoxin levels should be monitored.

The single pivotal efficacy study demonstrated that in hospitalised patients with an index event of non-ST or ST segment elevation ACS and at high risk of a secondary thrombotic event:

- TIC was significantly better than CLO in preventing an event in the composite of CV death, MI (excluding silent MI), and stroke over a 12 month period (Primary Efficacy Endpoint).
- TIC was significantly better than CLO in preventing the individual endpoints of CV death and MI but not stroke, over a 12 month period.
- TIC was nominally better than CLO in preventing all cause mortality over a 12 month period,  $p < 0.05$ , although the result was not significant.
- TIC was significantly better than CLO in achieving the primary efficacy endpoint over the first 30 days, and from after the first 30 days and up to 12 months, following an ACS event

- Age, gender and race had no clinically significant effect on the primary efficacy endpoint.
- Final diagnosis (NSTEMI, STEMI, UA) had no clinically significant effect on the primary efficacy endpoint.
- A significant effect of region on the primary efficacy endpoint lead to the *post hoc* suggestion that high dose aspirin coadministered with TIC might decrease efficacy of TIC on the primary efficacy endpoint.
- Intended treatment (invasive vs medical management) had no clinically significant effect on the primary efficacy endpoint.
- Actual treatment had no clinically significant effect on the primary efficacy endpoint for those patients receiving PCI or CABG. No analysis was given in those patients who actually received only medical management, however as these analyses are akin to a per protocol analysis, they provide supportive rather than pivotal data.

***Comment regarding the use of a single pivotal study***

Despite the need to further examine the subgroup data for the North American ‘region’ subpopulation (and possible high dose aspirin involvement), the evaluator considered the single pivotal study provided was “compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency” and hence complies with TGA-adopted EU guidelines regarding the use of a single pivotal study in a submission:<sup>8</sup>

- the mechanism of action of TIC was known;
- the hypothesis was plausible;
- the Phase I and Phase II data were extensive and convincing;
- there were no indications of a potential bias;
- inclusion of STEMI and NSTEMI ACS patients (managed both medically and with interventions) enabled results to be applicable to the entire ACS population;
- NNT of 54 for the primary endpoint (54 patients need to be treated to prevent one event of {CV death, MI or stroke}) demonstrated clinical relevance;
- the primary endpoint had a narrow confidence interval (0.77, 0.92) and a p-value of 0.0003 which is “considerably stronger than  $p < 0.05$ ”;
- analysis of the primary endpoint by 25 pre-specified and 6 *post hoc* subpopulations identified only one that required further examination (region);
- no study centre dominated results.

The safety studies demonstrated:

- The safety profile of TIC was consistent with the current standard of care, CLO. In the pivotal study up to 12 months, there were slightly more AEs, SAEs, and DAEs with TIC compared to CLO but there were fewer deaths.

<sup>8</sup> EMEA, Committee for Proprietary Medicinal Products (CPMP), 31 May 2001. Points to Consider on Application with 1. Meta-analyses, 2. One Pivotal Study, CPMP/EWP/2330/99.

- There was no significant difference between TIC and CLO for the primary safety endpoint, PLATO defined 'total major' bleeding nor for 'Major fatal/life threatening' bleeding or TIMI defined 'major+minor' or TIMI defined 'major' bleeding. There were fewer overall fatal bleeds with TIC but more fatal intracranial bleeds, compared to CLO. There was increased 'minor' and 'minimal' bleeding with TIC compared to CLO. No risk factors for intracranial bleeding were identified.
- There is an increased rate of dyspnoea with TIC compared to CLO, but no dose adjustment is required.
- AEs with TIC appeared to increase with age and with the female gender.

A pre-specified safety efficacy composite endpoint in PLATO found that TIC was significantly better than CLO for combined (prevention of CV death, MI, and stroke; CABG related PLATO defined fatal/life threatening bleeding; and non CABG related PLATO defined major bleeding) with ARR 1.4%, RRR 8%, NNT 71, p=0.0257.

### ***Comments regarding the Indication***

1. Whilst the wording of the indication is accurate and consistent with wording of indications for similar drugs (Effient [prasugrel] and Plavix [clopidogrel]), it runs the risk of being misinterpreted to mean TIC is superior to CLO in the prevention of the secondary individual endpoints, CV death, MI and stroke. Evidence was provided to support this in the case of CV death and MI but there was insufficient evidence to support this in the case of stroke.

Failure to show superiority does not prove equivalence, nor does it prove non-inferiority. A negative result in a superiority trial could simply mean there is no evidence of a difference (for example if the study was not powerful enough to show a small difference). The NNT figures appear to suggest that one patient will have a stroke for every 500 patients treated with TIC compared to CLO. But this statistically insignificant finding needs to be offset by the statistically significant findings that one patient will fail to have a CV death, MI or stroke for every 53 patients treated with TIC compared to CLO; one patient will fail to have a CV death for every 91 patients treated with TIC compared to CLO; and one patient will fail to have an MI for every 91 patients treated with TIC compared to CLO. The TGA-adopted EU guidelines state that a concern with composite outcome measures is that an adverse effect on one of the components of a composite outcome measure may be masked by the composite outcome, but "there is no general agreement how much less than statistical significance in the wrong direction will generate suspicion of an adverse effect".<sup>6</sup>

Thus, the most accurate indication statement in this case would include a phrase to the effect that TIC has been proven superior to CLO in the prevention of CV death and MI but TIC has not been proven superior to CLO in the prevention of stroke. The evaluator indicated that such an addition would not aid the 'readability' or clarity of the indication, and instead suggested adding the shorter sentence, "Brilinta is not indicated for the prevention of stroke alone."

2. In PLATO, power calculations were given for the full analysis set and for the set of patients with intent for invasive management at randomisation but not for the subgroups of patients medically managed; those managed with PCI and those managed with CABG. It would be incorrect to leave all the various subgroups off the indication as all the subgroups were included in the study that produced the superiority results. In this case consideration should be given to statistically significant results in the individual subgroups, the fact that those subgroups were appropriately defined and their analyses pre-specified and the overall results for the trial (that is the positive primary endpoint

results) which can indicate treatment effects if the trial was designed with insufficient power for the individual subgroups.<sup>9</sup>

The evaluator believed that overall the submission supports the efficacy/safety claims for TIC.

Thus, it was recommended that Brilinta (ticagrelor; 90 mg) tablets be registered *for the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with Acute Coronary Syndromes (unstable angina, non ST elevation MI or ST elevation MI) including patients managed medically, and those who are managed with percutaneous coronary intervention (with or without stent) or coronary artery-bypass grafting.*

## V. Pharmacovigilance Findings

### Risk Management Plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

### Safety Specification

The sponsor identified the following risks:

#### Important identified Risks

- Increased risk of bleeding
- Dyspnoea

#### Important Potential Risks

- Renal impairment

#### Important Missing Information

- Use in children
- Use in pregnant and lactating females

The clinical evaluator found that the Safety Specification reflects the safety information in the submission. However consideration should be given to a number of points.

Under 'Limitations of the human safety database' it states that "a wide range of ethnicities was studied". Whilst this is true, it should be clearly stated in the main text that the vast majority of patients studied were Caucasian and whilst perhaps not as relevant to the Australian population as for other countries, it should be stated that the number of Black patients in the PLATO study was particularly low initially (112 TIC, 110 CLO) and even lower by 12months (34 TIC, 21 CLO).

Under 'Important identified risks', the data regarding intracranial haemorrhage is discussed along with the conclusion that the clinical significance is not known. Although fatal intracranial haemorrhage with TIC was 'balanced' by other fatal bleeds with CLO, the evaluator found that intracranial haemorrhage should be particularly mentioned in the pharmacovigilance plan because no explanation has been forwarded to account for the greater number of intracranial haemorrhage with TIC compared to CLO.

<sup>9</sup> Cook DI, GebSKI VJ, Keech AC. Subgroup analysis in clinical trials. MJA 2004; 180: 289-291.



Although aspirin dose has been identified as potentially affecting an efficacy outcome but had no effect on bleeding outcomes, if it is a true effect (that a patient taking a higher aspirin dose is at greater risk of the primary event) this would reflect a safety issue of coadministration of TIC with aspirin and should therefore be mentioned at some point in the Safety Specification. In addition to the sponsor outlining what further investigations they are performing, aspirin dose should be recorded for any reported event and the data analysed at regular intervals, until it is known whether this is a true effect or a chance finding.

The OPR reviewer recommended that interactions involving CYP3A4 should be added as an identified risk.

### **Pharmacovigilance Plan and Risk Minimisation Activities**

The sponsor proposed routine pharmacovigilance and risk minimisation measures for all risks and areas of missing information.<sup>10,11</sup> In addition, the sponsor indicated it would explore the feasibility of conducting studies to clarify the potential risk of renal impairment in the early post-launch period.

The pharmacovigilance and risk minimisation plan was accepted by the OPR reviewer pending assessment of the following issues which required closer consideration:

- Renal impairment

The sponsor was requested to provide further information about ticagrelor use in various degrees of renal impairment.

- Use in pregnancy

More information was requested concerning the method of pharmacovigilance in this area.

- Use during coronary artery bypass surgery
- Interactions with other anticoagulation agents

Both of these issues were related to information in the Product Information which is beyond the scope of this AusPAR.

- Interactions with CYP3A4

The sponsor was requested to list this as a potential risk and provide more information on the issue.

With the exception of the final point, the sponsor provided an acceptable response to all issues raised.

<sup>10</sup> Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

<sup>11</sup> Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

## VI. Overall Conclusion and Risk/Benefit Assessment

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

### Quality

The quality evaluator recommended approval with respect to chemistry and quality control. In relation to bioavailability, it was noted that the absolute bioavailability of ticagrelor was 36% and food increased its AUC by 21% and  $t_{max}$  by 45 minutes but did not alter  $C_{max}$ . The AUC of the ticagrelor's active metabolite was not affected by food. The formulation of the product used in the Phase III pivotal trial was the same as proposed for marketing. Five bioavailability studies were submitted that examined different tablet compression, food effects, bioequivalence between tablets containing micronised vs non-micronised ticagrelor and bioequivalence for the pilot batch of tablets used in the pivotal clinical trial and the commercial batch. PSC has also considered this submission and had no objections on pharmaceutical or biopharmaceutical grounds.

### Nonclinical

The nonclinical evaluator had no objections to the registration of ticagrelor for the proposed indication. The data package was extensive and of high quality. The nonclinical evaluator commented that ticagrelor binds reversibly with high affinity for P2Y<sub>12</sub> receptors and does not require metabolic activation. It acts to inhibit platelet aggregation in a concentration dependent manner. A close relationship was seen between pharmacodynamic and pharmacokinetic profiles of ticagrelor. Ticagrelor augments adenosine induced coronary blood flow and is an antagonist of a receptor that mediates ischaemia induced tissue damage. Ticagrelor inhibits organic anion transporters and renal secretion of urate but increases in plasma levels were not seen in animals. Safety pharmacology did not raise issues of clinical concern and no dyspnoea was consistently seen in rats. Pharmacokinetic studies indicated dose proportionality and ticagrelor is a P-glycoprotein substrate and weak P-gp inhibitor. It is widely distributed and rapidly eliminated. It is metabolised by and inhibits CYP3A4 and 3A5. Toxicity studies were performed in rats, mice, rabbits and marmosets which showed stomach irritancy, distended intestines and elevations in haemopoiesis which may indicate bleeding. Genotoxicity assays were negative and there was no increase in tumour incidence in male and female mice or male rats, but there was an increase in uterine adenocarcinoma in female rats at 30 times human exposure which was considered species specific and not clinically relevant. There were no significant effects on fertility, embryofetal development or pre/post-natal development.

### Clinical

#### Clinical Evaluation

The clinical evaluator reviewed the submitted data, which relies on the pivotal PLATO trial in 18,624 patients exposed to ticagrelor for a mean 246 days. The dataset included the following studies:

- 45 pharmacology studies
- 1 clinical study (PLATO)
- 4 Phase II supportive studies in different populations (DISPERSE 2 in ACS)

The clinical evaluator recommended approval. The concerns noted by the evaluator in this submission included:

- The evidence to support the inclusion of stroke in the indication
- Power calculations for the subgroups of patients managed medically, with PCI or CABG.
- The use of high dose aspirin
- Increased dyspnoea with ticagrelor

## Pharmacology

The following comments were noted from the clinical evaluation report:

- Clopidogrel 75 mg od only partially blocked the P2T receptor (46-53%) with slow onset and high variability of inhibition whereas the addition of ticagrelor demonstrated further inhibition of 70-97%.
- Multiple dose ticagrelor+ASA inhibited both ADP and collagen induced IPA to a greater degree compared to multiple dose clopidogrel+ASA and compared to ASA.
- Loading dose ticagrelor inhibited ADP induced IPA to a greater degree compared to loading dose clopidogrel.
- Single and multiple dose ticagrelor showed a dose related inhibition of ADP induced platelet aggregation.
- All doses of ticagrelor increased bleeding times with no relationship to dose or plasma concentration, except for high doses of ticagrelor 900 mg and 1260 mg showing a dose related increase.
- In patients with stable coronary artery disease, the effect of ticagrelor 90 mg bd+ASA on IPA showed a more rapid onset, a greater maintained maximum effect and a more rapid offset, compared to clopidogrel 75 mg od+ASA. Thus, a patient could miss a dose of ticagrelor and still maintain equivalent IPA effect for 24 h as if taking clopidogrel.
- In patients with stable coronary artery disease previously identified as clopidogrel nonresponders or responders, ticagrelor 90 mg bd+ASA was superior to clopidogrel +ASA in achieving >10% and >50% inhibition of ADP induced platelet aggregation but the effect was not statistically significant for the primary endpoint of >10% 4 h post dose at steady state in clopidogrel nonresponders. Patients can switch directly from clopidogrel to ticagrelor treatment without a washout period, so antiplatelet effect will be maintained and increase by ~26%.
- In patients with non-ST segment elevation ACS in the previous 48 h, accumulation of ticagrelor and its metabolite after multiple doses of ticagrelor was demonstrated from Day 1 to 4 weeks.
- In patients with atherosclerosis, all doses of ticagrelor increased bleeding times compared to clopidogrel, with no relationship to dose.
- A suprathreshold dose of ticagrelor (900 mg) did not increase the QTc interval in a clinically significant way compared to placebo.
- Serum uric acid levels increased approximately 10% in a reversible manner with ticagrelor and there was no relationship between ticagrelor plasma concentration and serum uric acid, xanthine or hypoxanthine levels.
- No clinically relevant changes in pulmonary function tests were seen with ticagrelor in healthy subjects (doses of 900 mg, 1260 mg), elderly subjects (doses of 450 mg, 180 mg bd) or in patients with mild asthma or COPD (doses of 450 mg, 180 mg bd) compared to placebo. Ticagrelor plasma concentrations had no effect on respiratory parameters.

