AstraZeneca

2.5 Clinical Overview

Drug Substance	Ticagrelor (formerly known as AZD6140)
Date	19 October 2009

2.5 Clinical Overview

Ticagrelor for the Prevention of Thrombotic Events (cardiovascular death, myocardial infarction, stroke) in Patients with Acute Coronary Syndromes

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Overview:

Abbreviation or special term	Explanation
ACS	Acute coronary syndromes
ADP	Adenosine diphosphate
ADR	Adverse drug reactions
AE	Adverse event
ARR	Absolute risk reduction/12 months post ACS event
ASA	Acetylsalicylic acid
AUC	Area under the concentration-time curve
AV	Atrioventricular
bd	Twice daily
CABG	Coronary artery by-pass grafting
CAD	Coronary artery disease
CHARISMA	The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance
CHF	Congestive heart failure
CHMP	Committee for medicinal products for human use
CI	Confidence interval
CLARITY-TIMI 28	Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-Thrombolysis in Myocardial Infarction (TIMI) 28 study.
C_{max}	Peak plasma concentration
COMMIT	Clopidogrel and Metoprolol in Myocardial Infarction Trial
COPD	Chronic obstructive pulmonary disease
CTD	Common technical document
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events trial
CV	Cardiovascular
CYP	Cytochrome P450
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EMEA	European Medicines Agency
FDA	Food and Drug Administration (US Department of Health and Human

Abbreviation or special term	Explanation
	Sciences)
GCP	Good clinical practice
GI	Gastrointestinal
GMP	Good manufacturing practice
HR	Hazard ratio
ICH	International Conference on Harmonisation
IPA	Inhibition of platelet aggregation
IPA_{max}	Maximum inhibition of platelet aggregation
IR	Immediate release
MI	Myocardial infarction
NDA	New drug application
NNT	Number needed to treat
NSTE	Non ST elevation
NSTE-ACS	Non ST elevation acute coronary syndrome
NSTEMI	Non ST elevation myocardial infarction
od	Once daily
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic
PDCO	EMEA Paediatric Committee
PK	Pharmacokinetic(s)
PLATO	Phase III Study D5130C05262 - A study of PLATelet inhibition and Patient Outcomes
PPI	Proton pump inhibitors
RRR	Relative risk reduction
SPA	Special protocol assessment
STEMI	ST elevation myocardial infarction
$T_{1/2}$	Terminal elimination half-life
TIMI	Thrombolysis in Myocardial Infarction
T_{max}	Time to reach peak concentration
UA	Unstable angina

INTRODUCTION

AstraZeneca seeks marketing approval for the use of ticagrelor 90 mg, previously known as AZD6140, for the reduction of risk of fatal and nonfatal vascular events following acute coronary syndromes (ACS).

> **Proposed indication:** Ticagrelor is indicated for 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 or CABG.

Cardiovascular (CV) disease represents the major cause of mortality in the developed world (World Health Organization 2009), with the majority of CV deaths due to coronary artery disease (CAD). ACS encompasses the spectrum of threatened, evolving, and completed myocardial infarction (MI). As the acute presentation of CAD, ACS accounts for the vast majority of CAD deaths and nonfatal CAD-related disability. Despite the widespread adoption of intensive monitoring and prompt treatment of cardiac electrical instability, thrombolytic therapy, acute invasive interventions, and dual antiplatelet therapy with acetylsalicylic acid (ASA) and thienopyridines, approximately 1 in 3 ACS patients dies, has a repeat MI, or requires re-hospitalisation within 6 months. Limitations in currently available antiplatelet medications contribute to this important need for better prevention. Patients need antiplatelet medications with better overall efficacy, quicker onset and offset of action, and less variable response in any given patient.

When patients present to health caregivers with signs and symptoms of ACS, they receive early antiplatelet treatment with ASA and also, in many instances, the platelet adenosine diphosphate (ADP)-receptor antagonist clopidogrel. An electrocardiogram (ECG) shows ST-elevation myocardial infarction (STEMI) or a non-ST elevation (NSTE) ACS event. Current guidelines indicate dual antiplatelet therapy with ASA and clopidogrel for all ACS patients. Those with STEMI usually receive accelerated care, including cardiac catheterisation, leading to percutaneous coronary intervention (PCI), coronary artery bypass (CABG) surgery, or management with medication alone. For them, time from presentation to re-establishing coronary flow impacts survival (Antman et al 2008). Those with NSTE-ACS have the same treatment options; however, interventions are less time-critical. NSTE-ACS patients will less urgently be diagnosed with either a documented MI (NSTEMI), or unstable angina (UA).

The keystone of the ticagrelor development programme, the multicentre, randomised, active control, double-blind, Phase III study PLATO, enrolled over 18 000 patients. The cohort contains the full spectrum of ACS patients as they present to healthcare professionals, consisting of STEMI, NSTEMI, and UA, and as they undergo treatment with PCI, CABG, or medicines and supportive therapy alone. No single category within the spectrum of ACS and no particular treatment path dominated the study cohort. The PLATO study design complied with current global ACS practice guidelines and accommodated evolving trends in clinical practice. Consequently, its results apply to contemporary clinical practice.

1. PRODUCT DEVELOPMENT RATIONALE

1.1 Clinical background

1.1.1 Acute coronary syndromes: a major public health concern

CV disease constitutes the single, largest cause of hospitalisations and of mortality and morbidity in the developed world, far outnumbering the mortality rates for cancer (World Health Organization 2009). It is the main cause of death in Europe, accounting for over 4.3 million deaths per year (Allender et al 2008a). Just under half of these deaths are from CAD and nearly a third are from stroke. The prevalence of CV disease varies with age and gender. Values in the UK span 1.6% to 14.4% for men between the ages of 65 and 74 years (Allender et al 2008b). ACS incidence, per 10 000 individuals per year, varies from 5 (Japan; Hoshida et al 2004) to 45 (US; Lloyd-Jones et al 2009) cases. It accounted for over 1.3 million unique hospitalisations in the US in 2006, and is predicted to account for 785 000 new cases there in 2009 (Lloyd-Jones et al 2009).

Despite dramatic improvement in preventing subsequent coronary and cerebral events following ACS in the last 20 years, large numbers of patients still suffer serious CV events including death. Patients with ACS have immediate, substantial risk: within 6 months, one-third will die, have a recurrent MI, or require re-hospitalisation (Collinson et al 2000).

1.1.2 Pathophysiology of acute coronary syndromes

Atherosclerotic CV disease is a world-wide public health concern because of the death and disability that result from coronary and cerebral thrombotic events. The disease process of atherosclerosis is well characterised and the key manifestation is the development of plaques in artery walls. Such plaques, containing focal accumulations of cholesterol and inflammatory cells, can grow in such a way as to partially occlude vessels and limit blood flow. Such flow limitations can produce chronic symptoms like exertional angina. Plaques can also abruptly erode or rupture due to mechanical instability of the plaque surface. When atherosclerotic plaques erode or rupture, the exposed contents of the plaque activate circulating platelets and the coagulation cascade. Aggregation of platelets follows quickly, and rapidly promotes the formation of thrombus, which partially or totally occludes the vessel, leading to an acute ischaemic syndrome. Antiplatelet drugs like ticagrelor reduce platelet aggregation, interrupting this process (Berger 2005).

When thrombus forms in coronary arteries, this sequence of events constitutes ACS. Depending on the location, degree of occlusion, and persistence of the thrombus, ACS represents a spectrum with varying severity of clinical consequences. These range from unstable angina (signs and symptoms of an MI but without identifiable permanent damage to heart muscle), to acute MI, with evidence of cardiac muscle death. Although the ECG further classifies MI as either STEMI or NSTEMI, and the extent of heart muscle damage and risk of acute complications differs for these subsets, the underlying pathophysiology is the same: platelet aggregation on extruded plaque. Thus, for all types of ACS, early, effective antiplatelet therapy impacts outcome.

1.1.3 Current standard of care in acute coronary syndromes

Patients with ACS receive antiplatelet therapy as soon as possible, before caregivers decide on a treatment path. Whether or not a patient with ACS undergoes coronary angiography, PCI, CABG surgery, or none of these, guidelines worldwide specify dual antiplatelet therapy consisting of ASA and an ADP receptor antagonist for all patients, during and following the index event (Anderson et al 2007; Antman et al 2008; King et al 2008).

ASA permanently disables an enzyme in platelets, cyclooxygenase, responsible for the production of thromboxane, which, when released by a variety of platelet activating stimuli, promotes platelet aggregation. In this way, ASA effectively inhibits platelet aggregation, reflected in the results of earlier clinical trials of ASA vs placebo in ACS (ISIS-2 1988). However, ASA does not directly interfere with the action of ADP, an endogenous mediator of platelet aggregation more powerful than thromboxane. Thus, ASA is only partially effective; it provides submaximal protection from various sources of platelet activation involved in ACS.

The ADP receptor antagonists ticlopidine, clopidogrel, and prasugrel inhibit the action of ADP at platelet receptors responsible for initial activation ($P2Y_1$) and for more prolonged or persistent aggregation ($P2Y_{12}$). These drugs share chemical structures classifying them as thienopyridines. As prodrugs, all thienopyridines in current clinical use require metabolic activation following oral administration. Thienopyridine efficacy at blocking platelet aggregation derives from irreversible chemical modification of the $P2Y_{12}$ receptor by the active metabolites of these prodrugs, rendering affected platelets inhibited for their lifetime. Recovery of platelet function thus depends on replacement of these permanently inhibited platelets by newly generated platelets released from the bone marrow.