- Near peak IPA was maintained from 2-8 h post dose in young and elderly, male and female healthy volunteers. Exposure to ticagrelor was higher in females compared to males (by 40-50%) and higher in the elderly compared to the young (by 50-60%).
- The effect of ticagrelor on platelet aggregation was not affected to a clinically significant degree in the presence of severe renal impairment or mild hepatic impairment. Severe renal impairment had no clinically relevant effect on the pharmacokinetics of ticagrelor and mild hepatic impairment resulted in increased exposure to ticagrelor due to decreased elimination.
- Bleeding time was generally more prolonged, slower to recover to baseline and more variable, in Japanese compared to Caucasian subjects on ticagrelor. There were no significant differences in exposure to ticagrelor between Japanese and Caucasian subjects although another study indicated increased exposure.
- Ketoconazole 200 mg bd with ticagrelor 90 mg markedly increased the AUC of ticagrelor by 7.3 fold and  $C_{max}$  by 2.4 fold and decreased AUC by 56% and  $C_{max}$  by 89% of the active metabolite.
- Diltiazem 240 mg od (a moderate CYP3A4 inhibitor) with ticagrelor 90 mg increased ticagrelor's AUC by 174% and  $C_{max}$  by 69% and decreased  $C_{max}$  of the active metabolite by 38% while addition of ticagrelor to diltiazem did not affect pharmacokinetics of diltiazem.
- Rifampicin 600 mg (a CYP3A and P-gp inducer) with ticagrelor 180 mg had no effect on  $IPA_{max}$  but decreased ticagrelor's AUC by 86% and  $C_{max}$  by 73% and decreased the metabolite's AUC by 46%.
- An oral contraceptive, Nordette, did not affect the endogenous hormone levels when taken with ticagrelor but addition of ticagrelor 90 mg bd to Nordette 0.03/0.15 mg mane increased exposure to ethinyl oestradiol by 20-30% but did not affect levonorgestrel.
- Desmopressin 0.3 µg/kg did not significantly affect the pharmacokinetics of ticagrelor 180 mg bd or platelet aggregation and bleeding time effects.
- Midazolam 7.5 mg (a weak CYP3A5 inhibitor) with ticagrelor 400 mg od decreased the extent of exposure and peak plasma concentration of midazolam and 4-OH midazolam (but not 1-OH midazolam) while addition of midazolam 7.5 mg to ticagrelor 400 mg did not affect pharmacokinetics of ticagrelor.
- Simvastatin 80 mg with ticagrelor 180 mg bd increased simvastatin's AUC by 56% and  $C_{max}$  by 81% while pharmacokinetics of ticagrelor were unaffected.
- Atorvastatin 80 mg with ticagrelor 90 mg bd increased atorvastatin acid's AUC by 36% and  $C_{max}$  by 23% while pharmacokinetics of ticagrelor were unaffected.
- Tolbutamide 500 mg with ticagrelor 180 mg did not significantly affect the pharmacokinetics of tolbutamide or ticagrelor.
- Digoxin (P-gp substrate) 0.25 mg od did not significantly affect ticagrelor's pharmacokinetics but ticagrelor 400 mg significantly increased digoxin's AUC by 28% and  $C_{max}$  by 75%.
- Aspirin, heparin and enoxaparin did not significantly affect the pharmacokinetics of ticagrelor. Platelet aggregation effects of ticagrelor were unaffected by concomitant aspirin, heparin or enoxaparin. APTT and ACT following heparin were unaffected by

concomitant ticagrelor and anti-factor Xa effects of enoxaparin were unaffected by ticagrelor.

- Absolute bioavailability for ticagrelor was 36% and food had no clinically relevant effect on its PKs.
- The primary route of excretion for ticagrelor was via faeces (57.8%) and urine (26.5%). Ticagrelor and its main metabolite were the main compounds in plasma and faeces, but <1% of either was found unchanged in urine, indicating extensive metabolism of ticagrelor.
- Ticagrelor  $C_{max}$  and AUC increased with increasing dose in an approximately dose proportional manner;  $t_{max}$  was 1.25-2.00 h,  $t_{1/2}$  was 7-8.5 h.
- There was no relationship between ticagrelor concentration and increases in QTc on ECG.

### **Efficacy**

The efficacy data comprised a single pivotal trial (PLATO) along with some supporting data from DISPERSE 2.

#### **PLATO**

This was a randomised, double blind, double dummy, multicentre, multinational parallel design superiority trial of ticagrelor (180 mg loading dose and 90 mg bd maintenance with clopidogrel placebo) vs clopidogrel (300 mg – 600 mg loading and 75 mg maintenance dosing with ticagrelor placebo) in 18,624 patients (92% Caucasian, 72% male, 43% >65yo) who were hospitalised with acute coronary syndrome (NSTEMI or STEMI) and symptom onset within 24 hours.

The primary efficacy endpoint of time to first occurrence of any event from the composite of death from vascular causes (cardiovascular, cerebrovascular or unknown), myocardial infarction or stroke occurred statistically significantly less on ticagrelor than clopidogrel (9.8% vs 11.7%, HR 0.84 [95%CI 0.77, 0.92]) with a relative risk reduction of 16% (absolute risk reduction of 1.9%) over 12 months (NNT of 54) (Table 4). An analysis showed the benefit for ticagrelor was seen in the first 30 days and also subsequently to 12 months compared to clopidogrel. The components of the primary endpoint showed ticagrelor had a relative risk reduction in vascular death of 22% (ARR of 1.1%, NNT 91) and a relative risk reduction in myocardial infarction of 16% (ARR of 1.1%, NNT 91) compared to clopidogrel. However there was a non-significant increase in strokes on ticagrelor compared to clopidogrel (HR 1.17, 95% CI 0.91, 1.52).

Subgroup analysis of the primary endpoint by 31 pre-specified groups showed similar results for those <65/≥65 years but perhaps less efficacy in those ≥75 years compared to <75 years, similar results by sex, similar results for STEMI/NSTEMI but perhaps less efficacy in unstable angina and an interaction by region that indicated similar results for the rest of the world except for North America where clopidogrel may be better than ticagrelor.

The secondary efficacy endpoints are included in Table 4 and were in order of importance for the hierarchical testing process to reduce the risk of a type I error. The components of the primary endpoint were considered a secondary endpoint in the order testing.

- Ticagrelor was significantly superior to clopidogrel for the composite of CV death/MI (excluding silent MI)/stroke in the subgroup of patients intended for invasive management with an ARR of 1.7%, NNT of 59.

- Ticagrelor was significantly superior to clopidogrel for the composite of all cause mortality/MI (excluding silent MI)/stroke with an ARR of 2.1%, NNT of 48.
- Ticagrelor was significantly superior to clopidogrel for the composite of CV Death /total MI/Stroke/ severe recurrent cardiac ischaemia / recurrent cardiac ischaemia / transient ischemic attack /Other arterial thrombotic events with an ARR of 2.1%, NNT of 48
- All cause mortality showed a benefit of ticagrelor over clopidogrel but since stroke did not reach significance in the hierarchical testing order then all endpoints below this are considered supportive only, despite the nominal p-value of 0.0003.

An analysis of patients by the intent to manage them medically or invasively showed similar results for the primary endpoint however about 25% of the medically managed patients went on to invasive procedures. An analysis of the primary endpoint by those patients who only received medical management showed the event rate of 9.7% ticagrelor vs 12.8% for clopidogrel (HR 0.77, 95% CI 0.65, 0.91). Patients who received a stent during the study had a rate of stent thrombosis lower on ticagrelor than clopidogrel (1.3% vs 1.9%). Quality of life measures were similar for ticagrelor and clopidogrel.

The supportive study (DISPERSE 2) showed more deaths on ticagrelor than clopidogrel but less myocardial infarction.

### **Safety**

Safety data were derived from the pivotal study, 4 Phase II studies and 40 Phase I studies comprising 18624 patients exposed to ticagrelor 90 mg with 9333 patients from the PLATO trial (mean exposure 246 days) of which 3138 patients were exposed for >360 days. In PLATO, adverse events overall were slightly higher on ticagrelor (72.7% vs 69.6%) with the majority mild-moderate, serious adverse events were similar (20.2% vs 20.3%), deaths were less (4.7% vs 5.8%) and discontinuations were slightly higher (7.4% vs 5.4%). The most frequent adverse events were dyspnoea (12% vs 6.5), followed by headache (6.5% vs 5.8%) and epistaxis (6% vs 3.4%). There were no clinically significant differences across age, sex or race. Dyspnoea that was serious was higher on ticagrelor (0.7% vs 0.4%) and discontinuations due to dyspnoea were also higher (0.8% vs 0.1%). Cardiac arrhythmias occurred to a similar degree with ticagrelor and clopidogrel, ventricular pauses were more common on ticagrelor but tachyarrhythmia was more common on clopidogrel. Renal function adverse events were higher on ticagrelor (4.9% vs 3.8%) with most being haematuria (1.9% vs 1.6%). Increases in serum creatinine were also seen (0.5% vs 0.3%) along with percentage increases in creatinine (creatinine increase of 50-100% was seen in 7.4% ticagrelor vs 5.9% clopidogrel patients). Uric acid showed a reversible 15% increase with ticagrelor vs an irreversible 7.5% increase with clopidogrel, however gout incidence was similar. Hepatic adverse events were similar with no evidence of drug induced liver injury. Neoplasia rates were also similar between both drugs.

Pooled Phase II studies showed a dose response for bleeding and dyspnoea with ticagrelor but overall safety profiles similar to PLATO. No dose response was seen for brady- or tachyarrhythmia, renal adverse events or hepatic function. Safety data from the pharmacology studies was in keeping with PLATO. The dose ranging study DISPERSE 2 showed bleeding adverse events were slightly less on 90 mg BD vs 180 mg bd but dyspnoea and ventricular pauses were also seen.

### ***Bleeding in PLATO trial***

Bleeding events were based on the definitions used in the CURE trial for clopidogrel in unstable angina. The primary safety endpoint in PLATO was total major bleeding which comprised:

- Major fatal/life threatening bleeding (fatal, intracranial, intrapericardial with cardiac tamponade, hypovolaemic shock/hypotension, with decrease in haemoglobin (Hb) >50 g/L or requiring transfusion  $\geq$ 4 units) and
- Major other bleeding (significantly disabling, with decrease in Hb 30-50 g/L or requiring transfusion 2-3units plus major other bleeding).

The results show no significant difference between ticagrelor and clopidogrel for total major bleeding (HR 1.04, 95% CI 0.95, 1.13) with the frequency of events being similar (10.4% vs 10.1%) (Table 7). Of these, major fatal/life threatening were similar (5.3% vs 5.2%) and fatal bleeds were also similar (0.2% vs 0.3%). Other subcategories were mostly similar.

A comparison with TIMI bleeding categories showed no significant difference between PLATO defined total major bleeding (that is, major fatal/life threatening bleeding plus major other bleeding) and TIMI defined major+minor bleeding. However when CABG related bleeding was removed there were significantly more bleeds on ticagrelor for PLATO defined total major bleeding and TIMI defined major and major+minor bleeding. There did not appear to be a relationship with age, sex, race or aspirin dose. PLATO defined combined major+minor bleeding was significantly higher for ticagrelor than clopidogrel with a HR 1.11 (95% CI 1.03, 1.20) which was driven by an increase in minor bleeds (4.8% vs 3.8%) that were non-procedural. Major bleeding associated with procedures showed a higher rate for ticagrelor for PCI (1.6% vs 1.2%) which was mainly fatal/life threatening but a similar rate for angiography and CABG related procedures. All cause mortality following CABG was higher with clopidogrel (8.6% vs 4.3%). Intracranial haemorrhage was higher on ticagrelor (26 patients vs 15 patients). For non-procedural bleeding events, gastrointestinal and intracranial haemorrhages were higher on ticagrelor along with fatal intracranial haemorrhages but fatal gastrointestinal haemorrhages were less on ticagrelor than clopidogrel (Table 9). Discontinuation due to non CABG and non-procedural bleeding was higher with ticagrelor (2.3 vs 1%). Minimal bleeding was also higher on ticagrelor (17.2% vs 10.6%).

A pre-specified safety efficacy composite endpoint in PLATO found that ticagrelor was significantly better than clopidogrel for the combined prevention of CV death, MI, and stroke; CABG related PLATO defined fatal/life threatening bleeding; and non CABG related PLATO defined major bleeding with ARR 1.4%, RRR 8%, NNT 71, p=0.0257.

### **Risk Management Plan**

The Office of Product Review has accepted the RMP (June 2010) for ticagrelor however has disagreed with the sponsor not incorporating the potential increased risk of myopathy/rhabdomyolysis with simvastatin when it is taken with ticagrelor.

### **Risk-Benefit Analysis**

#### **Delegate Considerations**

#### ***Efficacy***

The PLATO study was a well designed trial that demonstrated superiority of ticagrelor over clopidogrel in reducing the composite of vascular death, MI and stroke over a 12 month period, with significant benefits for MI and vascular death but a non-significant

increase for stroke. The number needed to treat to prevent one primary event was 53. Ticagrelor appeared to show a benefit over clopidogrel for all cause mortality but this was not statistically significant. Other secondary composite endpoints were supportive of the primary endpoint and subgroup analyses showed the benefit was seen within 30 days of treatment. Age, gender and race did not significantly alter the endpoint, although those over 75 years may have reduced benefit. Results were similar for STEMI vs NSTEMI patients but slightly less for unstable angina patients. Similar results were seen for patients who had invasive vs medical management. The use of a single pivotal study was accepted and in line with the TGA-adopted EU guideline.

Regarding the examination of multiple endpoints in a clinical trial, the following comments are noted from the clinical report. Multiple endpoints in a trial increase the likelihood of false positive findings (type I error). Hierarchical analysis in a 2 arm study like PLATO allows for testing of multiple endpoints without adjustment of the type I error. The endpoints must be ranked in a pre-specified order of importance, no confirmatory claims can be based on variables equal to or below that of the first variable whose null hypothesis cannot be rejected, and the likelihood of false negative findings (type II error) increases as one moves down the hierarchy. The secondary endpoints and subgroup analyses give supportive evidence. The combination of a number of relatively rare events into a composite variable increases the power of the study and allows for a smaller sample size than would otherwise be required. The components should be analysed singularly, to provide supportive information. There is a concern that an adverse effect by the treatment on one or more components may be masked by the combined endpoint, however it is unclear on what amount of negative findings indicate an adverse effect. The clinically more important components should not be affected negatively. As mortality is more important than morbidity, then vascular death would be of greater importance than MI or stroke. The TGA guideline for treatment of NSTEMI state that the majority of studies are required to use a combined endpoint as the primary efficacy variable (for example death/new MI/refractory angina) and that at least the hardest objective components of death and/or MI should contribute to the treatment effect. Thus, the primary composite endpoint can be considered significant, even if the individual components of that endpoint lower in the hierarchical analysis do not reach significance.

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

The safety profile of ticagrelor compared to clopidogrel showed slightly higher rates of adverse events and discontinuation due to adverse events but similar serious adverse event rates and fewer deaths. Bleeding, dyspnoea, ventricular pauses, renal function (creatinine increases) and uric acid elevation were the main concerns. The primary safety endpoint of total major bleeding was not different to clopidogrel as was major fatal/life threatening and fatal bleeds. TIMI defined bleeding was also similar between ticagrelor and clopidogrel for total major bleeding and major+minor bleeding. Total major intracranial haemorrhage and major gastrointestinal bleeding, along with fatal intracranial haemorrhage were higher on ticagrelor but with less fatal gastrointestinal bleeds and overall fatal bleeds were similar to clopidogrel. Minimal bleeding was also higher on ticagrelor and there were differences seen when analysed by procedure status. A pre-specified safety efficacy composite endpoint in PLATO found that ticagrelor was significantly better than clopidogrel but this was supportive only. The RMP has been noted as acceptable.

### ***Indication***

The indication is long and reflects the trial population and results but is similar in style to that approved for prasugrel. The sponsor should consider an abbreviated wording that instead includes the trial population (that is, patients managed medically, and those who



are managed with percutaneous coronary intervention or coronary artery bypass grafting) in the Clinical Trials section of the PI. The information on stenting should be placed in the clinical trials section of the PI as it was not a primary endpoint of the trial.

### ***Bleeding***

The potential for increased bleeding is the major concern as noted from the nonclinical and clinical data.

### ***Dyspnoea***

The dyspnoea seen in the clinical trials was not replicated consistently in rat studies and the mechanism for this unexpected finding is unclear. Overall dyspnoea was higher on ticagrelor, as was serious dyspnoea and discontinuations due to dyspnoea. These patients were often older or had a history of respiratory problems but pulmonary function tests did not show a difference in FEV<sub>1</sub> for ticagrelor vs clopidogrel. Dyspnoea did not appear to be related to heart failure or lung disease.

### ***Elderly***

Exposure to ticagrelor was 50-60% higher in the elderly compared to younger patients and the PLATO trial showed similar efficacy results for those <65/≥65 years but perhaps less efficacy in those ≥75 years compared to <75 years for ticagrelor vs clopidogrel.

### ***Aspirin dose***

The TGA requested further information from the sponsor. The sponsor provided further data from the PLATO trial and references to guidelines that recommend a lower dose of aspirin be used. The FDA has extended its review of ticagrelor by 6 months until 20 July 2011 to further analyse this interaction and the appropriate aspirin dose.

### ***PLATO trial data***

The PLATO trial indicated an interaction by region (p=0.045) whereby the North American results showed a favouring of clopidogrel over ticagrelor whereas the other regions (Europe, Central and South America, Asia and Australia) favoured ticagrelor over clopidogrel. Given this, the sponsor undertook an evaluation of 31 pre-specified and *post hoc* demographic and clinical management factors to explain the interaction and found that aspirin dose accounted for 90-100% of the observed interaction. This was investigated further by the sponsor and thought not to be a regional interaction as such but an interaction by the maintenance dose of aspirin which is higher in the US compared with the rest of the world. A subgroup analysis of the PLATO trial for this finding found ticagrelor had greater efficacy for the primary endpoint when used with lower doses of aspirin but clopidogrel had greater efficacy at higher doses of aspirin. An independent group analysed the pivotal trial data and concluded in line with the sponsor that aspirin played a role in the primary endpoint.

In PLATO, 97.4% of patients received maintenance doses of aspirin. Of the total PLATO population, 17211/18624 (92%) patients were in the non-US population and only 1413/18624 (8%) patients were in the US population, thus a small population finding. The recommended dose of aspirin in PLATO was 75-100 mg daily in addition to study medication, according to local practice, unless patients were allergic or intolerant to aspirin. Following bare metal or drug eluting stenting, the protocol allowed an aspirin dose of 325 mg for up to 6 months as per the American College of Cardiology/American Heart Association Guidelines. A dose of 325 mg was the predominant dose of aspirin administered to North American patients and only 16% lowered this dose after 6 months, whereas Australia and other regions predominantly used a chronic dose of 75 to 100 mg

aspirin. An analysis of stenting found that a very similar proportion of patients had a stent in the US and non-US populations in both ticagrelor and clopidogrel arms.

The mean dose of aspirin used in the US population was 217 mg (median 325 mg), whereas in the non-US population it was 99 mg (median 100 mg). By aspirin dose, 84% of non-US population had an aspirin dose of  $\leq 100$  mg whereas only 38% of US population had such a dose. By contrast, 1.4% of non-US population had an aspirin dose of  $\geq 300$  mg compared to 45% of the US population. The cohort of Australian patients in PLATO showed a median dose of 100 mg aspirin and mean dose of 122 mg. Between 72.5% and 74.4% of Australian patients received a 100 mg aspirin dose and between 9.3% and 15% received a 150 mg aspirin dose. Those receiving a dose higher than 150 mg were between 9.3% and 10%, thus indicating 83.7-87.5% of patients on  $\leq 150$  mg aspirin.

An analysis of the primary endpoint indicates that the primary efficacy endpoint was significant for ticagrelor at aspirin doses of  $\leq 100$  mg (HR 0.79) but not for higher doses. An analysis by the sponsor of the primary efficacy endpoint by aspirin dose, as shown in Table 21, indicates a favouring of clopidogrel over ticagrelor at aspirin doses  $\geq 300$  mg with similar patterns for the components of the primary endpoint, except for stroke but the event numbers are low.

**Table 21: Univariate analysis of the primary endpoint and components by median aspirin dose**

Endpoint	Category	Ticagrelor (90 mg bd) N=9333			Clopidogrel (75 mg od) N=9291			Hazard Ratio (95% CI)	p-value
		n	Patients with Events	KM %	n	Patients with Events	KM %		
CV death/MI (exc silent)/Stroke	Low: $<300$ mg	8258	629 ( 7.6%)	8.1	8233	788 ( 9.6%)	10.3	0.79 (0.71, 0.88)	$<0.0001^{***}$
	High: $\geq 300$ mg	464	68 (14.7%)	15.8	492	50 (10.2%)	10.7	1.45 (1.01, 2.09)	0.0449*
All cause mortality	Low: $<300$ mg	8258	287 (3.5%)	3.7	8233	394 (4.8%)	5.2	0.72 (0.62, 0.84)	$<0.0001^{***}$
	High: $\geq 300$ mg	464	24 (5.2%)	5.4	492	21 (4.3%)	4.9	1.21 (0.68, 2.18)	0.5178
CV death	Low: $<300$ mg	8258	249 (3.0%)	3.2	8233	339 (4.1%)	4.5	0.73 (0.62, 0.86)	0.0002***
	High: $\geq 300$ mg	464	23 (5.0%)	5.1	492	16 (3.3%)	3.7	1.53 (0.81, 2.89)	0.1944
MI (exc silent)	Low: $<300$ mg	8258	377 (4.6%)	4.9	8233	467 (5.7%)	6.2	0.80 (0.70, 0.92)	0.0012**
	High: $\geq 300$ mg	464	50 (10.8%)	11.9	492	34 (6.9%)	7.3	1.57 (1.02, 2.43)	0.0412*
Stroke	Low: $<300$ mg	8258	99 (1.2%)	1.3	8233	87 (1.1%)	1.2	1.13 (0.85, 1.51)	0.3974
	High: $\geq 300$ mg	464	5 (1.1%)	1.0	492	7 (1.4%)	1.5	0.76 (0.24, 2.38)	0.6329

Patients that were ASA intolerant or allergic or who had missing data were not included in this analysis.

An analysis of bleeding events showed similar results for both aspirin groups in both treatment arms as seen in Table 22.

**Table 22: Number (%) of patients with PLATO defined bleeding events, by treatment and ASA maintenance dose**

Adverse effect	High-dose ASA <sup>a</sup> (≥300 mg)		Low-dose ASA <sup>a</sup> (<300 mg)	
	Ticagrelor 90 mg bid N=464	Clopidogrel 75 mg qd N=492	Ticagrelor 90 mg bid N=8258	Clopidogrel 75 mg qd N=8233
Major bleeding	46 (9.9%)	46 (9.3%)	834 (10.1%)	804 (9.8%)
Major+Minor bleeding	64 (13.8%)	58 (11.8%)	1176 (14.2%)	1064 (12.9%)
Non-procedural Major bleeding	14 (3.0%)	14 (2.8%)	207 (2.5%)	155 (1.9%)
Non-procedural Major+Minor bleeding	27 (5.8%)	22 (4.5%)	405 (4.9%)	290 (3.5%)

<sup>a</sup> Median ASA based on ASA usage from Day 2 to end of study drug period (or censored at primary event) for patients with at least 2 days of ASA.

AE Adverse event; ASA Acetylsalicylic acid; bid Twice daily dosing; qd Once daily dosing.

The sponsor has hypothesised a mechanism below to explain these findings and this is being investigated further in preclinical work:

*Data suggest that when a high degree of P2Y<sub>12</sub> inhibition is achieved (that is, by ticagrelor, prasugrel, or high clopidogrel response), thromboxane (TXA<sub>2</sub>)-dependent pathways of platelet activation are potently and consistently inhibited even in the absence of ASA. This gives rise to a hypothesis that ASA, especially at high doses, would not further improve platelet inhibition, but the additional dose-dependent reduction in prostacyclin (PGI<sub>2</sub>) levels could leave unopposed the thrombogenic and vasoconstrictive effect of ASA therapy. When a lower degree of P2Y<sub>12</sub> inhibition exists (that is, low-to-medium clopidogrel response), TXA<sub>2</sub> pathways are not potently inhibited. Thus, ASA can further improve platelet inhibition and thus to some extent counterbalance the detrimental effect on PGI<sub>2</sub> levels (that is, the net effect would be a decrease in the relative risk of thrombus formation). However since the antiplatelet effect of ASA will reach maximum at relatively low doses, the reduction in PGI<sub>2</sub> levels by higher ASA doses cannot be counterbalanced and this negative effect should be equal regardless of P2Y<sub>12</sub> antagonist used.*

#### Guidelines

Australian and European guidelines support a low dose of aspirin however they were prepared prior to the PLATO trial. The Therapeutic Guidelines Cardiovascular, Version 5, 2008, recommends a 75-150 mg dose be used for long term use in STEMI patients. The National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand “Guidelines for the management of acute coronary syndromes 2006” recommend long term management with 75-150 mg daily. The European Society of Cardiology guidelines on management of acute coronary syndromes also recommend a dose of 75-100 mg daily for NSTEMI-ACS and 75-160 mg following PCI.

#### European status

Ticagrelor was approved in Europe on 3 December 2010. The EMA noted that in the North American region, ticagrelor had a negative treatment effect compared to clopidogrel. The EPAR for Brilique states that “A remarkable finding is the lower efficacy of ticagrelor in the

North American population, although this is of less importance for the marketing authorisation in the EU as enough patients remain for evaluation of the target EU population (only 1300 patients in US).<sup>12</sup> A higher ASA dose was the main identifiable reason of the negative effect also for non-US patients". The approved Brilique (EU name) Summary of Product Characteristics aspirin dosage recommendation is "Patients taking Brilique should also take ASA daily, unless specifically contraindicated. Following an initial dose of ASA, Brilique should be used with a maintenance dose of ASA of 75-150 mg".

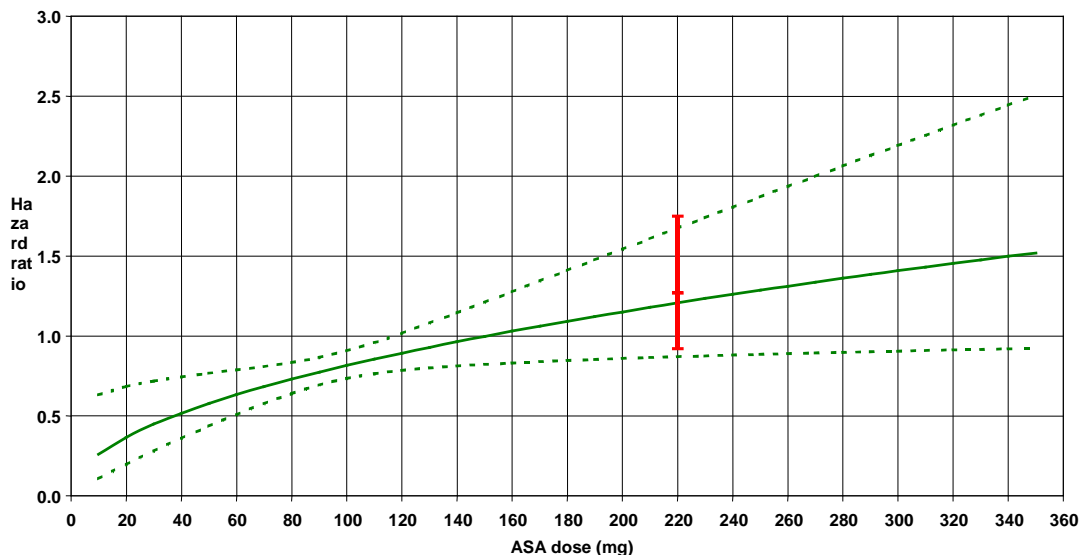
*Australian supportive registry and letters*

The sponsor has provided letters from Australian cardiologists supporting a low dose aspirin approach of 100-150 mg daily. This was supported by the CONCORDANCE registry, a prospective investigator initiated ACS registry in Australia covering 16 hospitals that follows up patients at 6 months and 2 years. The registry indicates that in those having PCI, discharge aspirin dose was ≤100 mg in 92% of patients and 100-150 mg in 5% of patients. Similar results were obtained for those not having PCI.

*Aspirin dose*

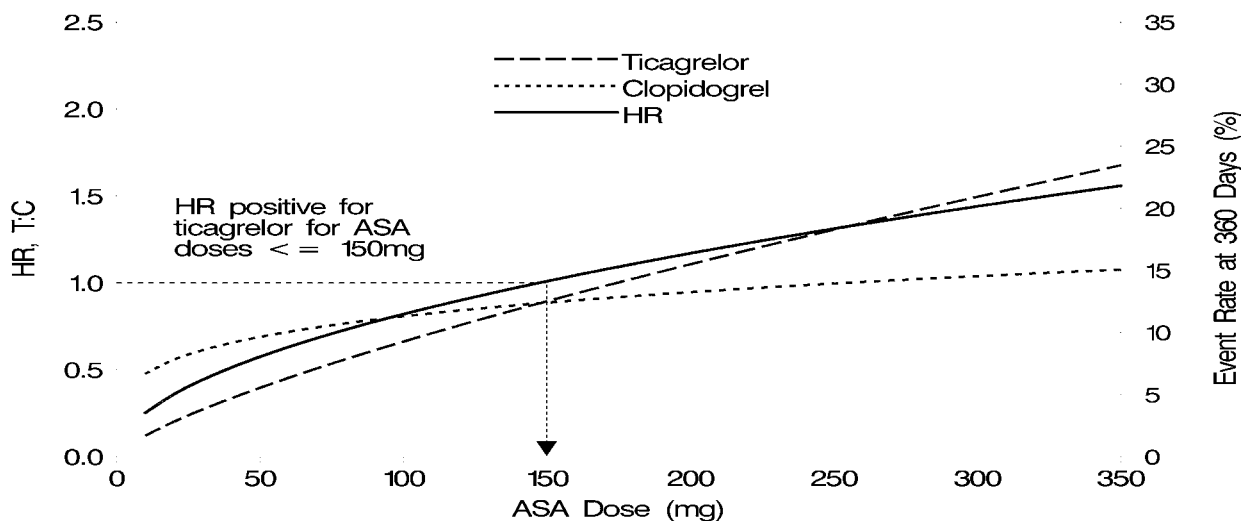
The ticagrelor PI proposes a precaution and dosing instruction that ticagrelor should be used with 75-150 mg daily aspirin and that doses >300 mg daily are not recommended. Both clopidogrel and prasugrel in Australia recommend 75-325 mg aspirin consistent with their trials. The sponsor analysed the primary endpoint for the change in the hazard ratio with increasing aspirin dose, that is, as the aspirin dose increases the hazard ratio also increases until ticagrelor is no longer superior to clopidogrel. As seen in Figures 1 and 2 for the non-US population, this crossover for the hazard ratio of 1 occurs at 150 mg aspirin. The upper limit of the 95% confidence interval crosses over at a hazard ratio of 1 at approximately a 120 mg aspirin dose.

**Figure 1: Cox regression analysis of the primary endpoint (non-US): HR, ticagrelor:clopidogrel and associated 95% confidence band. Also highlighted in red is the observed HR and 95% CI in US patients.**



<sup>12</sup> EMA. Assessment report for Brilique (EPAR). Available at: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Public\\_assessment\\_report/human/001241/WC500100492.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001241/WC500100492.pdf)

**Figure 2: Analysis of the primary endpoint by ASA dose as a continuous variable (Non-US cohort)**



ASA Acetylsalicylic acid; HR Hazard ratio.

Aspirin dose was not a baseline characteristic in the PLATO trial and a *post hoc* subgroup analysis of such data has the potential for drawing incorrect conclusions. The large number of subgroups tested without adjustment for multiplicity effects has the potential for the observed interaction by region to be a chance finding and it was noted by the sponsor that one less primary event in the North America region with ticagrelor and one more event with clopidogrel would have resulted in a treatment by interaction p value of >0.05. Nevertheless, given the implications for efficacy and the unexplained mechanism of this interaction, further analyses were undertaken.

Clinical practice and guidelines in Australia and Europe support the use of an aspirin dose of 75-150 mg and the approved dose of aspirin in the EU for use with ticagrelor is 75-150 mg. It appears that the concern raised of a difference in efficacy from use with aspirin is a matter pertaining to the dose of aspirin which was higher in North America than Australia/EU and therefore may be the explanation for the superior efficacy of clopidogrel observed with a higher aspirin dose. Therefore, a lower dose of aspirin (75-150 mg) was recommended here that is consistent with the results of the PLATO trial.

### **Drug Interactions**

Ticagrelor when given with ketoconazole markedly increased ticagrelor's exposure by 7.3 fold and  $C_{max}$  by 2.4 fold with markedly reduced exposure to the active metabolite. This could have significant effects on the safety profile for patients and therefore strong CYP3A4 inhibitors should not be used concomitantly. There was no drug interaction study conducted with warfarin which the sponsor should perform and an appropriate precaution should be included in the PI. Drug interaction with a moderate CYP3A4 inhibitor, diltiazem, showed ticagrelor's AUC increased 2.7 fold. This could pose safety risks of bleeding for patients given any moderate CYP3A4 inhibitor and strong precautionary advice should be included in the PI.

### **Food**

It was noted that food increased the bioavailability of ticagrelor by 21% but there was no change in  $C_{max}$ . This change is unlikely to be clinically significant and as a result the sponsor has proposed that the drug be given with or without food.

### **Data deficiencies**

There was no drug interaction study with warfarin or potent P-glycoprotein inhibitors. There was also no data on patients with moderate hepatic impairment and no data in children. Longer term data would have been useful to ascertain the longer term efficacy and safety.