Evidence of the value of ADP-receptor antagonists in treating ACS has accumulated by ACS type. The CURE study showed that, in 12 562 NSTEMI patients, clopidogrel 75 mg daily plus ASA 75 to 325 mg daily, started within 24 hours of symptoms, reduced the risk of a major adverse CV event by 20% per year: 9.4% compared to 11.4% for ASA alone. Death from CV causes did not differ between treatment groups: 5.1% vs 5.5% for ASA alone. Major bleeding, 3.7% vs 2.7% ($p=0.001$), and total bleeding, 8.5% vs 5.0% ($p<0.001$), occurred more with clopidogrel (Yusuf et al 2001).

The COMMIT trial (Chen et al 2005) compared clopidogrel 75 mg plus 162 mg ASA daily to ASA alone in 45 852 STEMI patients in China. Death, reinfarction, or stroke reduced to 9.2% from 10.1% (9% relative risk reduction [RRR] over 4 weeks) with addition of clopidogrel to ASA within 24 hours of symptoms. Fewer patients taking clopidogrel plus ASA died from any cause, 7.5% vs 8.1% ($p=0.03$), before first discharge from hospital. No difference in bleeding emerged during the treatment period lasting up to 4 weeks.

The CLARITY-TIMI 28 study of 1863 STEMI patients also reported reduced risk when clopidogrel 75 mg daily was added to ASA 75 to 162 mg daily plus fibrinolytic and heparin, for a composite primary endpoint that included angiographic artery patency (Sabatine et al 2005b): 15.0% vs 21.7% after 30 days follow-up. Artery patency (11.7% vs 18.4%, $p<0.001$)

accounted for the bulk of the composite result, with no difference in death (2.6% vs 2.2%, p=0.49) or recurrent MI (2.5% vs 3.6%, p=0.08).

No prior trial has demonstrated a mortality benefit for NSTEMI in ACS, and only COMMIT has shown such for STEMI. These trials form the basis for approved indication for clopidogrel in the treatment of ACS and for current ACS practice guidelines recommending its use.

The TAXUS-IV (Stone et al 2004) and SIRIUS (Holmes et al 2004) trials specified 325 mg of daily ASA after PCI with drug-eluting stents. Incorporation of results from those trials into treatment guidelines in the US progressed just prior to finalisation of the PLATO clinical study protocol, allowing PLATO to have a provision for administration of 325 mg ASA in patients with stents. The development programme up to that time had specified ASA in doses up to 100 mg.

The CHARISMA study (Bhatt et al 2006) failed to show a benefit of clopidogrel 75 mg daily plus ASA 75 to 162 mg daily compared to ASA alone in non-ACS patients with atherosclerotic CV disease, including those with ACS events more than 12 months prior to study. Based on no demonstrated advantage beyond 12 months in CHARISMA for the planned PLATO comparator, clopidogrel plus ASA, the PLATO protocol limited ACS patient participation to 12 months for ethical reasons.

Current guidelines include recommendations for initiation of therapy with clopidogrel plus ASA as early as possible during an ACS event, including prior to angiography (Anderson et al 2007). Following the initial ACS event, patients should receive dual antiplatelet therapy for at least 1 month and ideally up to 1 year (Anderson et al 2007; Antman et al 2008). After drug-eluting stent implantation, therapy should continue for at least 12 months (Antman et al 2008, King et al 2008). European Guidelines further recommend treatment for 9 to 12 months for all ACS patients (Bassand et al 2007, Van de Werf et al 2008), regardless of management strategy.

1.1.4 Unmet need leading to rationale for ticagrelor development

Even with the current standard of care, ie, dual antiplatelet therapy with clopidogrel and ASA, serious CV events recur in approximately 11% of ACS patients, most of them within several months of the index ACS event (Yusuf et al 2001; Wiviott et al 2007). The need remains for antiplatelet therapy that provides greater efficacy over dual therapy with clopidogrel and ASA, preferably without increased risk of serious bleeding. Several of clopidogrel's properties underscore the need for a better antiplatelet medicine:

- The onset of action is relatively slow, with time to maximal inhibition of platelet aggregation (IPA) of approximately 8 hours even after a 600 mg loading dose (see Module 5.3.4.2, Study D5130C00048 CSR). However, the high-risk ACS setting often demands antiplatelet effect as quickly as possible after an ACS event.

- Clopidogrel's inhibition of platelets is incomplete. After a 600 mg loading dose, patients responsive to clopidogrel display a mean peak IPA of only 50%. At steady state, with chronic administration of 75 mg, clopidogrel-responsive patients have a mean IPA of only 60%. Higher IPA associates with better efficacy (Wiviott et al 2007).

- Clopidogrel's platelet inhibition is not consistently observed in all patients. Many patients, up to 30%, have a minimal or poor IPA response to clopidogrel plus ASA, manifest as a high interpatient variability in IPA (Gurbel et al 2003; Jernberg et al 2006). To be effective, the inactive prodrug clopidogrel requires transformation to its active metabolite. Inconsistent effect associates with major cardiac events (Matetzky et al 2004; Simon et al 2009).

- Irreversibility of antiplatelet effect also restricts the utility of clopidogrel and other thienopyridines. Irreversible platelet inhibition means that offset of effect requires the generation of new platelets. Scheduling of elective invasive procedures for patients receiving thienopyridines must balance the risks of thrombosis prior to surgery, due to interruption of antiplatelet therapy, and bleeding during and following surgery due to persistent antiplatelet effect. Because of this feature of thienopyridines, trauma or emergency surgical procedures in such patients frequently entail use of banked blood products, which carry their own short- and long-term risks.

The newest approved thienopyridine, prasugrel, provides substantially better (>80%) IPA and clinical efficacy than clopidogrel, but at the cost of a marked increase in major bleeding events, especially in patients over 75 years old, those with body weight <60 kg, those with a history of transient ischaemic attack or stroke, and in those undergoing CABG surgery (Wiviott et al 2007). Like clopidogrel, prasugrel inhibits aggregation permanently in circulating platelets. Its greater antiplatelet effect, coupled with the same property of irreversible binding leading to permanent platelet inhibition, seems to translate into a higher bleeding risk.

Based on the above, patients could benefit substantially from an antiplatelet agent with both quick onset and offset of action, one active upon absorption without requiring metabolic activation, with effects more consistent from patient to patient, and achieving better IPA than clopidogrel but without an increased risk of bleeding. This was the overall rationale for developing ticagrelor and the central goal of the development programme.

1.2 Overview of the ticagrelor development programme

1.2.1 Ticagrelor properties

Ticagrelor, formerly AZD6140, substantially reduces platelet aggregation, blocking the pathophysiologic process leading to intracoronary thrombosis in ACS. The first of a new chemical class of antiplatelet agents called cyclopentyltriazolopyrimidines, it has properties that importantly distinguish it from the thienopyridines. Ticagrelor is rapidly absorbed

following oral administration, and binds reversibly to the $P2Y_{12}$ platelet ADP receptor. In the acute setting, a rapid onset of effect gives the ability to provide better protection during a period of particularly high risk for the ACS patient. The pharmacodynamic (PD) effect of antiplatelet agents is traditionally assessed in blood samples from patients by measuring IPA. Because ticagrelor is not a prodrug requiring metabolic activation, it promptly achieves both a higher and more consistent IPA than clopidogrel. For example, following oral administration of a 600 mg loading dose of clopidogrel, measured IPA increases gradually, reaching a level after 8 hours that is achieved after only 30 minutes following a 180 mg loading dose of ticagrelor, which then continues to increase to 87% to 89% by 2 hours.

Non-clinical studies have shown that ticagrelor is metabolised mainly via cytochrome P450 CYP3A4/5, leading to the generation of an active metabolite (AR-C124910XX) and other, inactive metabolites. The active metabolite is at least as potent as ticagrelor at blocking the $P2Y_{12}$ receptor *in vitro*. As CYP3A4 enzymes are mainly responsible for ticagrelor metabolism and the formation of its active metabolite, the potential for important drug-drug interactions involving other substrates, inhibitors or inducers of this common metabolic pathway was assessed carefully in the development program. Elimination of ticagrelor is mainly via metabolism and excretion through the bile, so reductions in renal function should not influence dosage and administration.

Ticagrelor's reversible binding to the $P2Y_{12}$ receptor permits the return of platelet aggregation upon cessation of therapy. This process does not require the generation of new platelets or platelet transfusions. In experiments designed to document this, ticagrelor demonstrated a statistically significant, faster rate of IPA offset compared with clopidogrel from 4 to 72 hours following cessation of administration; IPA measurements are similar for ticagrelor at 3 days and for clopidogrel at 5 days following the last dose. Current labelling recommends stopping clopidogrel at least 5 to 7 days before elective surgery.

The pharmacologic and clinical profile of ticagrelor suggests that it has the potential to provide more consistent, more rapid, and more efficacious antiplatelet effects than does clopidogrel.

1.2.2 Objectives of the clinical development program

The development programme for ticagrelor focussed on patients with ACS. Data shown in the following sections of this summary support that the following has been achieved:

- to characterise ticagrelor's clinical pharmacology in sufficient depth and breadth to determine that it is suitable and tolerable for treating ACS and to provide ample prescribing information for physicians, considering their patients' complex health histories, medical conditions, and their variety of concomitant medications.

- to determine whether or not ticagrelor plus ASA is superior to clopidogrel plus ASA in the reduction of thrombotic vascular events in patients with ACS.

- to quantify in various ways the bleeding risks that accompany ticagrelor's antiplatelet effect.

- to probe for and discover other effects of ticagrelor, evaluate each thoroughly for its clinical impact, present a full safety profile to judge the balance of benefit and risk, and define an appropriate risk management plan.