### **Summary**

Ticagrelor when given with aspirin has demonstrated a superior efficacy profile to clopidogrel in the treatment of patients with acute coronary syndromes with a similar rate of total major bleeding, major fatal/life threatening and fatal bleeds as clopidogrel. However intracranial haemorrhage, fatal intracranial haemorrhage and gastrointestinal haemorrhage that were non-procedurally related were higher on ticagrelor but there was less gastrointestinal fatal bleeds. An increase in non CABG major bleeding and minimal bleeding was also seen. Dyspnoea was an unexpected safety finding that requires further investigation by the sponsor and other notable findings were ventricular pauses, creatinine increases and uric acid increases. The dose of aspirin was important as seen by the efficacy data favouring clopidogrel in the USA where higher doses of aspirin were used. Overall the submission appears approvable.

The Delegate proposed to approve this submission for the following indication:

*Brilinta, co-administered 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 should address the following issues in the Pre-ACPM response:

- What is the mechanism for the dyspnoea seen in the clinical trial program and how does the dyspnoea rate or rate of other respiratory adverse effects compare with data from other ADP antagonists acting via P2Y<sub>12</sub>-receptor?
- What further studies are planned for ticagrelor, including any further drug interaction studies, for example warfarin?
- Would the sponsor provide the results in a table for body weight and age (<65/≥65 years and <75/≥75 years) for the primary endpoint and major bleeding.

The Delegate also directed a question to the Advisory Committee on Prescription Medicines (ACPM):

- Should the use of ticagrelor with moderate CYP3A4 inhibitors be contraindicated given the 2.7 fold increase in exposure to ticagrelor when given with diltiazem?

### **Response from Sponsor**

#### **Dyspnoea**

Dyspnoea has been extensively investigated during the ticagrelor development program. Several studies have been conducted to elucidate the nature of dyspnoea in connection with ticagrelor treatment. They include a respiratory function study in elderly healthy volunteers, a study in volunteers with asthma and/or COPD, a Phase II Study in patients with stable CAD (the OFFSET Study) and a pulmonary function substudy in PLATO. None of these studies demonstrated an effect of ticagrelor on pulmonary function.

The mechanism of ticagrelor associated dyspnoea is unknown at this time. Currently, the proposed mechanism is a direct effect of adenosine because ticagrelor inhibits adenosine uptake into human erythrocytes, which could increase the adenosine plasma level in vivo. Furthermore, intravenous adenosine is associated with dyspnoea. Direct measurement of adenosine plasma levels is difficult due to its short half-life. Several nonclinical studies have been conducted. In one initial safety pharmacology study in the rat, a slight but significant and dose dependent increase in respiratory rates was seen. Further studies failed to show effects at similar or higher exposure levels. It was concluded that the rat model was too variable to produce reliable data on ticagrelor and, in the opinion of the sponsor, there are presently no suitable animal models for exploring ticagrelor associated dyspnoea. Although the exact mechanism of the dyspnoea remains unknown, there is no evidence that ticagrelor exposure is associated with lung toxicity or affects lung function. The most robust data available to the sponsor on the comparative rates of dyspnoea is from the PLATO study, which compared ticagrelor and clopidogrel. In PLATO, dyspnoea was more common in the ticagrelor group than in the clopidogrel group (13.8% vs 7.8%); however, few patients discontinued study drug because of dyspnoea (0.9% of patients in the ticagrelor group and 0.1% in the clopidogrel group). Information on the comparative rates of dyspnoea is included in the proposed Australian Brilinta PI under Adverse Effects/Dyspnoea section. Most dyspnoea AEs occurred soon after treatment, were mild to moderate in intensity and two thirds resolved prior to study completion.

#### ***Further Studies***

The following clinical studies are ongoing:

- A randomised, double blind, parallel group, International (Asian), multicenter study, to assess pharmacokinetic and pharmacodynamic profile of 2 doses of ticagrelor on low dose acetylsalicylic acid therapy on platelet aggregation in Japanese and Asian patients with stable coronary artery disease. The study report will be available in late 2011.
- 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. The study report will be available in 2014.
- A randomised, double blind, placebo controlled, crossover, single centre Phase I study to assess the effect of ticagrelor on adenosine induced coronary blood flow velocity in healthy male subjects. The study report will be available in mid 2011.
- A drug utilisation study, designed as a retrospective cohort study using the HEALTH Improvement Network (THIN) primary care database in the UK; this study is comprised of a drug utilization part extended with a follow up of selected outcomes. The study report will be available in late 2012.

Planned studies include:

- A sequential, open label study to compare the pharmacokinetics, pharmacodynamics, safety and tolerability of ticagrelor and venlafaxine (a serotonin norepinephrine reuptake inhibitor [SNRI] and a CYP2D6 substrate) given concomitantly in healthy subjects age 18 to 45 years. The study report will be available in mid 2012.
- An interaction study evaluating the potential effect of cyclosporine, a probe P-gp inhibitor at a high dose, on pharmacokinetics of ticagrelor in healthy volunteers, and the effects of ticagrelor on the pharmacokinetics of cyclosporine. The study report will be available in late 2012.

- A randomised, double blind, double dummy, parallel group, international (Asian), multicenter, Phase 3 study to assess safety and efficacy of ticagrelor on top of low dose acetylsalicylic Acid (ASA) versus clopidogrel on top of low dose ASA in Asian/Japanese patients with non-ST or ST elevation acute coronary syndromes (ACS). The study report will be available in late 2012.

The sponsor does not intend to conduct additional drug-drug interaction studies with warfarin. In a clinical pharmacology study, concomitant administration of ticagrelor with tolbutamide, a representative CYP2C9 substrate, had no effect on PK of tolbutamide or its primary metabolite, 4-hydroxytolbutamide; likewise, tolbutamide did not affect the PK of ticagrelor. This suggests that ticagrelor does not inhibit CYP2C9 in vivo; drugs metabolised via CYP2C9, such as S-warfarin, are therefore unlikely to be affected. Although no PK interaction is predicted, a PD interaction could still impact the degree of anticoagulation or international normalised ratio (INR), based on differential binding to albumin or other mechanisms. Also, PD interactions between anticoagulants and antiplatelet agents could result in an increased bleeding risk. Hence the proposed Australian Brilinta PI includes the appropriate precautionary statement within the Precautions/Bleeding Risk section.

### ***Body weight and age***

The data for the PLATO primary endpoint and major bleeding for subgroups of patients by body weight group and age group were provided. The results of this analysis are consistent with those in all PLATO patients for the primary composite efficacy endpoint and safety endpoints. No dose adjustment is needed based on weight or age for patients taking ticagrelor.

### ***Conclusion***

The sponsor agreed with the Delegate and the clinical, nonclinical and quality evaluators' positive recommendations to approve Brilinta for marketing in Australia. The sponsor also agreed with the Delegate's recommendation that the "difference in efficacy from use with aspirin is a matter pertaining to the dose of aspirin which was higher in North America than Australia/EU and therefore may be the explanation for the superior efficacy of clopidogrel observed with a higher aspirin dose". The PLATO data demonstrate that ticagrelor provides a clear CV benefit when used chronically with low dose ASA. In the primary analysis in PLATO, ticagrelor was superior to clopidogrel in reducing the rate of the composite efficacy endpoint after acute coronary syndromes (ACS) events. The primary endpoint was met with a hazard ratio (HR) 0.84 (95% confidence interval [CI] 0.77, 0.92, p=0.003). The recommendation for the chronic use of low dose ASA (75-150 mg) in the Australian PI is consistent with the PLATO trial and Australian guidelines/clinical practice.

### ***Advisory Committee Considerations***

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission for the indication:

*Brilinta, co-administered 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).*

In making this recommendation, the ACPM considered that the use of a single pivotal study was acceptable, and generally in line with the adopted EU guideline. The PLATO



study demonstrated superior efficacy of ticagrelor over clopidogrel. There may be a greater inhibition of platelet aggregation but this may be a dose effect. It was noted that those over 75 years may have reduced benefit.

However, the safety profile of ticagrelor compared to clopidogrel showed slightly higher rates of adverse events and discontinuation due to adverse events but similar serious adverse event rates and fewer deaths. The potential for increased bleeding is the major concern as noted from the nonclinical and clinical data. All doses of ticagrelor increased bleeding times with no relationship to dose or plasma concentration. For non-procedural bleeding events, gastrointestinal and intracranial haemorrhages were higher on ticagrelor along with fatal intracranial haemorrhages but fatal gastrointestinal haemorrhages were less on ticagrelor than clopidogrel. Minimal bleeding was also higher on ticagrelor.

Strong CYP3A4 inhibitors should not be used concomitantly as this could cause significant increases in exposure and  $C_{max}$  affecting the safety profile for patients. In regards to moderate CYP3A4 inhibitors, the committee advised that this was adequately addressed in the Precautions section of the PI. Longer term data on efficacy and safety would have been useful.

Clinical practice and guidelines in Australia and Europe support the use of an aspirin dose of 75-150 mg and the approved dose of aspirin in the EU for use with ticagrelor is also 75-150 mg. Australia also has an approved indication that includes co-administration with aspirin for ACS. The PLATO trial required patients to be on maintenance dosing of aspirin at 75-100 mg for Australia and therefore the indication should reflect the trial population dose.

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy, considered there is a favourable benefit-risk profile for this product.

The Committee was of the view that there was an element of promotion in the trade name which was unnecessary.

## **Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration of Brilinta tablets containing ticagrelor 90 mg indicated for:

*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).*

Among the specific conditions of registration were the following:

- The implementation in Australia of the ticagrelor (Brilinta) Risk Management Plan (RMP) Version 6, dated 17 March 2011, including all of the patient questionnaires referred to in the RMP, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.
- The sponsor must maintain close pharmacovigilance monitoring of the reporting of any adverse effects involving patients on both ticagrelor and statins metabolised by CYP3A4 and that there should be reporting of events in the PSURs.
- The sponsor is required to lodge, as evaluable data within the context of a Category 1 submission or submissions, the final clinical study reports of the three clinical trials described as ongoing and of the three clinical trials described as planned in the

*Sponsor's Response* above. These final clinical study reports are to be submitted to the TGA as soon as they are available.

## **Attachment 1. Product Information**

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at [www.tga.gov.au](http://www.tga.gov.au).

# BRILINTA<sup>®</sup>

ticagrelor

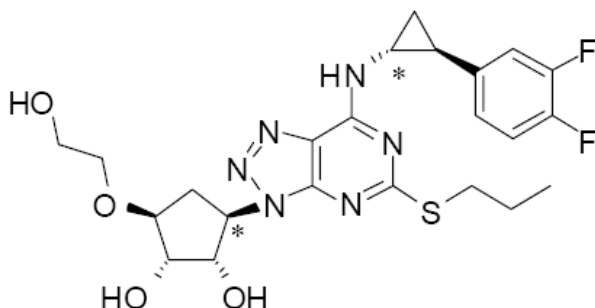
## PRODUCT INFORMATION

### NAME OF THE MEDICINE

Ticagrelor

Chemical Name (IUPAC): (1*S*,2*S*,3*R*,5*S*)-3-[7-[[*(1R,2S)*-2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol

The chemical structure of ticagrelor is:



CAS number: 274693-27-5

Molecular weight: 522.57

### DESCRIPTION

Ticagrelor is a white or off-white to pale pink crystalline powder. The log P (octanol/water) has been measured to > 4.0 at pH 7.4. The molecule has no pKa values within physiological range and does not demonstrate pH dependent solubility. It is non-hygroscopic, exhibiting no significant increase in water content after exposure at 40°C/75% RH.

Each tablet contains 90 mg of ticagrelor. The tablets also include the following excipients - mannitol, calcium hydrogen phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hypromellose, titanium dioxide, purified talc, macrogol 400, iron oxide yellow. BRILINTA does not contain gluten.

## PHARMACOLOGY

### *Mechanism of action*

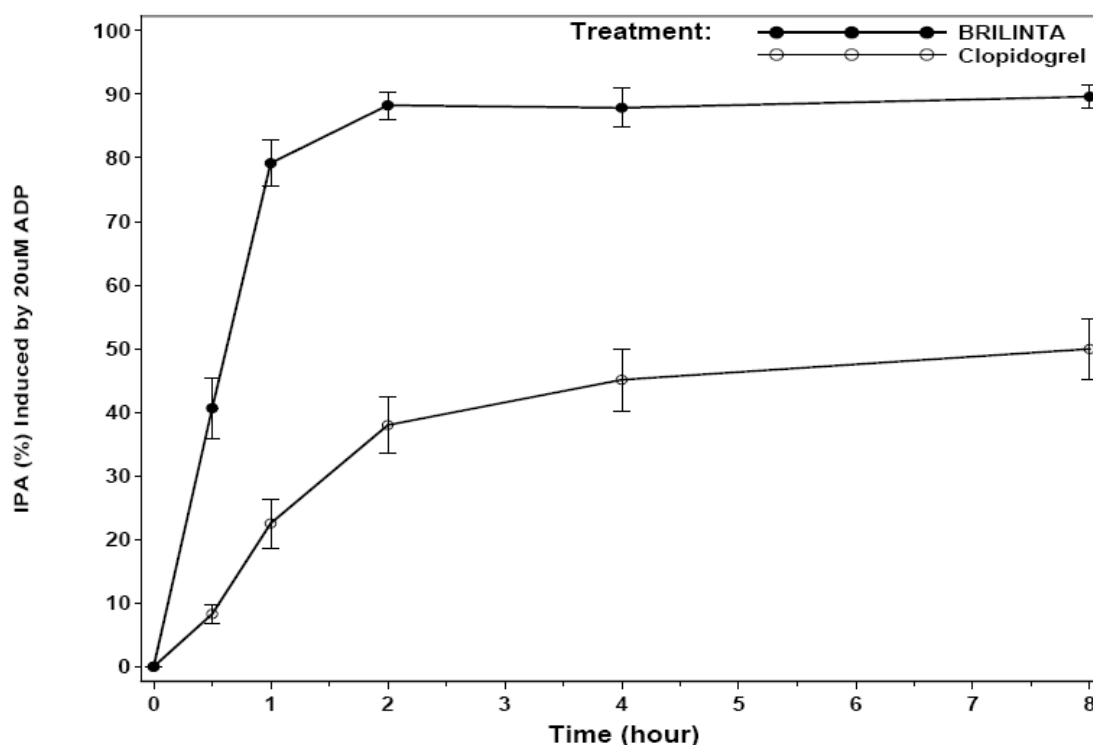
BRILINTA contains ticagrelor, a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), which is a selective and reversible adenosine diphosphate (ADP) receptor antagonist acting on the P2Y<sub>12</sub> ADP-receptor that can prevent ADP-mediated platelet activation and aggregation. Ticagrelor is orally active, and reversibly interacts with the platelet P2Y<sub>12</sub> ADP-receptor. Ticagrelor does not interact with the ADP binding site itself, but its interaction with platelet P2Y<sub>12</sub> ADP-receptor prevents signal transduction.

### *Pharmacodynamic effects*

#### **Onset of Action**

In patients with stable coronary artery disease on acetylsalicylic acid (ASA), ticagrelor demonstrates a rapid onset of pharmacological effect as demonstrated by a mean Inhibition of Platelet Aggregation (IPA) for ticagrelor at 0.5 hours after 180 mg loading dose of about 41%, with the maximum IPA effect of 87.9% to 89.6% by 2-4 hours post dose, see Figure 1. 90% of patients had final extent IPA >70% by 2 hours post dose. The high IPA effect of ticagrelor between 87%-89% was maintained between 2-8 hours.

**Figure 1 Mean final extent Inhibition of Platelet Aggregation (IPA) ( $\pm$ SE) following single oral doses of 180 mg BRILINTA or 600 mg clopidogrel in patients with stable Coronary Artery Disease (CAD)**

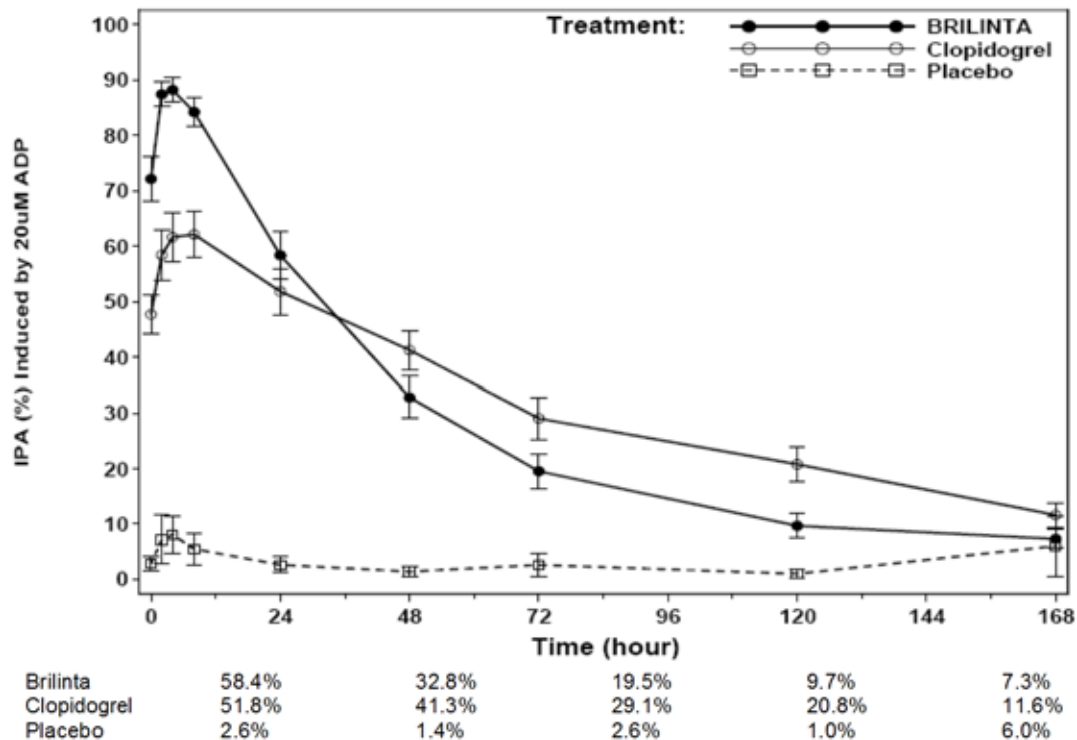


## Offset of Effect

After the ticagrelor and the active metabolite concentrations decline to a level less than that required for receptor saturation, IPA gradually decreases with declining plasma concentrations. Since ticagrelor binds reversibly, the recovery of platelet function does not depend on replacement of platelets. Ticagrelor has a faster rate of offset of IPA as compared to clopidogrel as determined by the slope of offset from 4-72 hours after last dose.

Median final extent IPA measured after the last dose of BRILINTA is approximately 20-30% higher for ticagrelor compared to clopidogrel. However, by 24 hours post-dose, %IPA is similar between ticagrelor and clopidogrel, indicating that patients who miss a dose of BRILINTA would have an IPA level comparable to those treated with once daily clopidogrel. In addition, %IPA is lower for ticagrelor from 72 hours through 7 days compared with clopidogrel. Mean %IPA for ticagrelor at 72 hours (Day 3) post last dose was comparable to clopidogrel at Day 5, and %IPA for ticagrelor at Day 5 was similar to clopidogrel at Day 7, which is not statistically different from placebo, see Figure 2.

**Figure 2 Mean final extent Inhibition of Platelet Aggregation (IPA) ( $\pm$ SE) following the last maintenance dose of 90 mg twice daily BRILINTA or 75 mg clopidogrel once daily or placebo**



## Responders to ticagrelor

The IPA induced by ticagrelor has less variability at peak plasma concentrations of ticagrelor and the active metabolite at peak plasma concentrations observed with the 90 mg bd dose compared to clopidogrel. Patients with stable coronary artery disease predetermined to have low IPA response to clopidogrel (non-responders), and given a concomitant dose of ASA, exhibited higher mean IPA response after administration of BRILINTA as compared to clopidogrel. In non-responders to clopidogrel, the IPA response to ticagrelor was observed to be higher and more consistent. BRILINTA treatment resulted in consistently higher IPA compared with clopidogrel, and this was apparent post dose for both responders and non-responders.

## Switching Data

Patients can be switched from clopidogrel to BRILINTA without interruption of anti-platelet effect. Patients switching from clopidogrel to BRILINTA results in an absolute IPA increase of 26.4% and switching from BRILINTA to clopidogrel results in an absolute IPA decrease of 24.5% (also refer to DOSAGE AND ADMINISTRATION). Switching from prasugrel to BRILINTA has not been investigated.

## Pharmacokinetics

Ticagrelor demonstrates linear pharmacokinetics. Exposure to ticagrelor and active metabolite AR-C124910XX are approximately dose proportional.

## Absorption

Absorption of ticagrelor is rapid with a median  $t_{max}$  of approximately 1.5 hours. The formation of the major circulating metabolite AR-C124910XX (also active) from ticagrelor is rapid with a median  $t_{max}$  of approximately 2.5 hours. The  $C_{max}$  and AUC of ticagrelor and the active metabolite increased in an approximately proportional manner with dose over the dose range studied (30-1260 mg).

The mean absolute bioavailability of ticagrelor was estimated to be 36%, (range 25.4% to 64.0%). Ingestion of a high-fat meal had no effect on ticagrelor  $C_{max}$  or the AUC of the active metabolite, but resulted in a 21% increase in ticagrelor AUC and 22% decrease in the active metabolite  $C_{max}$ . These small changes are considered of minimal clinical significance; therefore, BRILINTA can be given with or without food.

## Distribution

The steady state volume of distribution of ticagrelor is 87.5 L. Ticagrelor and the active metabolite is extensively bound to human plasma protein (>99.7%).

## Metabolism

CYP3A is the major enzyme responsible for ticagrelor metabolism and the formation of the active metabolite and their interactions with other CYP3A substrates ranges from activation through to inhibition. Ticagrelor and the active metabolite are P-glycoprotein weak inhibitors.

The major metabolite of ticagrelor is AR-C124910XX, which is also active as assessed by *in vitro* binding to the platelet P2Y<sub>12</sub> ADP-receptor. The systemic exposure to the active metabolite is approximately 30-40% of that obtained for ticagrelor.

## Excretion

The primary route of ticagrelor elimination is via hepatic metabolism. When radiolabelled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (57.8% in faeces, 26.5% in urine). Recoveries of ticagrelor and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the active metabolite is mostly via biliary secretion. The mean  $t_{1/2}$  was approximately 6.9 hours (range 4.5-12.8 hours) for ticagrelor and 8.6 hours (range 6.5-12.8 hours) for the active metabolite.

## Clearance of ticagrelor

The systemic clearance of ticagrelor is 14.2 L/h.

## Special populations

### *Elderly*

Higher exposures to ticagrelor (approximately 60% for both  $C_{max}$  and AUC) and the active metabolite (approximately 50% for both  $C_{max}$  and AUC) were observed in elderly ( $\geq 65$  years) subjects compared to younger subjects. These differences are not considered clinically significant. No dose adjustment is needed for elderly patients.

### *Paediatric*

BRILINTA has not been evaluated in a paediatric population.

### *Gender*

Higher exposures to ticagrelor (approximately 52% and 37% for  $C_{max}$  and AUC, respectively) and the active metabolite (approximately 50% for both  $C_{max}$  and AUC) were observed in women compared to men. These differences are not considered clinically significant.

### *Body weight*

Body weight was determined to have less than 20% change in the population mean clearance for both ticagrelor and the active metabolite at the 10<sup>th</sup> or 90<sup>th</sup> percentile of the body weight distribution compared to the population mean clearance at the median. This small effect on the clearance is not considered clinically relevant. Accordingly, no dose adjustment is necessary for ticagrelor based on weight.

### *Smoking*

Habitual smoking increased population mean clearance of ticagrelor by approximately 22%. This effect on the clearance is not considered clinically relevant.

### *Renal impairment*

Exposure to ticagrelor and the active metabolite were approximately 20% lower in patients with severe renal impairment compared to subjects with normal renal function. The IPA effect of ticagrelor was similar between the two groups, however there was more variability observed in individual response in patients with severe renal impairment. These differences are not considered clinically significant. No dosing adjustment is needed in patients with renal impairment.

No information is available concerning treatment of patients on renal dialysis.

### *Hepatic impairment*

The  $C_{max}$  and AUC for ticagrelor were 12% and 23% higher in patients with mild hepatic impairment compared to matched healthy subjects, respectively, however the IPA effect of ticagrelor was similar between the two groups. These differences are not considered clinically significant. No dose adjustment is needed for patients with mild hepatic impairment.

BRILINTA has not been studied in patients with moderate or severe hepatic impairment (refer to CONTRAINDICATIONS)

### *Race*

Patients of Asian descent have a 39% higher mean bioavailability of ticagrelor compared to Caucasian patients. Patients self-identified as Black had an 18% lower bioavailability of ticagrelor compared to Caucasian patients. In clinical pharmacology studies, the exposure ( $C_{max}$  and AUC) to ticagrelor in Japanese subjects was approximately 40% (20% after adjusting for body weight) higher compared to that in Caucasians. These differences are not considered clinically significant.



## CLINICAL TRIALS

The clinical evidence for the efficacy of BRILINTA is derived from the PLATO [PLATElet Inhibition and Patient Outcomes] study, a randomised, double-blind comparison of BRILINTA to clopidogrel, both given in combination with ASA and other standard therapy.

The PLATO study was a Phase III randomised, double-blind, parallel group, efficacy and safety study with 18,624 patients comparing BRILINTA with clopidogrel for prevention of vascular events in patients with acute coronary syndromes (unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]). The study was comprised of patients who presented within 24 hours of onset of the most recent episode of chest pain or symptoms. Patients could have been medically managed, treated with percutaneous coronary intervention (PCI) (with or without stent) or coronary artery bypass graft (CABG).

Patients were excluded from participation in the study for any of the following: 1) Active bleeding, history of previous intracranial bleed, gastrointestinal (GI) bleed within the past 6 months, major surgery within 30 days 2) Moderate or severe liver disease 3) Patient required dialysis 4) Oral anticoagulation therapy that could not be stopped. 5) Fibrinolytic therapy in the 24 hours prior to randomisation, or planned fibrinolytic treatment following randomisation. 6) Known clinically important anaemia or thrombocytopenia, 7) Increased risk of bradycardic events unless treated with a pacemaker 8) A need for chronic concomitant oral strong CYP3A inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers.

Patients were randomised to receive a loading dose of 180 mg of BRILINTA followed by a maintenance dose of 90 mg of BRILINTA twice daily or clopidogrel 75 mg once daily, with an initial loading dose of 300 mg if previous thienopyridine therapy had not been given; an additional loading dose of 300 mg was allowed at investigator discretion. Patients were to receive concomitant ASA 75-100 mg daily. For patients not previously on ASA a loading dose of 160mg to 500mg was allowed.

The patient population was 92% Caucasian, 28% female, 42% greater than 65 years of age with 15% greater than 75 years of age. Concomitant medications taken post-randomization included beta-blockers (86%), lipid-lowering agents (93%) and ACE inhibitors (79%).

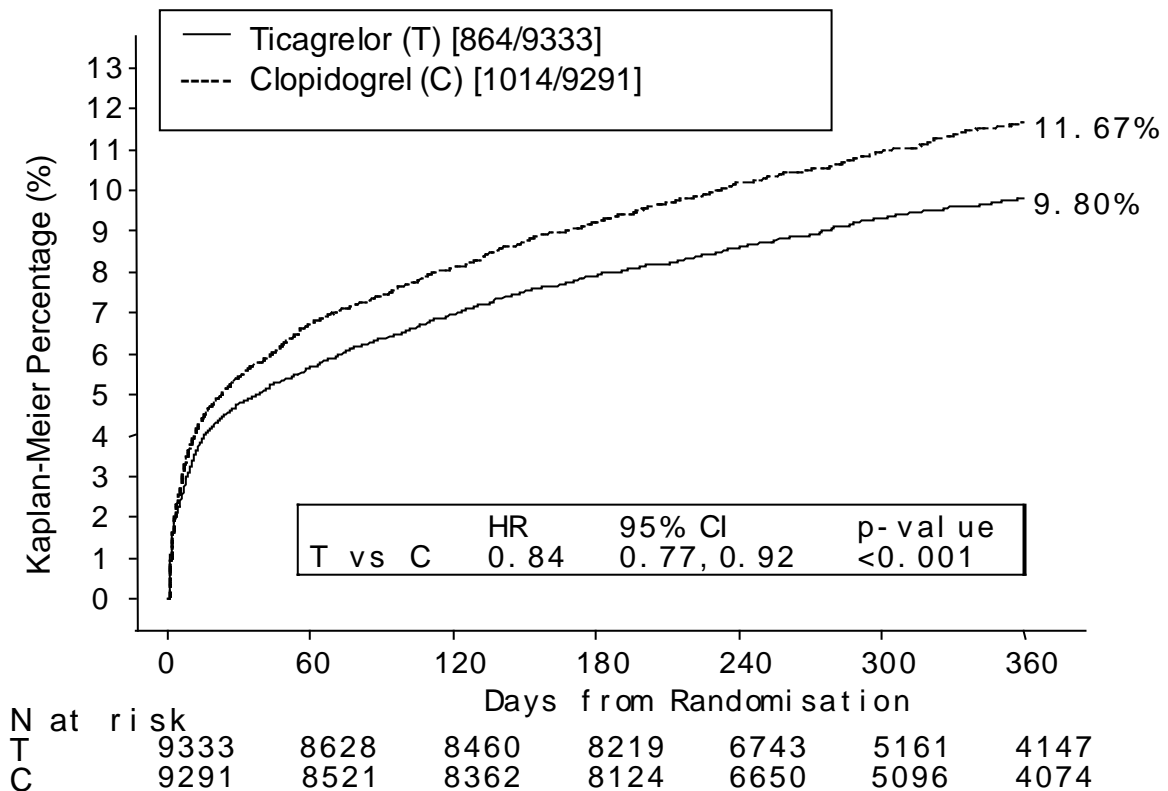
Planned treatment duration was a minimum of 6 months to a maximum of 12 months. Mean exposure to study drug in PLATO was 246 days for ticagrelor; median exposure was 276 days (interquartile range 177-365 days). Patients who prematurely discontinued study drug, but did not withdraw from the study, continued to be followed for study endpoint events. Study visits were scheduled 1, 3, 6, 9 and 12 months following randomization. Enrolment was stopped based on primary endpoint projections. To ensure 6 months minimum treatment, patients continued on-trial until their next scheduled visit at 6, 9 or 12 months, which became their final visit. Of the randomised patients, 18062 (98%) completed the

study. Patients were considered to have completed the study if they had a final visit (81.9% for ticagrelor, 81.2% for clopidogrel) died (4.4% for ticagrelor, 5.6% for clopidogrel), or were followed-up/alive (vital status collected when contacted, but patient did not want to continue participation in the study (10.4% for ticagrelor, 10.5% for clopidogrel). The most common reason for premature termination of study participation was withdrawal of informed consent (2.9%). There were 2 patients on the ticagrelor arm (none on clopidogrel) for whom vital status was unknown at the end of the study period.

The primary endpoint was time to first occurrence of any event from the composite of death from vascular causes, MI and stroke. Planned accrual of 1780 primary endpoint events in PLATO provided 90% power to detect a relative risk reduction of 13.5% with ticagrelor compared with clopidogrel over a 12-month period given an event rate of 11% in the clopidogrel group at 12 months.

BRILINTA reduced the occurrence of the primary composite endpoint compared to clopidogrel in both the UA/NSTEMI and STEMI population (Figure 3 and Table 1). Primary and Secondary efficacy endpoints were hierarchically tested in the sequence shown in Table 1.

**Figure 3 Time to first occurrence of CV death, MI and stroke (PLATO)**



**Table 1 Outcome Events in PLATO**

<b>Primary Endpoints</b>	<b>Ticagrelor (+ASA) % N=9333 % Patients with events (KM %/Year<sup>b</sup>)</b>	<b>Clopidogrel (+ASA) % N=9291 % Patients with events (KM %/Year<sup>b</sup>)</b>	<b>Absolute Risk Reduction %</b>	<b>Relative Risk Reduction<sup>a</sup> %</b>	<b>Hazard Ratio (95% CI)</b>	<b>p-value</b>
Composite of CV Death/MI (excl. silent MI)/Stroke	9.3 (9.8)	10.9 (11.7)	1.9	16	0.84 (0.77, 0.92)	p=0.0003
<b>Secondary Endpoints</b>						
Composite of CV Death/MI (excl. silent MI)/Stroke – intent to invasively manage	8.5 (8.9)	10.0 (10.6)	1.7	16	0.84 (0.75, 0.94)	p=0.0025
Composite of all-cause mortality/MI (excl. silent MI)/Stroke	9.7 (10.2)	11.5 (12.3)	2.1	16	0.84 (0.77, 0.92)	p=0.0001
Composite of CV Death/Total MI/Stroke/SRI/R I/TIA/ Other ATE	13.8 (14.6)	15.7 (16.7)	2.1	12	0.88 (0.81, 0.95)	p=0.0006
<b>Each component of primary efficacy endpoints:</b>						
• MI (excl. silent MI)	5.4 (5.8)	6.4 (6.9)	1.1	16	0.84 (0.75, 0.95)	p=0.0045
• CV death	3.8 (4.0)	4.8 (5.1)	1.1	21	0.79 (0.69, 0.91)	p=0.0013
• Stroke	1.3 (1.5)	1.1 (1.3)	-0.2	-17	1.17 (0.91, 1.52)	p=0.2249
All-cause mortality	4.3 (4.5)	5.4 (5.9)	1.4	22	0.78 (0.69, 0.89)	**

<sup>a</sup> RRR = (1-Hazard Ratio) x 100%. Values with a negative relative risk reduction indicate a relative risk increase.