Clinical pharmacology

The clinical pharmacology programme, comprised of 41 studies with approximately 1000 volunteers, has characterised well the pharmacokinetic (PK), PD, absorption, distribution, metabolism, excretion, and drug-drug interactions of ticagrelor (Table 1). PD studies included *ex vivo* assessments of platelet activation and aggregation, indices of bleeding risk, and adverse drug effects and their relationships to dose or exposure (see Module 2.7.2, Section 1.3). Ticagrelor demonstrates a profile appropriate for administration to ACS patients, with few issues warranting caution or special management.

Phase II

The Phase II programme consisted of 4 studies. Two of these (DISPERSE; DISPERSE2) led up to, and provided important design information for, the pivotal Phase III study. The other 2 studies (OFFSET; RESPOND) provide clinical insights into onset, offset, and extent of IPA following ticagrelor administration. The Phase II programme achieved its goals of identifying several potential safety concerns associated with ticagrelor administration, among them dyspnoea, ventricular pauses, and increase serum uric acid, so that the pivotal study could explore them in depth (see Section 5.1.1 of this Overview). The Phase II programme provided the evidence supporting the dosing regimen taken forward. The more than 1400 patients with either atherosclerosis/stable CAD (DISPERSE, OFFSET, RESPOND) or NSTE-ACS (DISPERSE2) participating in the Phase II programme formed a substantial safety database.

Phase III: the PLATO study

PLATO (Wallentin et al 2009) constitutes the single, pivotal efficacy and safety Phase III study of the ticagrelor development programme. The purpose was to confirm the findings obtained from pre-clinical, tolerability, dose-finding, and other Phase II studies. This large outcome study (N>18 600) compared efficacy, safety, and tolerability of ticagrelor with the current standard, clopidogrel. Its design encompassed clinically relevant aspects of ACS and its current, guideline-recommended treatment:

- Enrolment included patients across the entire spectrum of ACS: UA, STEMI, and NSTEMI. PLATO provided for all ACS treatment strategies, including PCI, CABG surgery, and medical management.

- Dual antiplatelet treatment began as soon as possible after randomisation, even before angiography, specifically within 24 hours of the index ACS event, to protect patients when they were at particularly high risk. Investigators had discretion to

provide an additional loading dose of the comparator, clopidogrel, as practiced in some regions depending on treatment strategy.

- Patients receiving chronic clopidogrel therapy could enrol, as could patients given open label clopidogrel upon admission to hospital prior to randomisation.
- Investigators could provide up to 325 mg ASA for up to 6 months, as recommended by guidelines in the US after stent placement (King et al 2008; Antman et al 2008).
- Based on the results of CHARISMA (Bhatt et al 2006), showing no dual antiplatelet advantage in non-ACS patients, treatment in PLATO extended no further than 12 months.

The results of PLATO thus deserve wide application to patients with ACS. Sections 1.1 and 1.4 of this Clinical Overview provide additional features, strengths, and limitations of the PLATO study design, conduct, and results.

Table 1 Scope of the clinical development program for ticagrelor

In vitro clinical pharmacology study	**1 study**
Phase I studies:	
Bioavailability, bioequivalence and food interaction	**9 studies**
Pharmacokinetics and initial tolerability	**5 studies**
Pharmacokinetics - intrinsic factors	**8 studies**
Pharmacokinetics - extrinsic factors (drug/drug interactions)	**15 studies**
Pharmacodynamics	**4 studies**

Phase II clinical pharmacology PK/PD studies			
Study name (number)	**No. and type of patients randomised**	**Doses and Duration of treatment**	**Condensed objective**
OFFSET (D5130C00048)	123 Patients with stable CAD	Ticagrelor: 180 mg loading dose then 90 mg bd + ASA 75 to 100 mg Clopidogrel: 600 mg loading dose then 75 mg od + ASA 75 to 100 mg 6 weeks	Assessment of onset and offset profiles by IPA of ticagrelor and of clopidogrel.
RESPOND (D5130C00030)	98 Patients with stable CAD 41 non-responders and 57 responders to clopidogrel	Ticagrelor: 180 mg loading dose then 90 mg bd + ASA 75 to 100 mg Clopidogrel: 600 mg loading dose then 75 mg od + ASA 75 to 100 mg 2 weeks	Assessment of IPA when switching from ticagrelor to clopidogrel; switching from clopidogrel to ticagrelor; and, giving ticagrelor to clopidogrel non-responders.

Table 1 Scope of the clinical development program for ticagrelor

Phase II studies providing design information for Phase III			
DISPERSE (D5130C00008)	201 Patients with documented atherosclerotic disease	Ticagrelor: 50, 100, 200, or 400 mg bd + ASA 75 to 100 mg Clopidogrel: 75 mg od + ASA 75 to 100 mg 28 days	Pharmacodynamic assessment by IPA after 14 and 28 days of various dosing regimens of ticagrelor plus ASA compared to clopidogrel plus ASA.
DISPERSE2 (D5130C00002)	990 Patients with non-ST segment elevation ACS	Ticagrelor: 270 mg loading dose then 90 or 180 mg bd +ASA 75 to 100 mg Clopidogrel: 300 mg loading dose then 75 mg od + ASA 75 to 100 mg 4, 8, or 12 weeks	Safety and tolerability assessment by adjudicated bleeding events after 4 weeks of 2 doses of ticagrelor plus ASA compared with clopidogrel plus ASA.
Phase III study			
Study name (number)	**No. of patients randomised**	**Dose of ticagrelor Comparator Duration of treatment**	**Primary objective**
PLATO (D5130C05262)	18 624 patients with ACS Ticagrelor: 9333 Clopidogrel: 9291	Ticagrelor: 180 mg loading dose then 90 mg bd + ASA 75 to 325 mg Clopidogrel: ≤600 mg loading dose then 75 mg od + ASA 75 to 325 mg 6 to 12 months	To test the hypothesis that ticagrelor is superior to clopidogrel for the prevention of vascular events in patients with ACS.
Planned studies			
PEGASUS (D5132C00001)	Planned: 13 500 Patients with ACS event 1 to 3 years in the past.	Ticagrelor: 90 mg bd + ASA 75 to 150 mg Placebo + ASA 75 to 150 mg At least 12 months up to 36 months	To compare long-term treatment with ticagrelor plus ASA to ASA alone in reducing the composite endpoint of CV death, non-fatal MI, and non-fatal stroke.

ACS Acute coronary syndromes; ASA acetylsalicylic acid; bd twice daily; CAD coronary artery disease; CV cardiovascular; IPA inhibition of platelet aggregation; MI Myocardial infarction; od once daily; PK/PD pharmacokinetic/pharmacodynamic.

A table of all studies completed in the ticagrelor program is presented in Common Technical Document (CTD) Module 5.2.

1.3 Compliance with GCP

AstraZeneca standard operating procedures, quality control measures, and internal audit programs provide reassurance that these clinical studies and this clinical program were carried out in accordance with Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines, as documented by the International Conference on Harmonization (ICH), the Food and Drug Administration (FDA), and the European Medicines Agency (EMEA).

PLATO featured the governance and operational committees commonly incorporated in large outcome trials, including an Executive Committee, and Operations Committee, each composed of international academic leaders in ACS and Sponsor representatives; an independent Data and Safety Monitoring Board (DSMB); and an independent Endpoint Adjudication Committee.

1.4 Regulatory guidance and advice

Regulatory advice

AstraZeneca sought regulatory advice from several Health Authorities, including the US FDA and the EMEA Committee for Medicinal Products for Human Use (CHMP), on the Phase III clinical development programme. A copy of the relevant minutes/advices from these interactions is provided (Refer to Module 1).

The following considerations were discussed and endorsed:

- The inclusion criteria for PLATO provided an appropriate patient population, which included the full spectrum of ACS.
- The use of CV death instead of all-cause mortality as a component of the primary composite endpoint.
- Approval could be based on a single study if statistically robust results were achieved.
- Use of the PLATO definitions to characterise bleeding
    - The CHMP expressed concern regarding the creation of a new bleeding scale and encouraged the use of bleeding scale used in other studies (eg TIMI).
- Use of a hierarchical testing procedure to test the secondary endpoints to achieve additional label claims.
- The proposal to allow an additional 300 mg loading dose of clopidogrel at the discretion of investigators.
- Use of a dosing regimen, which utilised a 180 mg bd dosing and allowed a dose reduction to 90 mg bd for patients on a moderate CYP3A4 inhibitor or for those intolerant to the 180 mg dose. After this advice was obtained, further analysis of the Phase I and Phase II data indicated that a single maintenance dose of 90 mg bd for all patients offered the best balance of safety with anticipated improved efficacy over clopidogrel. Since this change was made prior to the start of the study, all patients in PLATO received the 90 mg bd maintenance dose.

- The CHMP advised AstraZeneca that the mechanism for dyspnoea should be determined, but acknowledged that the safety data from PLATO would override safety data from exploratory studies.

The clinical programme was discussed prior to the start of the PLATO study at pre-Clinical Trial Application meetings with Health Canada and with the State Food and Drug Administration Center for Drug Evaluation in China.

Furthermore, agreement on the overall study design for the RESPOND study including the endpoints and definitions for the non-responders was obtained through a Special Protocol Assessment (SPA) with the US FDA. The FDA noted that all label claims would be discussed during the new drug application (NDA) review and that claims could only be based on a proper statistical significance decision tree.

Regulatory guidance

There is a CHMP 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). These notes, however, only consider drugs that are intended for use in the acute symptomatic phase of ACS (1 to 7 days) but are not intended for use with drugs for long-term prevention of CV events in stabilised patients. The guideline also does not consider the inclusion of patients with STEMI. The relevance of this guideline to the PLATO design was discussed during Scientific Advice and the key topics, which were endorsed, are described below.

In April of 2009, a CHMP guideline on evaluation of medicinal products for CV disease prevention came into effect in the EU (CHMP/EWP/311890/2007). This guideline is not relevant for this well-defined population of ACS and is therefore not applicable. Since this guideline came into effect after the PLATO trial was discussed, agreed with regulatory Health Authorities, and initiated, and also after the database was locked, the relevance of this guideline is not discussed in this Clinical Overview.

In addition, there is a CHMP 'Points to Consider on Multiplicity Issues in Clinical Trials' guidance document, CPMP/EWP/908/99. The PLATO analysis plan is consistent with this guideline.

Finally, there exists the CHMP 'Points to Consider on Application with 1. Meta-Analysis; 2. One Pivotal Study' guidance document(CPMP/EWP/2330/99), as well as the FDA Guidance for Industry 'Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products' regarding a single pivotal study. AstraZeneca believes that a regulatory submission based on the pivotal Phase III PLATO study satisfies the criteria laid out in those guidances, ie, compelling results with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency.

2. OVERVIEW OF BIOPHARMACEUTICS

Ticagrelor is provided as round, biconvex, yellow, film-coated tablets containing 90 mg of ticagrelor and intagliated with "90" above "T" on one side and plain on the other. Ticagrelor is an immediate release (IR) formulation intended for twice-daily (bd) administration for the prevention of thrombotic events in patients with ACS. The 90 mg ticagrelor IR tablet formulations were used in the Sponsor's worldwide clinical development program, and the Phase III tablet (FDN 334, 90 mg) is the proposed commercial formulation of ticagrelor.

Nine biopharmaceutic studies were conducted to determine the absolute bioavailability, bioequivalence, and effect of food on the PK of ticagrelor (see Module 2.7.1). Initial studies utilized a lactose-based formulation, FDN 239, at strengths 50, 100, 200, and 400 mg. Study D5130C00019 showed a 117% relative bioavailability for a mannitol-based formulation (FDN 299) to FDN 239, leading to 90 mg and 180 mg tablets for subsequent studies that would have utilized 100 mg and 200 mg FDN239 tablets.

Mean absolute bioavailability of ticagrelor following oral administration of the 90 mg IR tablet is 36% (95% confidence interval [CI]: 30%, 42%). Following 90 mg oral dosing to healthy volunteers in the fasted state, ticagrelor was rapidly absorbed with a mean peak plasma concentration (C_{max}) of approximately 500 ng/mL occurring approximately 1.5 hours after dosing. Ticagrelor converts rapidly to an active metabolite with a median time to reach peak concentration (t_{max}) of 2.5 hours. Mean terminal elimination half-life ($t_{1/2}$) for ticagrelor was 6.9 hours (range 4.5 to 12.8 hours). Ingestion of a high-fat meal had no effect on ticagrelor C_{max}, but resulted in a 21% increase in the area under the concentration-time curve (AUC). These small changes are considered of minimal clinical significance; therefore, ticagrelor can be given with or without food. No studies on bioavailability with crushed tablets or tablets dissolved prior to ingestion have been conducted.

Prior to the start of the Phase III study, the non-functional coating on the ticagrelor tablet was changed from a polyvinyl alcohol-based coating to an hydroxypropyl-methyl cellulose-based coating to produce FDN 334 (90 mg), which was the only formulation used in the Phase III study. These minor changes in the tablet coating did not affect *in vitro* dissolution performance, so a specific study to demonstrate bioequivalence for the coating modification was not considered necessary. In addition, the ticagrelor Phase III tablets manufactured at a commercial-scale facility (FDN 334 – Sweden) in Gartuna, Sweden were shown to be bioequivalent to those manufactured in a pilot-scale plant (FDN 334 - UK) in Charnwood, UK. Tablets manufactured at the commercial-scale site were used in the Phase III clinical study. The proposed commercial ticagrelor tablet is identical to the formulation used in the Phase III study, apart from the addition of intagliation, and that it will be manufactured at the same commercial-scale site.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

3.1 Pharmacokinetics

3.1.1 Absorption, distribution, metabolism, and excretion

Ticagrelor undergoes rapid absorption with peak plasma concentrations attained 2 to 3 hours after oral administration to patients with ACS. An active metabolite forms rapidly, attaining peak plasma concentrations 2 to 3 hours after oral ticagrelor ingestion. Pharmacokinetic results in ACS patients resemble closely those of patients with stable CAD and those of healthy volunteers (see Module 2.7.2, Section 3.1.1 and Section 3.1.6).

Ticagrelor's steady-state volume of distribution, 87.5 L, indicates it does not extensively distribute into or bind to tissues. Both ticagrelor and its primary active metabolite bind extensively (>99.7%) to plasma proteins; age, gender, severe renal impairment, and mild hepatic impairment do not affect protein binding. The unbound fraction, similar across populations studied, is relatively independent of plasma concentration (see Module 2.7.2, Section 3.1.2).

Both the AUC and C_{max} of both ticagrelor and its active metabolite show approximately proportional increases with increasing oral doses, indicating linear PK (see Module 2.7.2, Section 3.1.4). A standard high-fat meal has small impact on the exposure to ticagrelor and its active metabolite, increasing ticagrelor AUC by 21%, decreasing metabolite C_{max} by 22%, and with no effect on parent C_{max} or metabolite AUC. These data indicate that ticagrelor can be given with or without food (see Module 2.7.2, Section 3.1.1).

Cytochrome P450 (CYP) 3A enzymes largely account for ticagrelor's metabolism. For the proposed pathway in man, see Module 2.7.2, Figure 2. CYP enzymes 1A2, 2C19, and 2E1, do not contribute meaningfully *in vitro* to ticagrelor metabolism. Clinical pharmacology data show ticagrelor does not inhibit CYP3A4 and weakly inhibits the P-glycoprotein transporter (see Module 2.7.2, Section 3.1.3).

The primary route of ticagrelor metabolism is via hepatic metabolism. The active metabolite most likely undergoes excretion in bile. Neither depend on renal excretion, with <1% recovery in urine for parent and active metabolite. Ticagrelor has a mean $t_{½}$ of 6.9 hours; the active metabolite, 8.6 hours (see Module 2.7.1, Table 8).

3.1.2 Drug interactions

3.1.2.1 Interactions with the potential to increase ticagrelor exposure

Avoid strong CYP3A4 inhibitors

Co-administration of ticagrelor with ketoconazole, a strong CYP3A4 inhibitor, increased ticagrelor C_{max} equal to 2.4-fold and AUC to 7.3-fold, with decreases in C_{max} (89%) and AUC (56%) of the active metabolite (see Module 2.7.2, Section 3.1.8.1 and Module 5.3.3.4, Study D5130C00022 CSR). Other CYP3A4 strong inhibitors such as itraconazole, clarithromycin, nefazadone, and ritonavir would be expected to have similar effects. The exposure-response

analysis indicates shallow relationships for exposure with bleeding and dyspnoea (see Module 5.3.4.2, Exposure-Response Technical Report – Safety). Nevertheless, concomitant administration of strong CYP3A4 inhibitors with ticagrelor should be avoided as proposed in the Product Information.

Allow moderate CYP3A4 inhibitors

Co-administration of ticagrelor with diltiazem, a moderate CYP3A4 inhibitor, increased ticagrelor C_{max} 69% and AUC 174%, with a 38% decrease in active metabolite C_{max} (AUC unchanged). Moderate CYP3A inhibitors decreased the population mean clearance of ticagrelor by about 64% in ACS patients (see Population PK Technical Report, Module 5.3.3.5). Concomitant administration of a moderate CYP3A inhibitor drug with ticagrelor increases ticagrelor exposure similar to a doubling of ticagrelor dose from 90 mg bd to 180 mg bd. The DISPERSE study indicated that both 100 mg and 200 mg bd maintenance regimens of a prior formulation, similar to the current 90 and 180 mg dosages, resulted in IPA near the top of the IPA concentration-effect curve. Thus the increased exposure resulting from concomitant administration of 90 mg bd ticagrelor with a moderate CYP3A4 inhibitor would not result in a much greater degree of IPA. The DISPERSE2 study confirmed the implications of this relationship, as it uncovered no safety differences, particularly for bleeding, for the 90 mg bd vs 180 mg bd doses in patients with ACS over 12 weeks. Exposure-response analyses predict a small impact on bleeding for this magnitude of exposure increase (see Module 5.3.4.2, Exposure-Response Technical Report – Safety).

PLATO uncovered no drug interaction-related adverse events (AE) for concomitantly administered moderate CYP3A4 inhibitors. Ticagrelor's efficacy benefit and the lack of difference in 'Major' bleeding were consistent for patients taking and those not taking moderate CYP3A4 inhibitors. These data indicate that moderate CYP3A4 inhibitors such as diltiazem, verapamil, fluconazole, erythromycin, aprepitant, and amprenavir can be co-administered with ticagrelor.

3.1.2.2 Interactions with the potential to decrease ticagrelor exposure

CYP3A inducers

Co-administration of ticagrelor and rifampin/rifampicin, a CYP3A inducer, decreased ticagrelor C_{max} by 73% and AUC by 86% in volunteers (see Module 2.7.2, Section 3.1.8.2 and Module 5.3.3.4, Study D5130C00039 CSR). This agrees with the findings of the population PK analysis of ACS patients in which patients co-administered CYP3A inducers had increased ticagrelor clearance of approximately 110% (see Module 5.3.3.5, Population PK Technical Report). Other CYP3A inducers such as dexamethasone, phenytoin, carbamazepine, and phenobarbital have the ability for a similar effect. This degree of reduced exposure could potentially impact clinical efficacy.