<sup>b</sup> Kaplan-Meier percentages calculated at 12 months

\*\* Formal hierarchical statistical testing of secondary endpoints concluded after stroke; all-cause mortality was evaluated for completeness resulting in a nominal p-value of p=0.0003

BRILINTA is superior to clopidogrel in the prevention of thrombotic events (RRR 16%, ARR 1.9%, NNT=54) of the composite efficacy endpoint (cardiovascular (CV) death, myocardial infarction (MI) or stroke) over 12 months. The difference in treatments was driven by cardiovascular death and myocardial infarction with no significant difference in the rate of strokes (1.5% on ticagrelor vs 1.3% on clopidogrel) BRILINTA demonstrated a statistically significant relative risk reduction of 16% (ARR 1.1%) for MI and a 21% relative risk reduction (ARR 1.1%) for CV death. Treating 91 patients with BRILINTA instead of clopidogrel will prevent 1 CV death.

The superiority of BRILINTA over clopidogrel appeared early ([ARR] 0.6% and [RRR] of 12% at 30 days), with a constant treatment effect over the entire 12 month period, yielding ARR 1.9% per year with RRR of 16%. This suggests it is appropriate to treat for at least 12 months. Figure 3 reveals that the estimate of the risk to the first occurrence of any event in the composite efficacy endpoint for BRILINTA and clopidogrel continues to diverge at 12 months.

In PLATO, a large number of subgroup comparisons were conducted for the primary efficacy endpoint to assess the robustness and consistency of the overall benefit. The treatment effect of BRILINTA over clopidogrel appears consistent across multiple patient subgroups by demographic characteristics including weight, gender, medical history, concomitant therapy, and by final index event diagnosis (STEMI, NSTEMI, and UA). The benefits associated with BRILINTA were also independent of the use of other acute and long-term cardiovascular therapies, including heparin, low molecular weight heparin (LMWH), intravenous GpIIb/IIIa inhibitors, lipid-lowering drugs, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, and proton pump inhibitors.

Patients  $\geq 65$  years or  $\geq 75$  years of age had a higher rate of major CV events in both treatment arms. For patients  $\geq 75$  years of age, the rate of major CV events was 15.9% on ticagrelor vs 16.9% on clopidogrel. For patients  $< 75$  years of age, the rate of major CV events was 8.1% on ticagrelor vs 9.8% on clopidogrel. Similar differences were seen in patients  $\geq 65$  years compared with those  $< 65$  years.

In addition, patients weighing  $< 60$ kg had a higher rate of major CV events in both treatment arms. For patients weighing  $< 60$ kg, the rate of major CV events was 12.4% on ticagrelor vs 16.4% on clopidogrel. For patients weighing  $\geq 60$ kg, the rate of major CV events was 9.0% on ticagrelor vs 10.4% on clopidogrel.

A weakly significant treatment interaction was observed with region whereby the HR for the primary endpoint favours BRILINTA in the rest of world but favours clopidogrel in North America, which represented approximately 10% of the overall population studied (interaction p-value=0.045). The explanation for this apparent treatment-by-region interaction observed in PLATO is uncertain. It could be due to chance, however additional analyses suggest that the efficacy of BRILINTA relative to clopidogrel is associated with ASA dose during maintenance therapy.

The data show greater efficacy of BRILINTA compared to clopidogrel when used in conjunction with low maintenance dose ASA (75-150 mg). The relative efficacy of BRILINTA versus clopidogrel when used with high doses of ASA (>300mg) is less certain.

Based on this observed relationship between maintenance ASA dose and relative efficacy of ticagrelor compared to clopidogrel, it is recommended that BRILINTA is used with a low maintenance dose of ASA 75-150 mg (refer to DOSAGE AND ADMINISTRATION and PRECAUTIONS).

BRILINTA demonstrated a statistically significant relative risk reduction (RRR) in the primary composite endpoint (cardiovascular (CV) death, myocardial infarction (MI) or stroke) in acute coronary syndromes (ACS) patients planned for invasive management (RRR 16%, absolute risk reduction (ARR) 1.7%,  $p=0.0025$ ). In a pre-specified, exploratory analysis, BRILINTA demonstrated a RRR of the primary composite endpoint in ACS patients intended for medical management (RRR 15%, ARR 2.3%, nominal  $p=0.0444$ ). Consistent with the primary endpoint of the study, the effect in these two groups was driven by CV death and MI with no effect on stroke. In patients receiving stents there were fewer definite stent thromboses among patients treated with BRILINTA compared to clopidogrel (73 vs. 107, RRR 32%, ARR 0.6%; nominal  $p=0.0123$ ).

BRILINTA demonstrated a statistically significant RRR of 16% ( $p=0.0001$ , ARR 2.1%) for the composite of all-cause mortality, MI and stroke compared to clopidogrel.

### **Holter Substudy**

To study the occurrence of ventricular pauses and other arrhythmic episodes during PLATO, investigators performed Holter monitoring in a subset of nearly 3000 patients, of whom approximately 2000 had recordings both in the acute phase of their ACS and after one month. The primary variable of interest was the occurrence of ventricular pauses  $\geq 3$  seconds. More patients had ventricular pauses with BRILINTA (6.0%) than with clopidogrel (3.5%) in the acute phase, and 2.2% and 1.6% respectively after 1 month.

The increase in ventricular pauses in the acute phase of ACS was more pronounced in BRILINTA patients with history of congestive heart failure (CHF) (9.2% versus 5.4% in patients without CHF history; for clopidogrel patients, 4.0% in those with versus 3.6% in those without CHF history). This imbalance did not occur at one month: 2.0% versus 2.1% for BRILINTA patients with and without CHF history respectively; and 3.8% versus 1.4% with clopidogrel. There were no adverse clinical consequences associated with this imbalance (including pacemaker insertions) in this population of patients.

### **Genetic Substudy**

In the PLATO genotyping substudy of 10,285 patients ticagrelor findings were consistent with overall PLATO findings. Ticagrelor was more efficacious than clopidogrel in reducing major CV events irrespective of CYP2C19 and ABCB1

polymorphisms. Similar to the overall PLATO study, total PLATO Major bleeding did not differ between ticagrelor and clopidogrel, regardless of CYP2C19 or ABCB1 genotype. Non-CABG PLATO Major bleeding was increased with ticagrelor compared clopidogrel in patients with one or more CYP2C19 loss of function alleles, but similar to clopidogrel in patients with no loss of function allele.

## **Renal**

The PLATO study included 15,202 ACS patients who had serum creatinine levels available at baseline. Of these patients, 3237 (21.2%) had chronic kidney disease (CKD) (defined as Creatinine Clearance < 60mL/min by the Cockcroft-Gault equation). In patients with CKD, treatment with ticagrelor resulted in a statistically significant reduction in major CV events compared with clopidogrel and absolute risk reduction with ticagrelor increased as renal function declined. No significant difference in major bleeding was observed between ticagrelor and clopidogrel irrespective of renal function, while numerically more non-procedure related bleeding was observed with ticagrelor.

## **Combined Efficacy and Safety Composite**

A combined efficacy and safety composite (CV death, MI, stroke, or PLATO-defined 'Total Major' bleeding) supports the clinical benefit of BRILINTA compared to clopidogrel (RRR 8%, ARR 1.4%, HR 0.92; p=0.0257) over 12 months after ACS events.

## **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).

## **CONTRAINDICATIONS**

- Hypersensitivity to ticagrelor or any of the excipients
- Active pathological bleeding
- History of intracranial haemorrhage
- Moderate to severe hepatic impairment
- Co-administration of ticagrelor with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) is contraindicated, as co-administration may lead to a substantial increase in exposure to ticagrelor (refer to PRECAUTIONS)

## PRECAUTIONS

### *Bleeding risk*

In the PLATO study, the key exclusion criteria included an increased risk for bleeding, clinically important thrombocytopenia or anaemia, previous intracranial bleed, gastrointestinal bleed within the past 6 months or major surgery within the past 30 days. Patients with ACS treated with BRILINTA and ASA showed an increased risk of non-CABG major bleeding and also more generally in bleeds requiring medical attention i.e. Major + Minor PLATO bleeds, but not Fatal or Life-threatening bleeds (refer to ADVERSE EFFECTS).

As with other anti-platelet agents, BRILINTA prolongs bleeding time and should be used with caution in patients who may be at risk of increased bleeding. Therefore, the use of BRILINTA in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events. If clinically indicated, BRILINTA should be used with caution in the following patient groups:

- Patients with a propensity to bleed (e.g. due to recent trauma, recent surgery, coagulation disorders or active or recent gastrointestinal bleeding). The use of BRILINTA is contraindicated in patients with active pathological bleeding in those with a history of intracranial haemorrhage, and in patients with moderate to severe hepatic impairment (refer to CONTRAINDICATIONS).
- Patients with concomitant administration of drugs that may increase the risk of bleeding (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants (eg. warfarin) and/or fibrinolytics/thrombolytics within 24 hours of BRILINTA dosing).

No data exist with BRILINTA regarding a haemostatic benefit of platelet transfusions; circulating ticagrelor may inhibit transfused platelets. Since co-administration of BRILINTA with desmopressin did not decrease template bleeding time, desmopressin is unlikely to be effective in managing clinical bleeding events.

Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa may augment haemostasis. BRILINTA may be resumed after the cause of bleeding has been identified and controlled.

### *Surgery*

Patients should be advised to inform physicians and dentists that they are taking BRILINTA before any surgery is scheduled and before any new medicinal product is taken. If a patient requires surgery, physicians should consider each patient's clinical profile as well as the benefits and risks of continued antiplatelet therapy when determining when discontinuation of BRILINTA treatment should occur.

Because of the reversible binding of BRILINTA, restoration of platelet aggregation occurs faster with BRILINTA compared to clopidogrel. In the OFFSET (refer to

Pharmacodynamic effects) study, mean IPA for BRILINTA at 72 hours post-dose was comparable to mean IPA for clopidogrel at 120 hours post-dose. The more rapid offset of effect may predict a reduced risk of bleeding complications, eg, in settings where antiplatelet therapy must be temporarily discontinued due to surgery or trauma.

In patients undergoing coronary bypass grafting (CABG) in PLATO, those on BRILINTA had a non-statistically significant higher rate of major bleeding compared with those on clopidogrel when the drug was stopped within 1 day prior to surgery but a similar rate of major bleeds compared with those on clopidogrel after stopping therapy 2 or more days before surgery.

Based on the results in PLATO, if a CABG procedure is planned the bleeding risk with BRILINTA is numerically increased compared to that seen with clopidogrel when therapy is discontinued within 96 hours prior to the procedure.

If a patient is to undergo elective surgery and antiplatelet effect is not desired, BRILINTA should be discontinued 5 days prior to surgery.

#### *Renal Dialysis*

As there is no safety and efficacy data for BRILINTA in patients undergoing renal dialysis, caution should be used with these patients as ticagrelor is not expected to be dialyzable.

#### *Patients at risk for bradycardic events*

Due to observations of mostly asymptomatic ventricular pauses in an earlier clinical study, patients with an increased risk of bradycardic events (e.g. patients without a pacemaker who have sick sinus syndrome, 2nd or 3rd degree AV block or bradycardic-related syncope) were excluded from the main study evaluating the safety and efficacy of BRILINTA. Therefore, due to the limited clinical experience in these patients, caution is advised.

In addition, caution should be exercised when administering BRILINTA concomitantly with drugs known to induce bradycardia. However no evidence of clinically significant adverse reactions was observed in the PLATO trial after concomitant administration with one or more drugs known to induce bradycardia (e.g. 96% beta blockers, 33% calcium channel blockers diltiazem and verapamil, and 4% digoxin).

During the Holter substudy in PLATO, more patients had ventricular pauses  $\geq 3$  seconds with ticagrelor than with clopidogrel during the acute phase of their ACS. The increase in Holter-detected ventricular pauses with ticagrelor was higher in patients with congestive heart failure (CHF) than in the overall study population during the acute phase of ACS, but not at one month with ticagrelor or compared to clopidogrel. There was no adverse clinical consequences associated with this imbalance (including syncope or pacemaker insertion) in this patient population (refer to CLINICAL TRIALS/Holter Study).



### *Dyspnoea*

Dyspnoea, usually mild to moderate in intensity and often resolving without need for treatment discontinuation, is reported by 13.8% in patients treated with BRILINTA in PLATO and by 7.8% treated with clopidogrel. Discontinuations due to dyspnoea were reported in 0.9% of patients taking BRILINTA and 0.1% of patients taking clopidogrel (refer to ADVERSE EVENTS).

Patients with asthma/ chronic obstructive pulmonary disorder (COPD) may have an increased absolute risk of experiencing dyspnoea with BRILINTA. BRILINTA should be used with caution in patients with a history of asthma and/or COPD. The mechanism has not been elucidated. If a patient reports new, prolonged or worsened dyspnoea, this should be investigated fully and if not tolerated, treatment with BRILINTA should be stopped.

### *Creatinine Elevations*

Creatinine levels may increase during treatment with ticagrelor (see ADVERSE EFFECTS/Lab Abnormalities/Creatinine Elevations). The mechanism has not been elucidated. Renal function should be checked after one month and thereafter according to routine medical practice paying special attention to patients  $\geq 75$  years and patients with moderate/severe renal impairment and those receiving concomitant treatment with an Angiotensin II Receptor Blocker (ARB).

### *Uric Acid Increase*

In the PLATO study, patients on ticagrelor had a higher risk of hyperuricaemia than those patients receiving clopidogrel. Caution should be exercised when administering ticagrelor to patients with history of hyperuricaemia or gouty arthritis. As a precautionary measure the use of ticagrelor in patients with uric acid nephropathy is discouraged.

### *Other*

Based on the relationship observed in PLATO between maintenance ASA dose and relative efficacy of BRILINTA compared to clopidogrel, co-administration of BRILINTA and high dose maintenance dose ASA ( $> 300\text{mg}$ ) is not recommended (refer to CLINICAL TRIALS).

In PLATO, patients weighing  $< 60$  kg were at greater risk of cardiovascular events and slightly higher risk of major bleeding compared with patients weighing  $\geq 60$  kg (refer to CLINICAL TRIALS and ADVERSE EFFECTS).

### *Discontinuations*

Patients who require discontinuation of BRILINTA are at increased risk for cardiac events. Premature discontinuation of treatment should be avoided. If BRILINTA must be temporarily stopped due to an adverse event(s), it should be re-initiated as soon as possible when the benefits outweigh the risks of the adverse event or when the adverse event has come to resolution.

## Effects on fertility

Ticagrelor was found to have no effect on fertility of female rats at oral doses up to 200 mg/kg per day (approximately 20 times the human therapeutic exposure) and had no effect on fertility of male rats at doses up to 180 mg/kg/day (about 16 times the human therapeutic exposure).

Ticagrelor had no effect on fetal development at oral doses up to 100 mg/kg per day in rats (about 5 times the recommended human therapeutic exposure) and up to 42 mg/kg per day in rabbits (equivalent to the human therapeutic exposure). Ticagrelor had no effects on parturition or postnatal development in rats at doses up to 60 mg/kg/day (just under 5 times the human therapeutic exposure).

## Use in pregnancy – category B1

No clinical data on exposed pregnancies are available for ticagrelor.

Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. Because animal reproduction studies are not always predictive of a human response, ticagrelor is not recommended for use during pregnancy.

## Use in lactation

It is not known whether ticagrelor is excreted in human milk. Studies in rats have shown that ticagrelor and active metabolites are excreted in the milk. The use of BRILINTA during breastfeeding is not recommended.