3.1.2.3 Interactions with potential to affect exposure of other drugs

Simvastatin

Co-administration of ticagrelor 180 mg bd for 7 days and simvastatin increased both simvastatin C_{max} by 81% and AUC by 56% and simvastatin acid C_{max} by 64% and AUC by 52%. Some individual increases reached 2- to 3-fold, so that a 40 mg simvastatin dose along with doubled exposure to ticagrelor could produce simvastatin exposure equivalent to that from 120 mg (see Module 2.7.2, Section 3.1.8.3). Consideration should be given to the clinical significance of the potential magnitude and range of changes on simvastatin exposure in patients requiring more than 40 mg of simvastatin. Ticagrelor PK was unaffected (see Module 5.3.3.4, Study D5130C00024 CSR). Ticagrelor may have similar effect on lovastatin, but is not expected to have a clinically meaningful effect on other statins, based on their clinical pharmacology and safety profiles.

Atorvastatin

Co-administration of ticagrelor and atorvastatin produced minor increases in atorvastatin acid C_{max} and AUC and similar increases (13% to 55%) for atorvastatin metabolites (see Module 2.7.2, Section 3.1.8.3). Ticagrelor and atorvastatin can be co-administered because the therapeutic profile of atorvastatin can accommodate these modest changes. Ticagrelor PK was unaffected (see Module 5.3.3.4, Study D5130C00025 CSR).

Oral contraceptive use

Co-administration of ticagrelor with levonorgestrel and ethinyl estradiol increased ethinyl estradiol exposure about 20% with no effect on PK of levonorgestrel or in concentrations of endogenous relevant hormones (see Module 5.3.3.4, Study D5130C00042 CSR). A decrease in contraceptive efficacy is not expected when co-administered with ticagrelor.

P-glycoprotein transporter

Ticagrelor and its major metabolite are in vitro substrates and inhibitors of MDR1. Co-administration of ticagrelor and digoxin, a P-glycoprotein substrate, increased mean trough digoxin levels about 30%, with some individual maximum increases about 200%. Ticagrelor PK was unaffected. Other P-gp substrate drugs might have similar exposure changes in the presence of ticagrelor. Appropriate clinical or laboratory monitoring is recommended when giving the narrow therapeutic index, P-gp-dependent drug digoxin concomitantly with ticagrelor (see Module 2.7.2, Section 3.1.8.5).

Commonly co-administered haemostatic and anti-haemostatic agents

Ticagrelor PK was unaffected with co-administration of ASA 75 to 300 mg daily, intravenous heparin, enoxaparin, or desmopressin. Ticagrelor did not affect the impact of heparin on activated partial thromboplastin time or activated coagulation time assays, or that of enoxaparin on factor Xa activity.

3.2 Pharmacodynamics

The ticagrelor development programme used final extent of IPA to 20 μM ADP via light transmission aggregometry as its prime biomarker for antiplatelet activity. A sigmoid E_{max} model describes the relationship of IPA to plasma concentrations of ticagrelor and/or its active metabolite. IPA increases with increasing ticagrelor dose, and then decreases as ticagrelor plasma concentrations decline, indicative of reversible receptor binding.

3.2.1 Onset of effect

Ticagrelor works rapidly, as shown by 47% mean IPA measured 30 minutes after a 180 mg loading dose. This approaches the 50% maximum IPA (IPA_{max}) attained 8 hours after a 600 mg clopidogrel loading dose. Ticagrelor's IPA_{max}, about 88%, is reached 2 hours after the loading dose and maintains for another 6 hours. The rapid onset of IPA closely follows the rise in ticagrelor plasma concentrations, reflecting an active drug that is rapidly absorbed (see Module 5.3.4.2, D5130C00048 CSR and Module 2.7.2, Section 3.2.5).

3.2.2 Offset of effect

In vitro studies indicate that ticagrelor reversibly binds to the $P2Y_{12}$-receptor, suggesting that recovery of platelet aggregation follows falling plasma concentrations of ticagrelor and its active metabolite, rather than it depends on replacement of irreversibly inhibited platelets, as occurs with clopidogrel and prasugrel.

Ticagrelor has a faster offset compared to clopidogrel, as shown by comparing the steepness of the slopes of the IPA vs time curves following cessation of therapy (–1.037 vs –0.482% per hour; $p<0.0001$). After 6 weeks dosing with ticagrelor, patients with stable CAD have IPA that is 20% to 30% absolute greater than that after 6 weeks dosing with clopidogrel. Despite starting from this greater level of inhibition, both treatment groups display similar IPA 24 hours after final dosing. Thus, patients who miss one 90 mg bd dose of ticagrelor maintain IPA no less than that of patients receiving clopidogrel 75 mg od (see Module 5.3.4.2, D5130C00048 CSR, Figure 18 and Module 2.7.2, Section 3.2.6). While lapses in therapy should be avoided, a patient who misses a dose of ticagrelor should take one 90 mg tablet (their next dose) at its scheduled time.

Moreover, 3 days after stopping ticagrelor, IPA measured as low as that obtained 5 days after stopping clopidogrel. Likewise, IPAs only 5 days after stopping ticagrelor but at 7 days after stopping clopidogrel achieve those of patients taking placebo (see Module 5.3.4.2, D5130C00048 CSR, Figure 18). Thus, restoration of platelet aggregation occurs faster with ticagrelor compared to clopidogrel.

3.2.3 Consistency of effect

Up to 30% of patients treated with standard clopidogrel doses have sub-optimal levels of platelet inhibition. These non-responders may experience greater risk of ischaemic events despite clopidogrel treatment (Gurbel et al 2003, Mobley et al 2004).

Ticagrelor does not depend on metabolic activation for its antiplatelet effect. It results in consistently higher IPA compared to that obtained with clopidogrel in both responders and non-responders: IPA as soon as 4 to 8 hours after a ticagrelor 180 mg loading dose was 80% to 96% mean in responders (see Module 5.3.4.2, Study D5130C00030, Figure 25) and 74% to 90% mean in non-responders (see Module 5.3.4.2, Study D5130C00030, Figure 5) with or without prior clopidogrel treatment.

Across all clinical pharmacology studies with IPA_{max} estimates, all 246 subjects receiving 90 mg or higher ticagrelor doses had an IPA_{max} >50%, suggesting that there are no non-responders to ticagrelor.

Ticagrelor achieves greater and more consistent IPA compared to clopidogrel in both stable CAD patients (see Module 5.3.3.2, Study D5130C00008 CSR) and ACS patients (see Module 5.3.3.2, Study D5130C00002 CSR). The extent of IPA at steady state is maintained, and does not decrease, in volunteers or in patients with stable CAD or ACS, following 6, 8, or 12 week dosing.

3.2.4 Switching between clopidogrel and ticagrelor

In patients with stable CAD judged responsive to clopidogrel, based on response to 20 μM ADP with light aggregometry, 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% (see Module 2.7.2, Section 3.2.4). Increased IPA occurred after the first dose when switching to ticagrelor. Patients with stable CAD judged non-responsive to a single 600 mg dose of clopidogrel showed a 40% absolute increase in mean IPA upon switching from stable dosing of clopidogrel to ticagrelor. Ticagrelor's IPA response occurs whether or not patients respond to clopidogrel.

A loading dose of ticagrelor achieves >90% IPA in clopidogrel responders and >70% IPA in clopidogrel non-responders, with or without prior clopidogrel treatment. Residual clopidogrel has little effect on the ticagrelor IPA profile. Patients can switch from clopidogrel to ticagrelor without interruption of antiplatelet effect (see Module 5.3.4.2, Study D5130C00030 CSR). The first dose of ticagrelor should be given 24 hours following the last dose of clopidogrel.

3.3 Special populations

3.3.1 Renal Impairment

Ticagrelor C_{max} and AUC, and the AUC of its active metabolite, each decreased minimally (about 20%) in patients with severe renal impairment, compared to respective values of matched subjects with normal renal function. The groups showed similar IPA, although the 10 subjects with severe renal impairment had greater variability of individual response. No dosing adjustment is required in patients with renal impairment. Patients undergoing renal dialysis have not been studied or treated with ticagrelor (see Module 5.3.3.3, D5130C00015 CSR and Module 2.7.2, Section 3.1.7.6).

3.3.2 Hepatic impairment

C_{max} and AUC for ticagrelor increased minimally (12% and 37% respectively) in 10 patients with mild hepatic impairment, compared to matched healthy subjects. IPA remained similar between the two groups. No dose adjustment is necessary for patients with mild hepatic impairment. Patients with moderate or severe hepatic impairment have not undergone study or treatment with ticagrelor (see Module 5.3.3.3, D5130C00016 CSR and Module 2.7.2, Section 3.1.7.5).

3.3.3 Age, race and gender

Increases in exposure to ticagrelor and its active metabolite (about 50% to 60% for C_{max} and AUC of both) occurred in 20 subjects ≥65 years compared to 19 younger subjects. Based on shallow exposure-response relationships (see Module 5.3.4.2, Exposure-Response Technical Report – Safety), these alterations do not impact efficacy or safety (see Module 2.7.2, Section 3.1.7.1). No subjects under age 18 years have received ticagrelor.

C_{max} and AUC for ticagrelor in Japanese subjects increased about 40% compared to those in Caucasians. When normalized by body weight, the exposure increased only about 20% in Japanese (see Module 2.7.2, Table 6 and Module 5.3.3.3, Study DC5130C05267 CSR). This exposure difference is not clinically meaningful. PK parameters for ticagrelor and its active metabolite in healthy Chinese subjects are similar to those in healthy Caucasian subjects (see Module 2.7.2, Table 7 and Module 5.3.3.3, Study DC5130C00054 CSR). Population PK modelling analysis revealed a 39% higher bioavailability for ticagrelor in patients of Asian descent (see Module 5.3.3.5, Population PK Technical Report) vs Caucasians, in agreement with the results in healthy Japanese vs Caucasians (see Module 5.3.3.3, Study DC5130C05266 CSR and Study DC5130C05267 CSR).

Modestly higher values for C_{max} and AUC for ticagrelor and its active metabolite, ranging from 37% to 52%, occurred in 19 women compared to 20 men (see Module 2.7.2, Table 5).

3.3.4 Summary for special populations

PK and PD studies of populations of special interest disclosed no clinical important results that would lead to dosing alterations or adjustment.

3.3.5 Population PK analysis

An extensive population PK analysis of samples in the clinical programme (see Population PK Technical Report, Module 5.3.3.5) disclosed additional smaller changes in PK, which, when considered along with the shallow exposure-response relationships for safety issues (see Module 5.3.4.2, Exposure-Response Report - Safety) indicate no cause for clinical concern:

- Habitual smoking increased ticagrelor clearance 22% (95% CI 19%, 25%).
- Body weight affected clearance <20% from median to either the 10^{th} or 90^{th} percentile.

- Women had 31% higher exposure to ticagrelor active metabolite compared to men (95% CI 30%, 33%).

- Asians had 39% higher bioavailability (95% CI 33%, 46%) compared to Caucasians.

4. OVERVIEW OF EFFICACY

Proposed indication: Ticagrelor is indicated for 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 or CABG.

This overview of efficacy focuses on PLATO with mention of results of other components of the development programme only as they relate to efficacy. It also discusses strengths and limitations of these efficacy data and their relevance to proposed labels.

4.1 Design of the pivotal study, PLATO, in ACS

Clinical evidence for the efficacy of ticagrelor derives from the PLATO study, a comparison of ticagrelor to clopidogrel, each given in combination with ASA and other standard therapy. This section supports the contention that the PLATO study design allows its results to apply to a broad spectrum of ACS patients worldwide.

4.1.1 Overall design aspects

PLATO, an 18 624 patient randomised, double-blind, parallel group, Phase III, efficacy and safety study, compared ticagrelor to clopidogrel for prevention of vascular events in patients with non-ST or ST- elevation ACS. PLATO enrolled a broad and inclusive population of patients with ACS (UA, NSTEMI, STEMI), including patients planned for invasive management, ie, coronary angiography with PCI or CABG, as well as patients intended for medical management. Consistent with current guidelines, PLATO initiated dual antiplatelet therapy within 24 hours of the index event, allowing early platelet inhibition, usually prior to coronary angiography.

PLATO meets ICH criteria for robust study design of a therapeutic confirmatory study, and contains the same features of previous trials of antiplatelet agents in ACS that provide scientifically valid results, ie, randomisation, double-blinding, and multinational, multisite involvement. The PLATO Executive and Operations Committees designed and oversaw the conduct of the study. An independent DSMB reviewed unblinded data to conduct a pre-specified interim analysis. These committees included international representation as per ICH guidance. A separate independent committee, also with multinational representation, adjudicated study endpoints.

PLATO enrolled patients presenting with all types of ACS, except those with low risk profiles, and allowed treatment with all management paths. This distinguishes PLATO from

previous antiplatelet trials that restricted enrolment to one type of ACS such as NSTEMI (Yusuf et al 2001), or STEMI (Chen et al 2005; Sabatine et al 2005a), or one treatment path (Wiviott et al 2007; Sabatine et al 2005a). The size of the PLATO study (N=18 624) allows application of its results to the breadth of ACS diagnoses and treatment paths, simplifying and unifying them to minimise potential errors, because a clinician needs to give dual antiplatelet therapy before collecting evidence that decides a treatment path, as guidelines indicate. Specific dual antiplatelet therapy that applies to all paths, helps by facilitating and simplifying treatment.

The PLATO enrolment criteria were applied to the 'Registry of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA)' database of ACS patients in Sweden admitted to coronary care units, to assess how well PLATO represents the whole ACS population. Only 8.9% of patients admitted for a suspected MI during 2007 in Sweden met an exclusion criterion for PLATO; fully 79.4% met all inclusion and no exclusion criteria (see Module 5.3.5.1, D5130C05262 CSR, Section 5.2.5).

4.1.1.1 Populations not studied

The clinical development programme excluded certain patients. Specifications for each patient group, along with rationale for exclusion, appear below.

- Patients with a propensity to bleed due to recent trauma, recent surgery, active or recent gastrointestinal (GI) or intracranial bleeding, or those with moderate or severe hepatic impairment. These exclusions generally apply to antiplatelet agents as a class.

- Patients receiving concomitant medicinal products that may increase the risk of bleeding, such as fibrinolytics or oral anticoagulants, within 24 hours of ticagrelor dosing. This exclusion applies to potent antiplatelet agents as a class.

- Patients with an increased risk of bradycardic events, such as patients without a pacemaker who have sick sinus syndrome, 2nd or 3rd degree atrioventricular (AV) block or bradycardic-related syncope. This exclusion arose from a safety signal of ventricular pauses detected in DISPERSE2. Limited clinical experience suggests that caution be advised when considering therapy with ticagrelor for patients with these conditions at risk of bradycardia who have no implanted pacemaker.

- PLATO enrolled a predominantly Caucasian (91.1%) population, with 5.8% Asians, 1.2% Blacks, and 1.4% other. PLATO's racial demographics resemble those of other worldwide ACS trials (Yusuf et al 2001).

- Pregnant or lactating women. These patients comprise a population generally excluded from large clinical studies.

- No clinical study has been conducted in the paediatric population to date. ACS occurs very rarely in children. The EMEA Paediatric Committee (PDCO) granted a waiver for ACS. The Sponsor intends to obtain a waiver from the US FDA as well.

4.1.2 Choice of ticagrelor dosing regimen

Those PLATO patients randomised to the ticagrelor treatment arm received a loading dose of 180 mg followed by 90 mg bd. Those undergoing PCI more than 24 hours after the loading dose received an additional 90 mg for protection against thrombosis incited by coronary manipulation; a 300 mg additional loading dose was allowed in the clopidogrel arm at any time prior to PCI.

Although no surrogate markers exist to predict the efficacy of antiplatelet agents for risk reduction in ACS, IPA provided a reasonable biomarker to guide initial dosing considerations. The Phase II DISPERSE study of patients with stable CAD determined that 50 mg bd of ticagrelor provided IPA no better than that provided by clopidogrel, while 100 mg bd or 200 mg bd doses substantially exceeded IPA from clopidogrel. Based on those results, and a formulation change to a tablet with increased bioavailability (see Section 2 of this Overview), DISPERSE2 enrolled 990 patients with ACS to compare the safety of 90 mg bd and 180 mg bd of ticagrelor to clopidogrel. Not powered for efficacy comparisons, DISPERSE2 indicated no increase in major bleeding at 180 mg bd compared to 90 mg bd, but did suggest an increased incidence of ventricular pauses. As a result of this potential safety issue, the Executive Committee and Sponsor chose 90 mg bd ticagrelor for PLATO.

The loading dose, 180 mg, results in a rapid, high degree of IPA: 43 of 48 patients with CAD (90%) attain at least 70% IPA measured 2 hours after oral administration (see Module 5.3.4.2, D5130C00048 CSR, Table 18). IPA values obtained from larger loading doses were viewed as not likely to provide additional clinical benefit. Special populations do not warrant loading dose reductions: the possibility of inadequate antiplatelet activity in acute settings creates greater risk than potential transiently increased exposure, especially since PK data indicate special populations experience only modest changes in exposure (see Module 2.7.2, Table 9).

4.1.3 Comparator choice and dosing regimen

PLATO compared ticagrelor against the thienopyridine clopidogrel, the standard of care for ADP-receptor antagonist antiplatelet agents, using a loading dose, 300 mg, and maintenance dose, 75 mg od, as specified in multiple guidelines (Anderson et al 2007; Antman et al 2008; Bassand et al 2007; Van de Werf et al 2008). Based on changing medical practice and evolving science, the PLATO protocol allowed for an additional 300 mg clopidogrel loading dose, for a total of 600 mg, for patients planned to undergo PCI. PLATO permitted investigators to have administered open label clopidogrel to any patient upon admission to hospital for index ACS event, prior to randomisation, and allowed enrolment of patients taking chronic open label clopidogrel at the time of the index ACS event. In this way, the protocol accommodated as many actual ACS situations as possible. All ACS trials, including PLATO, use a background of ASA therapy with lower maintenance doses (75 to 150 mg) after variable loading doses.

4.1.4 Study endpoints for efficacy

The components of the primary efficacy composite endpoint of PLATO, CV death, MI, and stroke, each represents objectively-determined permanent loss of vital organ function. Previous outcome trials in ACS have established this composite as a well-accepted indicator of risk reduction for thrombotic events following ACS (Yusuf et al 2001; Wiviott et al 2007). An independent adjudication committee blinded to treatment group evaluated relevant clinical data for every endpoint. Adjudication utilised pre-specified definitions for every component of the primary and secondary endpoints, including silent MI, and for stent thrombosis and for all bleeding endpoints (see Module 5.3.5.1, D5130C05262 CSR, Appendix 12.1.1, Clinical Study Protocol, Section 4.6.1).