## Paediatric use

The safety and efficacy of BRILINTA has not been established in patients under 18 years of age.

## Use in the elderly

Higher exposures to ticagrelor and the active metabolite were observed in elderly ( $\geq 65$  years) subjects compared to younger subjects. These differences are not considered clinically significant. No dose adjustment is needed for elderly patients.

In PLATO, patients  $\geq 65$  years or  $\geq 75$  years of age were at greater risk of cardiovascular events and slightly higher risk of major bleeding compared with younger patients (refer to CLINICAL TRIALS and ADVERSE EFFECTS).

## Carcinogenicity

No compound-related tumours were observed in a 2-year mouse study at oral doses up to 250 mg/kg/day (*ca.* 18-fold the human therapeutic exposure to ticagrelor). There was no increase in tumours in male rats oral doses up to 120 mg/kg/day (*ca.* 15-fold the human therapeutic exposure). Increases in uterine adenocarcinomas and hepatocellular adenomas /adenocarcinomas and decreases in pituitary adenomas and mammary fibroadenomas were observed in female rats at more than 25 times the human therapeutic exposure to ticagrelor, with no change in tumour incidence seen at around 8 times the human therapeutic

exposure. The uterine tumours seen only in rats were hypothesized to result from a hormonal imbalance present in rats given high doses of ticagrelor. The benign liver tumours are considered secondary to the response by the liver to the metabolic load placed on the liver from the high doses of ticagrelor.

### **Genotoxicity**

Ticagrelor showed no genotoxic potential in assays for gene mutations (bacterial reverse mutation, mouse lymphoma TK) and chromosomal damage (rat micronucleus *in vivo*).

### **Interactions with Other Medicines**

Ticagrelor is primarily a CYP3A4 substrate and a mild inhibitor of CYP3A4. Ticagrelor is also a P-gp substrate and a weak P-gp inhibitor and may increase the exposure of P-gp substrates.

### **Effects of Other Drugs on BRILINTA**

#### ***Drugs metabolised by CYP3A4***

##### **Ketoconazole and other strong CYP3A4 inhibitors**

Co-administration of ketoconazole with ticagrelor increased the ticagrelor  $C_{max}$  and AUC equal to 2.4-fold and 7.3-fold, respectively. The  $C_{max}$  and AUC of the active metabolite were reduced by 89% and 56%, respectively. Other strong inhibitors of CYP3A4 (clarithromycin, nefazadone, ritonavir and atazanavir) would be expected to have similar effects and their concomitant use with BRILINTA is contraindicated.

##### **Diltiazem and other moderate CYP3A4 inhibitors**

Co-administration of ticagrelor with diltiazem increased the ticagrelor  $C_{max}$  by 69% and AUC by 174% and decreased the active metabolite  $C_{max}$  by 38% and AUC was unchanged. There was no effect of ticagrelor on diltiazem plasma levels. Other moderate CYP3A4 inhibitors (e.g. amprenavir, aprepitant, erythromycin, fluconazole, and verapamil) would be expected to have a similar effect as diltiazem leading to increased exposure to ticagrelor, therefore caution is advised.

##### **Rifampin and other CYP3A4 inducers**

Co-administration of rifampin with ticagrelor decreased the ticagrelor  $C_{max}$  and AUC by 73% and 86%, respectively. The  $C_{max}$  of its active metabolite was unchanged and the AUC was decreased by 46% respectively. Other CYP3A4 inducers (e.g. dexamethasone, phenytoin, carbamazepine and phenobarbital) would be expected to decrease the exposure to BRILINTA as well and may result in reduced efficacy of BRILINTA.

## **Effects of BRILINTA on Other Drugs**

### ***Drugs metabolised by CYP3A4***

#### **Simvastatin**

Co-administration of ticagrelor with simvastatin increased the simvastatin  $C_{max}$  by 81% and AUC by 56% and increased simvastatin acid  $C_{max}$  by 64% and AUC by 52% with some individual increases equal to 2 to 3 fold. There was no effect of simvastatin on ticagrelor plasma levels. There is the potential for an increase in simvastatin-related adverse events such as myopathy and rhabdomyolysis with co-administration; no cases of rhabdomyolysis were reported when ticagrelor was co-administered with simvastatin 40 mg daily or lower. Therefore concomitant use of ticagrelor with doses of simvastatin greater than 40 mg daily is not recommended.

A similar effect on other statins metabolised by CYP3A4 cannot be excluded.

#### **Atorvastatin**

Co-administration of atorvastatin and ticagrelor increased the atorvastatin acid  $C_{max}$  by 23% and AUC by 36%. Similar increases in AUC and  $C_{max}$  were observed for all atorvastatin acid metabolites. These increases are not considered clinically significant.

BRILINTA is not expected to have a clinically meaningful effect on other statins which are not metabolised by CYP3A4.

#### **Other**

Ticagrelor is a mild CYP3A4 inhibitor. Co-administration of BRILINTA and CYP3A4 substrates with narrow therapeutic indices (i.e. ergot alkaloids) is not recommended, as ticagrelor may increase the exposure to these drugs.

### ***Drugs metabolised by CYP2C9 - Tolbutamide***

Co-administration of ticagrelor with tolbutamide resulted in no change in the plasma levels of either drug, which suggest that ticagrelor is not a CYP2C9 inhibitor and unlikely to alter the CYP2C9 mediated metabolism of drugs like warfarin and tolbutamide.

### ***Oral Contraceptives***

Co-administration of ticagrelor and levonorgestrel and ethinyl estradiol increased the ethinyl estradiol exposure approximately 20% but did not alter the PK of levonorgestrel. No clinically relevant effect on oral contraceptive efficacy is expected when levonorgestrel and ethinyl estradiol are co-administered with BRILINTA.

### ***P-glycoprotein (P-gp) substrates (including digoxin and cyclosporin)***

Concomitant administration of ticagrelor increased the digoxin  $C_{max}$  by 75% and AUC by 28%. The mean trough digoxin levels were increased about 30% with ticagrelor co-administration with some individual maximum increases to 2 fold. In the presence of digoxin, the  $C_{max}$  and AUC of ticagrelor and its active metabolite were not affected. Therefore, appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent drugs like digoxin and cyclosporin concomitantly with BRILINTA.

No data are available on concomitant use of BRILINTA with potent P-gp inhibitors (e.g. verapamil, quinidine, cyclosporin) that may increase ticagrelor exposure.

### **Other Concomitant Therapy**

In clinical studies, BRILINTA was commonly administered with ASA, heparin, low molecular weight heparin, intravenous GpIIb/IIIa inhibitors, proton pump inhibitors, statins, beta-blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers as needed for concomitant conditions. These studies did not produce any evidence of clinically significant adverse interactions. Due to potential pharmacodynamic interactions, caution should be exercised with the concomitant administration of BRILINTA and medicinal products known to alter haemostasis.

Aspirin: Clinical pharmacology interaction studies showed that co-administration of ticagrelor with ASA did not have any effect on ticagrelor or its active metabolite plasma levels.

Heparin and enoxaparin: Clinical pharmacology interaction studies showed that co-administration of ticagrelor with heparin did not have any effect on ticagrelor or its active metabolite plasma levels. Co-administration of ticagrelor and heparin had no effect on heparin based on activated partial thromboplastin time (aPTT) and activated coagulation time (ACT) assays. Co administration of ticagrelor and heparin had no effect on enoxaparin based on factor Xa assay.

### **Non Steroidal Anti-Inflammatory Drugs (NSAIDs)**

Concomitant administration with chronic NSAIDs has not been studied. Because of the potential for increased risk of bleeding, chronic NSAIDs and ticagrelor should be co-administered with caution (refer to PRECAUTIONS/Bleeding Risk).

### **Clopidogrel and Prasugrel**

Ticagrelor and clopidogrel or prasugrel should not be co-administered.

Concomitant administration with clopidogrel has not been studied. Switching from clopidogrel to ticagrelor results in an absolute IPA increase of 26.4% and switching from ticagrelor to clopidogrel results in an absolute IPA decrease of 24.5%. Patients can be switched from clopidogrel to BRILINTA without interruption of anti-platelet effect (refer to PHARMACOLOGY/Switching Data).

Switching from prasugrel to BRILINTA has not been investigated.

Drugs known to induce bradycardia: Due to observations of mostly asymptomatic ventricular pauses and bradycardia, caution should be exercised when administering BRILINTA concomitantly with drugs known to induce bradycardia. However no evidence of clinically significant adverse reactions was observed in the PLATO trial after concomitant administration with one or more drugs known to induce bradycardia (e.g. 96% beta blockers, 33% calcium channel blockers diltiazem and verapamil, and 4% digoxin).

### Selective Serotonin Reuptake Inhibitors (SSRIs)

Due to reports of cutaneous bleeding abnormalities with SSRIs, caution is advised when administering SSRIs with BRILINTA as this may increase the risk of bleeding. In PLATO, there was no increase in major bleeding in patients taking BRILINTA concomitantly with SSRIs.

### **Effects on ability to drive and use machines**

No studies on the effects of BRILINTA on the ability to drive and use machines have been performed. BRILINTA is expected to have no or negligible influence on the ability to drive and use machines. During treatment for ACS, dizziness and confusion have been reported. Therefore, patients who experience these symptoms should be cautious while driving or using machines.

## **ADVERSE EFFECTS**

The safety profile of BRILINTA in patients with ACS (UA, NSTEMI and STEMI) was evaluated in PLATO study, which compared patients treated with BRILINTA (loading dose of 180 mg of BRILINTA and a maintenance dose of 90 mg bd) to patients treated with clopidogrel (300-600 mg loading dose followed by 75 mg od maintenance dose) both given in combination with ASA and other standard therapies.

Median treatment duration for BRILINTA was 276 days (of the 9333 ticagrelor patients, 6762 patients were treated for greater than 6 months and 3138 were treated for greater than 12 months).

The most commonly reported adverse events in patients treated with ticagrelor were dyspnoea, headache, and epistaxis and these events occurred at higher rates than in the clopidogrel treatment group. Serious adverse events were reported in a similar frequency between BRILINTA (20.2%) and clopidogrel (20.3%) treated patients. The most frequent serious adverse events observed were cardiac failure (1.1% vs 1.0%), non-cardiac chest pain (0.9% vs 0.9%) and dyspnoea (0.7% vs 0.4%).

### **Discontinuation**

The ticagrelor group had a higher discontinuation rate due to AEs than clopidogrel (7.4% vs. 5.4%). The difference was driven mainly by dyspnoea (0.8% vs. 0.1%) and epistaxis (0.4% vs. 0.1%). The ticagrelor and clopidogrel groups had a similar discontinuation rate due to other AEs.

The discontinuation rate due to serious adverse events was 2.8% for ticagrelor and 2.4% for clopidogrel.

## Bleeding Events

The following bleeding definitions were used in the PLATO study:

**‘Major Fatal/Life-threatening’:** fatal, or intracranial, or intrapericardial bleed with cardiac tamponade, or hypovolaemic shock or severe hypotension due to bleeding and requiring pressors or surgery, or clinically overt or apparent bleeding associated with a decrease in haemoglobin of more than 50 g/L, or transfusion of 4 or more units (whole blood or PRBCs) for bleeding.

**‘Major Other’:** Significantly disabling (e.g. intraocular with permanent vision loss), or clinically overt or apparent bleeding associated with a decrease in haemoglobin of 30 to 50 g/L, or transfusion of 2-3 units (whole blood or PRBCs) for bleeding.

**‘Minor’:** Requires medical intervention to stop or treat bleeding (e.g. epistaxis requiring visit to medical facility for packing).

**Minimal bleeds** included all other bleeds not requiring intervention or treatment (eg. bruising, bleeding gums, oozing from injection sites, etc); these were collected but not adjudicated.

The primary safety endpoint in the PLATO study was the composite endpoint of ‘Total Major’ bleeding, which consisted of the components of ‘Major Fatal/Life-threatening’ and ‘Major Other’. In PLATO, the rate of ‘Total Major’ bleeding did not significantly differ for BRILINTA compared to clopidogrel (Figure 4).

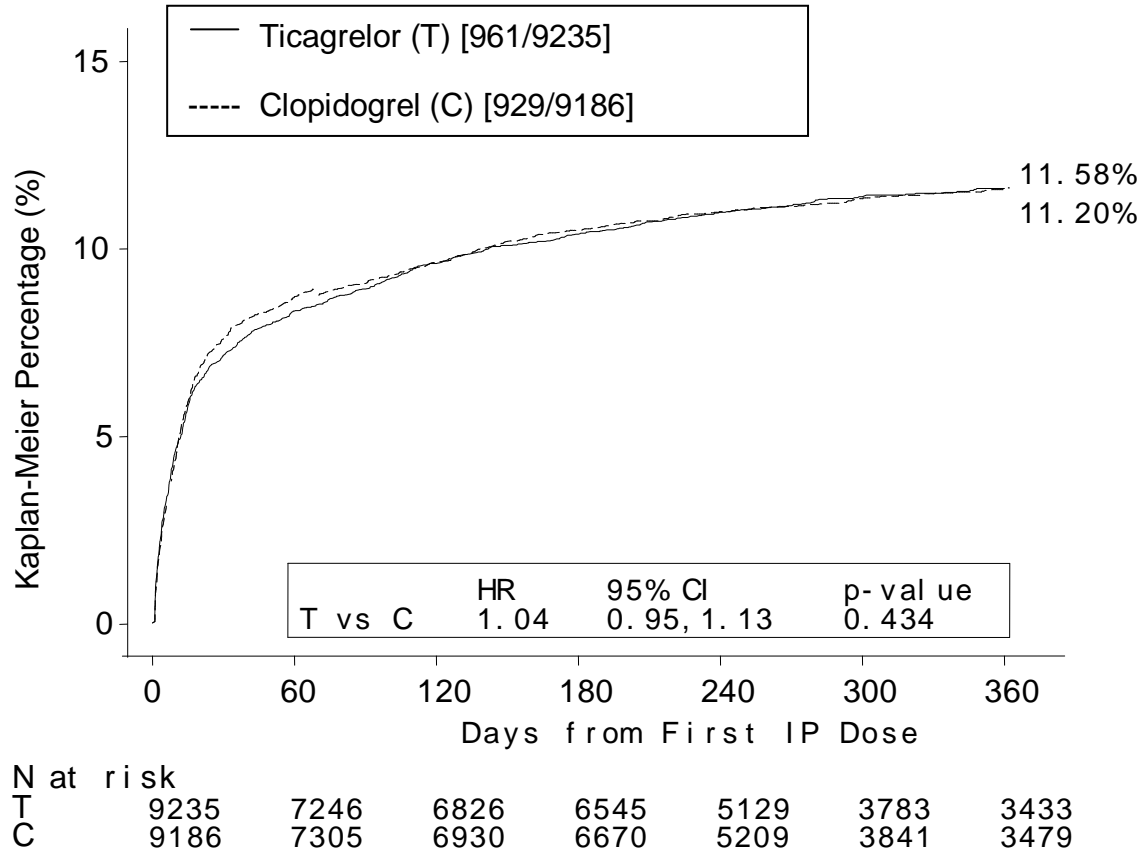
Overall outcome of bleeding events in the PLATO study are shown in Table 2.

Bleeding events reported in PLATO were also mapped to the TIMI (Thrombolysis in Myocardial Infarction) scale, to facilitate comparison with other similar studies. The following TIMI bleeding definitions were used:

- **TIMI Major:** Clinically overt bleeding associated with a fall in haemoglobin > 50 g/L, or intracranial haemorrhage.
- **TIMI Minor:** Overt bleeding associated with a fall in haemoglobin of  $\geq 30$  g/L but  $\leq 50$  g/L.

PLATO definitions are more inclusive when compared to TIMI definitions of bleeding. Compared to TIMI, the PLATO definitions feature lower thresholds to capture bleeding events during both acute and chronic phases of ACS.