The first secondary endpoint tested the composite of MI, stroke, and CV death in the subgroup of patients with intent for invasive management at randomisation. Subsequent secondary efficacy endpoints, evaluated on the whole population and, enumerated here in pre-specified order of testing, provided important perspective on robustness of the primary result by testing (1) substituted elements; (2) an expanded composite with more subjectively defined events; and (3) individual components of the primary composite:

- the composite of MI, stroke, and all-cause mortality
- the composite of all MI (includes silent MI by ECG), stroke, CV death, severe recurrent cardiac ischaemia, recurrent cardiac ischaemia, transient ischaemic attack, and other arterial thrombotic events
- each component of the primary composite efficacy endpoint individually in the order of MI, CV death, and then stroke
- all-cause mortality alone

4.1.5 Statistical issues

The intention-to-treat approach for efficacy analyses utilised the Full Analysis Set, consisting of all patients randomised to study treatment, for their duration of participation in PLATO. The primary analysis employed Cox proportional hazards of time to event with treatment group as factor. The formal hierarchical analysis pre-specified the order of consideration for secondary endpoints, thus controlling the experiment-wise type I error. The composite endpoint specified for the intent for invasive management subpopulation headed the sequence, followed by the list of endpoints for the entire cohort in order of appearance in Section 4.1.4 above.

Sample size determination

Based on an expected event rate in the clopidogrel treatment arm of 11% over 12 months (Mehta et al 2000; Yusuf et al 2001), approximately 1780 events in the primary composite would yield 90% power to detect a target RRR of 13.5%, accounting for study medication

discontinuations. As an event-driven study, final enrolment and duration of treatment in PLATO depended on the event rate estimated during the study.

Subgroup analyses

An exploratory analysis of the primary efficacy and safety endpoints evaluated the robustness and consistency of treatment effect using 29 categories pre-specified in the Statistical Analysis Plan (see Module 5.3.5.1 D5130C05262 CSR, Appendix 12.1.9, Statistical Analysis Plan). These 29 categories involved 31 separate treatment-by-subgroup statistical interaction tests, because age and weight each have 2 defined dividing criteria. Three additional subgroups were added after database lock: whether or not new ST-segment elevation or left bundle branch block was present at randomisation; history of prior stroke or TIA at randomisation; and whether or not the patient received a proton pump inhibitor medication on the day of randomisation. The 34 tests for treatment-subgroup interaction did not undergo adjustment for multiple comparisons. One pre-specified category, clopidogrel loading dose (see Section 4.3.3 of this Overview), did not appear in the supplement to the initial publication (Wallentin et al 2009).

4.2 Results of the pivotal study, PLATO, in ACS

4.2.1 Patient population studied

PLATO enrolled a population generally representative of ACS patients globally with respect to demographic and disease characteristics at baseline, based on comparisons to registries and reports of other trials in ACS patients (Mehta et al 2000; Wiviott et al 2007; Fox et al 2002; Peterson et al 2006; see Module 2.7.3, Table 5). The predominantly male population (72%) of median age 62, of whom 15% were at least 75 years old, had an average body weight of 80 kg, with 1312 of 18 624 patients (7%) weighing less than 60 kg (see Module 5.3.5.1, D5130C05262 CSR, Table 11.1.3.1.2). Like other ACS trials, PLATO enrolled a predominantly Caucasian cohort (92%) (Peterson et al 2006; Wiviott et al 2007). PLATO investigators indicated an intent for invasive management in 72% of the 18 624 patients randomised. Of those designated for invasive management at randomisation, 76.8% subsequently had PCI and 4.7% early CABG.

By final diagnosis at discharge from hospital for index event, 42.7% had NSTEMI, 37.7% STEMI, and 16.7% UA, similar to distributions reported in other large ACS endeavours (Fox et al 2002; Peterson et al 2006). Nearly all (93.6%) patients with a final diagnosis of STEMI (92% of those with ST-elevation on initial ECG) had an invasive treatment strategy.

The treatment groups were balanced with respect to disposition, demographic and baseline characteristics, pre-, post-, and concomitant medications, and treatment compliance. No one country or site dominated enrolment. The similarities between treatment groups validate and reflect the process of randomisation, which reduces bias and ensures independence of observations. Treatment patterns displayed consistency across geographic regions and adhered to global ACS guidelines. Demographics of patients enrolled in the Phase II studies showed strong similarity to those in PLATO (see Module 2.7.3, Table 3).

Premature permanent discontinuation of study drug occurred in 21.8% of patients randomised to clopidogrel and 23.7% of those randomised to ticagrelor. Investigators then often treated these patients with open-label clopidogrel. Mean exposure to study drug was 248 days. At study conclusion, vital status remained unknown for only 5 of the 18 624 patients randomised; investigators performed premature code breaks on only 32 (0.17%) patients, of whom only 3 continued on study drug (see Module 5.3.5.1, D5130C05262 CSR, Table 7).

Figure 2 in Section 4.2.2.1 shows the ACS patient journey beginning with initial presentation to emergency room or casualty ward. Numbered asterisks denote population subgroups with pre-specified analyses, including those in the formal statistical hierarchy of testing, and those that are exploratory (see Module 5.3.5.1, D5130C05262 CSR, Appendix 12.1.9, Statistical Analysis Plan).

4.2.2 Efficacy of ticagrelor in ACS

For all patients presenting with ACS enrolled in PLATO (*1 in Figure 2, displayed in Section 4.2.2.1), ticagrelor showed superiority to clopidogrel in reducing the rate of the composite efficacy endpoint of CV death, MI, or stroke after ACS events, with a RRR of 16%, absolute risk reduction/12 months post ACS event (ARR) of 1.9%, number needed to treat (NNT) of 54, and hazard ratio (HR) of 0.84 (95% CI 0.77, 0.92; p=0.0003). The actual clopidogrel event rate of 11.67% came quite close to the 11% expected (see Section 4.1.5 of this Overview).

Figure 1 displays the Kaplan-Meier estimated composite event rate vs time for the primary efficacy composite endpoint. An examination of the contributions of individual components of the composite, reveals that this result derives strongly from both CV death and MI, each individually statistically significant, but with no contribution from stroke (Table 2).

Figure 1 **Kaplan-Meier plot of primary clinical endpoint events - estimate of the risk to the first occurrence of any event in the composite efficacy endpoint - full analysis set**

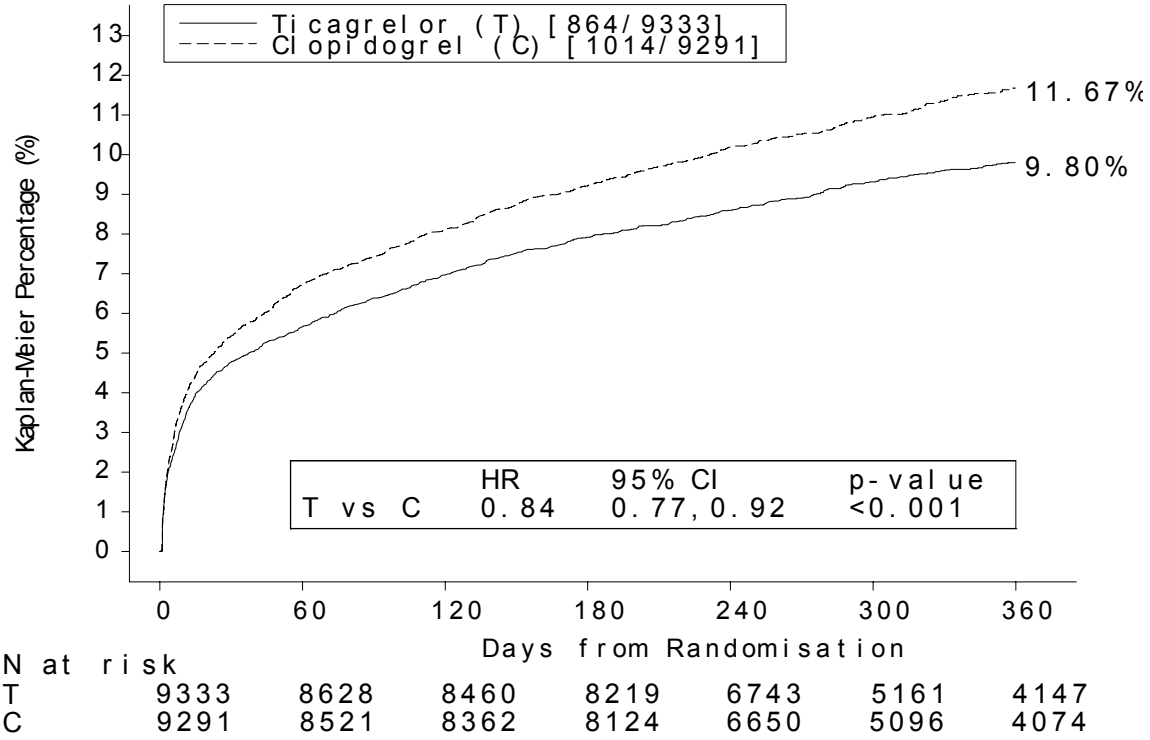


Table 2 presents the results of formal statistical hierarchical testing of secondary endpoints. The primary composite endpoint proved robust to examination of the intent for invasive management subgroup, to substitution of all-cause mortality for CV death, to augmentation with additional components, and to division into its separate components, with the exception of stroke. Of note, ticagrelor demonstrates a 16% relative reduction in risk of MI (p=0.0045) and a 21% relative reduction in risk of CV death (p=0.0013), the latter effect not diminished by inclusion of deaths from other causes (numerical relative reduction of 22% for all cause mortality, nominal p=0.0003). The ARR of 1.1% for CV mortality, saving 1 life for every 91 patients treated with ticagrelor instead of clopidogrel for 12 months, represents a compelling, noteworthy therapeutic advance in the treatment of ACS.