**Figure 4 – Kaplan Meier estimate of time to first PLATO-defined ‘Total Major’ bleeding event**





**Table 2 Analysis of Overall Bleeding Events**

	<b>Ticagrelor (+ASA) (%) N=9235</b>	<b>Clopidogrel (+ASA) (%) N=9186</b>	<b>p-value*</b>
<b>Primary Safety Endpoint</b>			
Total Major	11.6	11.2	0.4336
<b>Secondary Endpoints</b>			
Major Fatal/Life-Threatening	5.8	5.8	0.6988
Combined Total Major + Minor	16.1	14.6	0.0084
Non-CABG Total Major	4.5	3.8	0.0264
Non-Procedural Major	3.1	2.3	0.0058
Non-Procedural Major + Minor	5.9	4.3	<0.0001
<b>TIMI-defined bleeding category</b>			
TIMI-defined Major	7.9	7.7	0.5669
TIMI-defined Major + Minor	11.4	10.9	0.3272

\*Nominal p-value not corrected for multiple testing

In PLATO, time to first PLATO-defined 'Total Major' bleeding for BRILINTA did not differ significantly from that of clopidogrel. The event rate for bleeding was higher for both treatment arms during the first 30 days compared to the remainder of the study; most events occurred during this period. There were few fatal bleeding events in the study, 20 (0.2%) for BRILINTA and 23 (0.3%) for clopidogrel. When minor bleeding was included, combined PLATO-defined Major and Minor bleeding events were significantly higher on BRILINTA than on clopidogrel. Minimal bleeding rates on BRILINTA were higher than on clopidogrel. Overall rates of TIMI-defined bleeding events did not differ significantly between BRILINTA and clopidogrel. Refer to the bleeding definitions under the subheading Bleeding Events. *CABG-related bleeding:* In PLATO, 1584 patients (12%) underwent coronary artery bypass graft (CABG) surgery. 'Major Fatal/Life-threatening' bleeding was approximately 42% in both treatment groups. There was no difference between the treatment groups with respect to risk of 'Major Fatal/Life-threatening' CABG bleeding relative to time of last dose before the procedure.

Fatal CABG bleeding occurred uncommonly, 6 patients in each treatment group (0.8% and 0.7% of CABG patients on BRILINTA and clopidogrel, respectively).

*Non-CABG related bleeding:* When CABG bleeding is removed from the analysis (Table 3), the absolute bleeding rates for all categories are lower. The groups did not differ in non-CABG PLATO-defined Major Fatal/Life-threatening bleeding, but PLATO-defined 'Total Major', TIMI Major, and TIMI Major + Minor bleeding was more common with BRILINTA.

**Table 3 Non-CABG Related PLATO-defined Major Bleeding Events and TIMI-defined Bleeding Events**

	<b>Ticagrelor (+ASA) (%) N=9235</b>	<b>Clopidogrel (+ASA) (%) N=9186</b>	<b>p-value</b>
<b>PLATO-defined bleeding category</b>			
Total Major	4.5	3.8	0.0264
Major Fatal/Life-Threatening	2.1	1.9	0.2516
<b>TIMI-defined bleeding category</b>			
TIMI-defined Major	2.8	2.2	0.0246
TIMI-defined Major + Minor	4.5	3.6	0.0093

*Bleeding unrelated to any procedure:* As shown in Table 2 PLATO-defined 'Major' and 'Major + Minor' non-procedural bleeding was more frequent with BRILINTA. Discontinuation of treatment due to non-procedural bleeding was more common for BRILINTA (2.9%) than for clopidogrel (1.2%;  $p < 0.001$ ). Clinically important locations for 'Major + Minor' bleeding in rank order by frequency were (BRILINTA vs clopidogrel): intracranial (27 vs 14 events), pericardial (11 vs 11), retroperitoneal (3 vs 3), intraocular (2 vs 4) and intra-articular (2 vs 1). Other common locations were in rank order of frequency: gastrointestinal (170 vs 135 events), epistaxis (116 vs 61), urinary (45 vs 37), subcutaneous/dermal (43 vs 38) and haemoptysis (13 vs 7).

There was no difference with BRILINTA compared to clopidogrel for fatal non-procedural bleeding.

*Intracranial bleeding:* There were more intracranial non-procedural bleeds with BRILINTA (n=27 bleeds in 26 patients, 0.3%) than with clopidogrel (n=14 bleeds, 0.2%), of which 11 bleeds with ticagrelor and 1 with clopidogrel were fatal. There was no difference in overall fatal bleeds.

Among ticagrelor-treated patients in PLATO, there were similar rates of haemorrhagic stroke between those with a history of prior TIA or ischaemic stroke and those without prior TIA or ischaemic stroke: 2/564 (0.35%) vs 21/8762 (0.24%).

*Gastrointestinal bleeding and Fatal gastrointestinal bleeding:* Total major GI bleeding was higher on ticagrelor than clopidogrel (1.3% vs 1%) however fatal/life threatening GI bleeding rates were similar and fatal GI bleeding events were less on ticagrelor (0 vs 5 events).

Baseline characteristics including age, gender, weight, race, geographic region, medical history, concurrent conditions and concomitant therapy were assessed to explore any increase in risk of bleeding with BRILINTA. No particular risk group was identified for any subset of bleeding.

Patients  $\geq 65$  or  $\geq 75$  years of age had a slightly higher rate of major bleeding in both treatment arms. For patients  $\geq 75$  years of age, the rate of major bleeding was 12.1% on ticagrelor vs 11.8% on clopidogrel. For patients  $< 75$  years of age, the rate of major bleeding was 10.1% on ticagrelor vs 9.8% on clopidogrel. Similar differences were seen in patients  $\geq 65$  years compared with those  $< 65$  years.

In addition, patients weighing  $< 60$ kg had a slightly higher rate of major bleeding in both treatment arms. For patients weighing  $< 60$ kg, the rate of major bleeding was 11.2% on ticagrelor vs 13.3% on clopidogrel. For patients weighing  $\geq 60$ kg, the rate of major bleeding was 10.3% on ticagrelor vs 9.9% on clopidogrel.

## **Dyspnoea**

Dyspnoea is reported by patients treated with BRILINTA. Dyspnoea adverse events (AEs) (dyspnoea, dyspnoea at rest, dyspnoea exertional, dyspnoea paroxysmal nocturnal, and nocturnal dyspnoea), when combined, were reported in 13.8% of patients taking BRILINTA and in 7.8% taking clopidogrel in the PLATO study. The study did not exclude patients with underlying CHF, COPD or asthma. Most of the dyspnoea AEs were mild to moderate in intensity. Dyspnoea Serious Adverse Events were reported in 0.7% taking BRILINTA and 0.4% taking clopidogrel. More patients taking BRILINTA 0.9% discontinued study drug than did patients taking clopidogrel 0.1% due to dyspnoea. Dyspnoea was usually reported in the initial phase of treatment; the time to the first dyspnoea AE was numerically shorter with ticagrelor (median of 20 days) than with clopidogrel (median of 33 days) during treatment with study medication.

Eighty-seven percent of patients taking BRILINTA that reported dyspnoea experienced a single episode.

Compared with clopidogrel, patients with asthma/COPD treated with ticagrelor may have an increased risk of experiencing non-serious dyspnoea (3.29% ticagrelor versus 0.53% clopidogrel) and serious dyspnoea (0.38% ticagrelor versus 0.00% clopidogrel).

Approximately 30% of all dyspnoea resolved within 7 days. Patients who reported dyspnoea tended to be older and more frequently had dyspnoea, CHF, COPD, or

asthma at baseline. PLATO data do not suggest that the higher frequency of dyspnoea with BRILINTA is due to new or worsening heart or lung disease.

In patients who underwent pulmonary function testing in the clinical program, there was no indication of an adverse effect of BRILINTA on pulmonary function.

In PLATO, the CV benefit of BRILINTA was maintained in patients who reported dyspnoea.

### **Lab Abnormalities**

Uric acid elevations: In PLATO, serum uric acid concentration increased to more than upper limit of normal in 22% of patients receiving BRILINTA compared to 13% of patients receiving clopidogrel. Mean serum uric acid concentration increased approximately 15% with BRILINTA compared to approximately 7.5% with clopidogrel and after treatment was stopped, decreased to approximately 7% on BRILINTA but with no decrease observed for clopidogrel. The hyperuricaemia AEs reported were 0.5% for BRILINTA vs. 0.2% for clopidogrel. Of these AEs 0.05% for BRILINTA vs. 0.02% for clopidogrel were considered causally related by investigators. For gouty arthritis, the AEs reported were 0.2% for BRILINTA vs 0.1% for clopidogrel; none of these adverse events were assessed as causally related by investigators.

Creatinine elevations: In PLATO, serum creatinine concentration significantly increased by >30% in 25.5% of patients receiving BRILINTA compared to 21.3% of patients receiving clopidogrel and by >50% in 8.3% of patients receiving BRILINTA compared to 6.7% of patients receiving clopidogrel. Creatinine elevations by >50% were more pronounced in patients > 75 years (BRILINTA 13.6% versus clopidogrel 8.8%), in patients with severe renal impairment at baseline (BRILINTA 17.8% versus clopidogrel 12.5%) and in patients receiving concomitant treatment with ARBs (BRILINTA 11.2% versus clopidogrel 7.1%). The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Signs of reversibility on discontinuation were observed even in those with the greatest on treatment increases. Treatment groups in PLATO did not differ for related serious adverse events. Within these subgroups renal-related serious adverse events and adverse events leading to discontinuation of study drug were similar between treatment groups. The totality of renal AEs reported were 4.9% for BRILINTA vs. 3.8% for clopidogrel, however a similar percent of patients reported events considered by the investigators as causally related to treatment; 54 (0.6%) for BRILINTA and 43 (0.5%) for clopidogrel.

The following adverse events have been identified following studies with BRILINTA (see Table 4).

**Table 4 Treatment Emergent Adverse Events Reported by at Least 2.5% of Patients in Either Group<sup>a</sup>**

	% Incidence <sup>b</sup>	% Incidence <sup>b</sup>
<b>SYSTEM ORGAN CLASS</b>	<b>Ticagrelor (+ASA)</b>	<b>Clopidogrel (+ASA)</b>
EVENT		
<b>Cardiac Disorders</b>		
Atrial Fibrillation	4.2	4.6
Bradycardia	2.9	2.9
Cardiac Failure	2.3	2.6
<b>Gastrointestinal Disorders</b>		
Nausea <sup>c</sup>	4.3	3.8
Diarrhea <sup>c</sup>	3.7	3.3
Vomiting <sup>c</sup>	2.5	2.3
Constipation <sup>c</sup>	2.2	2.6
<b>General Disorders and Administration Site Conditions</b>		
Non-cardiac chest pain	3.7	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5
Pyrexia	2.9	2.8
Oedema peripheral	2.3	2.5
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Back pain	3.6	3.3
<b>Nervous System Disorders</b>		
Headache <sup>c</sup>	6.5	5.8
Dizziness <sup>c</sup>	4.5	3.9
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Dyspnoea <sup>c,d</sup>	13.8	7.8
Epistaxis	6.0	3.4
Cough	4.9	4.6
<b>Skin and subcutaneous tissue disorders</b>		
Contusion	3.9	2.0
<b>Vascular Disorders</b>		
Hypertension	3.8	4.0
Hypotension	3.2	3.3

<sup>a</sup>These adverse events are from the PLATO study

<sup>b</sup>Very common:  $\geq 1/10$  ( $\geq 10\%$ ); Common:  $\geq 1/100$  ( $\geq 1\%$ ) and  $< 1/10$  ( $< 10\%$ )

<sup>c</sup>These events are considered causally related to ticagrelor.

<sup>d</sup>Several MedDRA PT combined

Additional adverse reactions that were reported in the PLATO study as possibly or probably related to BRILINTA are listed below by body system. Frequency categories are defined according to the following conventions: Very common ( $\geq 1/10$ ), Common ( $\geq 1/100$ ,  $< 1/10$ ), Uncommon ( $\geq 1/1000$ ,  $< 1/100$ ), Rare ( $\geq 1/10,000$ ,  $< 1/1000$ )

*Eye disorders:*

- *uncommon:* eye haemorrhage (intraocular, conjunctival, retinal)

*Ear and labyrinth disorders:*

- *common:* vertigo
- *uncommon:* ear haemorrhage

*Nervous system disorders:*

- *uncommon:* intracranial hemorrhage (includes the following related terms: cerebral haemorrhage, haemorrhage intracranial, haemorrhagic stroke), confusion, paraesthesia

*Gastrointestinal disorders:*

- *common:* abdominal pain, dyspepsia, gastrointestinal haemorrhage (includes the following related terms: rectal haemorrhage, intestinal haemorrhage, melaena, occult blood).
- *uncommon:* retroperitoneal haemorrhage, gastritis, haematemesis, gastrointestinal ulcer haemorrhage (includes the following related terms: gastric ulcer haemorrhage, duodenal ulcer haemorrhage, peptic ulcer haemorrhage), haemorrhoidal haemorrhage, oral haemorrhage (including gingival bleeding), retroperitoneal haemorrhage

*Injury, poisoning and procedural complications:*

- *common:* post-procedural hemorrhage, procedural site haemorrhage (includes the following related terms: vessel puncture site haemorrhage, vessel puncture site haematoma, injection site haemorrhage, puncture site haemorrhage, catheter site haemorrhage), haemorrhage
- *uncommon:* wound haemorrhage, traumatic haemorrhage

*Investigations:*

- *common:* blood creatinine increased

*Renal and urinary disorders:*

- *common:* urinary tract bleeding

*Respiratory, thoracic and mediastinal disorders:*

- *uncommon:* haemoptysis

*Reproductive system and breast disorders*

- *uncommon:* vaginal bleeding (including metrorrhagia)

*Musculoskeletal connective tissue and bone disorders:*

- *rare:* haemarthrosis

*Skin and subcutaneous tissue disorders:*

- *common:* rash, pruritus, subcutaneous or dermal bleeding or bruising (includes the following related terms: subcutaneous haematoma, skin haemorrhage, haemorrhage subcutaneous, petechiae, haematoma, ecchymosis, increased tendency to bruise, traumatic haematoma)

## **DOSAGE AND ADMINISTRATION**

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.

For oral use. BRILINTA can be taken with or without food.

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.

Lapses in therapy should be avoided. A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time.

Physicians who desire to switch patients from clopidogrel to BRILINTA should administer the first 90 mg dose of BRILINTA 24 hours following the last dose of clopidogrel. Switching from prasugrel to BRILINTA has not been investigated.

Treatment is recommended for at least 12 months unless discontinuation of BRILINTA is clinically indicated. In patients with ACS, premature discontinuation with any antiplatelet therapy, including BRILINTA, could result in an increased risk of cardiovascular death, or myocardial infarction due to the patient's underlying disease.

### **Special Populations**

#### **Elderly:**

No dose adjustment is required.

#### **Patients with renal impairment:**

No dose adjustment is necessary for patients with renal impairment. No information is available concerning treatment of patients on renal dialysis and therefore BRILINTA is not recommended in these patients.

### **Patients with hepatic impairment:**

No dose adjustment is necessary for patients with mild hepatic impairment. BRILINTA has not been studied in patients with moderate or severe hepatic impairment (refer to CONTRAINDICATIONS).

### **OVERDOSAGE**

BRILINTA is well tolerated in single doses up to 900 mg. GI toxicity was dose-limiting in a single ascending dose study. Other clinically meaningful adverse effects which may occur with overdose include dyspnoea and ventricular pauses.

In the event of overdose, observe for these potential adverse effects and consider ECG monitoring.

There is currently no known antidote to reverse the effects of BRILINTA, and BRILINTA is not expected to be dialysable. Treatment of overdose should follow local standard medical practice. The expected effect of excessive BRILINTA dosing is prolonged duration of bleeding risk associated with platelet inhibition. If bleeding occurs appropriate supportive measures should be taken.

Contact the Poisons Information Centre on 131126 for advice on management.

### **PRESENTATION AND STORAGE CONDITIONS**

BRILINTA tablets are presented as round, biconvex, yellow, film-coated tablets. The tablets are marked with "90" above "T" on one side and plain on the other.

Calendar blister in cartons of 14 (1x14 tablets sample pack) and 56 (4x14 tablets),

#### **Storage conditions**

Store below 30°C.

### **NAME AND ADDRESS OF SPONSOR**

AstraZeneca Pty Ltd  
ABN 54 009 682 311  
Alma Road  
NORTH RYDE NSW 2113

### **POISON SCHEDULE OF THE MEDICINE**

Prescription only medicine (Schedule 4)



## **DATE OF APPROVAL**

Date of TGA approval: 9 June 2011

BRILINTA is a trade mark of the AstraZeneca group of companies.

© AstraZeneca, 2011

## **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

**[www.tga.gov.au](http://www.tga.gov.au)**

Reference/Publication #