A sensitivity analysis of all-cause mortality using information gathered on vital status from all but 5 of the 18 624 randomised patients confirms the mortality benefit of ticagrelor: RRR 19%, ARR 1.1%, HR 0.81 (95% CI 0.71, 0.91), nominal p=0.0009 (see Module 5.3.5.1, D5130C05262 CSR, Table 11.2.20).

Table 2 Efficacy endpoints hierarchy - full analysis set

	Ticagrelor 90 mg bd N = 9333		Clopidogrel 75 mg od N = 9291			
Secondary objective	**Patients with events**	**KM %/ YEAR**	**Patients with events**	**KM %/ YEAR**	**Hazard ratio (95% CI)**	**p-value**
(i) Composite of CV death/MI (excl. silent MI)/stroke - intent to invasively manage[a]	569 (8.5%)	8.9%	668 (10.0%)	10.6%	0.84 (0.75, 0.94)	**0.0025**
(ii) Composite of all-cause mortality/MI (excl. silent MI)/stroke	901 (9.7%)	10.2%	1065 (11.5%)	12.3%	0.84 (0.77, 0.92)	**0.0001**
(iii) Composite of CV Death/Total MI/Stroke/SRI/RI/TIA/ Other ATE	1290 (13.8%)	14.6%	1456 (15.7%)	16.7%	0.88 (0.81, 0.95)	**0.0006**
(iv) Each component of primary efficacy endpoint:						
MI (excl. silent MI)	504 (5.4%)	5.8%	593 (6.4%)	6.9%	0.84 (0.75, 0.95)	**0.0045**
CV death	353 (3.8%)	4.0%	442 (4.8%)	5.1%	0.79 (0.69, 0.91)	**0.0013**
Stroke	125 (1.3%)	1.5%	106 (1.1%)	1.3%	1.17 (0.91, 1.52)	0.2249
(v) All-cause mortality	399 (4.3%)	4.5%	506 (5.4%)	5.9%	0.78 (0.69, 0.89)	0.0003

Data derived from Module 5.3.5.1, D5130C05262, Table 11.2.1.
Note: Hazard ratio and p-value calculated from Cox proportional hazards model with study treatment as only explanatory variable.
Note: Kaplan-Meier percentage calculated at 12 months.
Note: Formal statistical testing performed in sequence presented above until first non-significant result observed.
Note: For patients with multiple events the analysis uses the time to the earliest event: each patient is counted only once in each row.
Note: A single event may be counted in more than 1 row.
[a] Percentages are calculated using different denominators for intent to invasively manage patients (see Module 5.3.5.1, D5130C05262 CSR, Table 11.2.3.2): Ticagrelor N=6732, Clopidogrel N=6676.
ATE Arterial thrombotic events; bd Twice daily dosing; CI Confidence interval; CV Cardiovascular (CV death is death from vascular causes); excl. Excluding; HR Hazard ratio; KM Kaplan-Meier; MI Myocardial infarction; od Once daily dosing; RI Recurrent cardiac ischaemia; SRI Severe recurrent cardiac ischaemia; TIA Transient ischaemic attack.

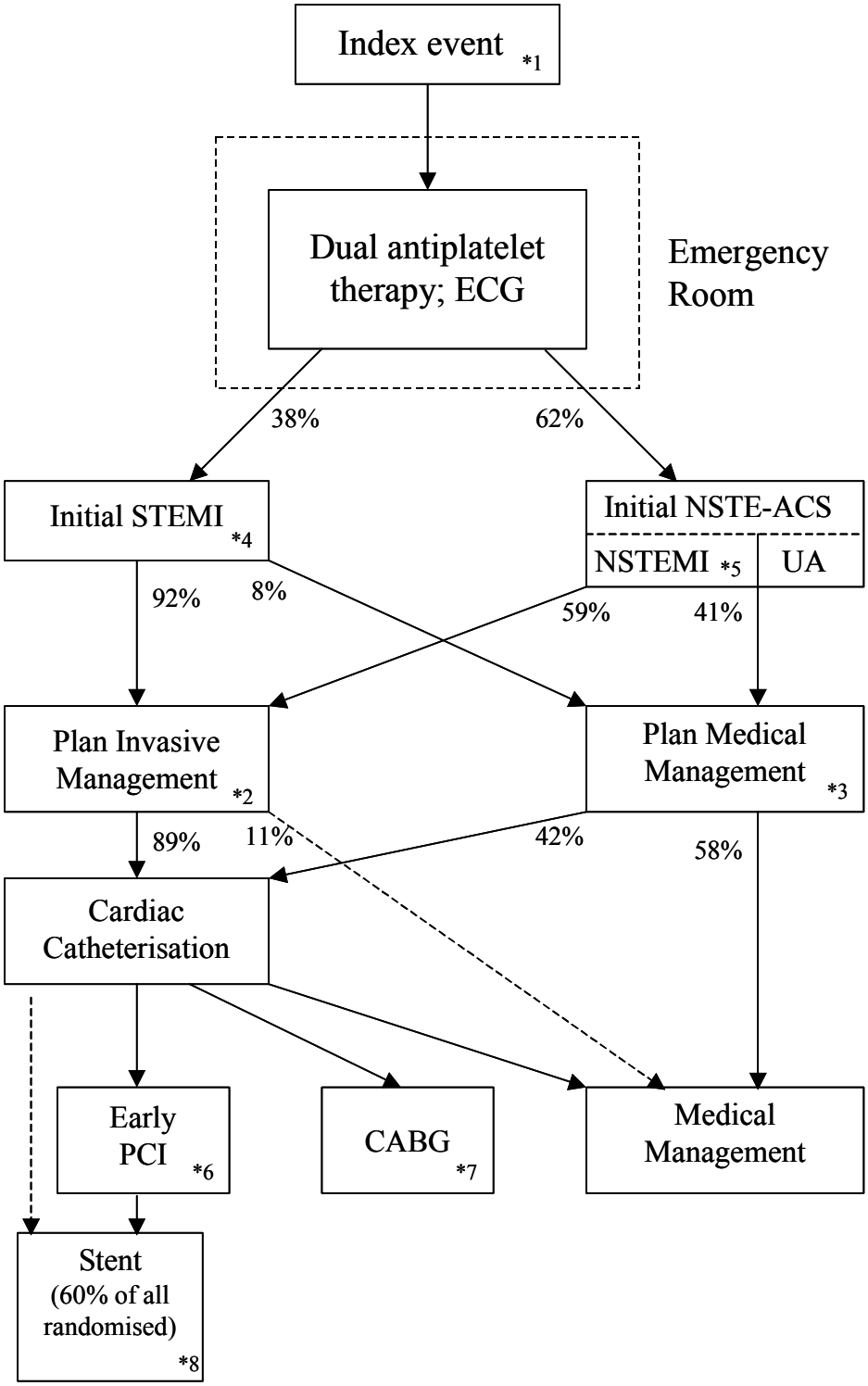
The efficacy advantage of ticagrelor appears early after treatment begins and persists throughout the 12-month study period. Indeed, Figure 1 shows monotonically increasing divergence of the event curves with time, so that the cumulative ticagrelor benefit achieved in the first 30 days after beginning treatment (RRR=12%; p=0.0446) not only persists, but also continues to increase over 1 to 12 months (RRR 20%; p=0.0008). These data, robust to other time division analyses, suggest that it is appropriate to treat ACS patients with ticagrelor for at least 12 months. (see Module 2.7.3, Section 3.4.1, Table 12; and Appendix 2.7.3.6, Figure 4, Figure 5, Figure 6, and Figure 7).

The early benefit may reflect ticagrelor's rapid onset of IPA, as seen in Study D5130C00048: median IPA achieved 30 min after 180 mg ticagrelor, 45%, was 9.6-fold that of 600 mg clopidogrel, 4.7%, and close to the maximum IPA ultimately achieved by clopidogrel (see Module 2.7.3, Figure 5). IPA measured 2 hours after 180 mg ticagrelor was 93%, compared to 31% for clopidogrel. Ticagrelor provides rapid, high, and consistent onset of IPA compared with that of clopidogrel (see Module 2.7.3, Section 3.2.1).

4.2.2.1 Robustness of the efficacy results

Multiple tests of robustness of efficacy results in PLATO confirm the advantage of ticagrelor over clopidogrel. These include the secondary efficacy endpoints presented above, and also analyses corresponding to subgroups formed along the patient journey depicted in Figure 2. Each junction represents a clinical decision or classification.

Figure 2 Treatment pathways for ACS patients in PLATO



Numbered asterisks denote population subgroups with specific pre-specified analyses, either in the formal statistical hierarchy of testing, or exploratory.

By planned management: invasive or medical (*2 and *3 in Figure 2)

Ticagrelor showed superiority to clopidogrel in reducing the rate of the composite efficacy endpoint in ACS patients planned for invasive management (RRR 16%, ARR 1.7%, HR 0.84 [95% CI 0.75, 0.94], p=0.0025). A pre-specified analysis of the complementary group of patients, those intended for medical management, demonstrated a RRR of 15% for the primary composite endpoint, with ARR 2.3%, HR 0.85 (95% CI 0.73, 1.00), and nominal p=0.0444 (see Module 5.3.5.1, D5130C05262 CSR, Table 30).

By final diagnosis: STEMI, NSTEMI, or UA (*4 and *5 in Figure 2)

Patients were categorised, by ECG and cardiac enzyme tests, with a final diagnosis at hospital discharge of STEMI, NSTEMI, or UA. Although Figure 2 depicts the initial, not final, categorisation for visual simplicity, the pre-specified STEMI and NSTEMI analyses used final categorisation. The STEMI and NSTEMI subgroups contained sufficient numbers of patients and events for meaningful interpretation. Each subgroup demonstrated ticagrelor's advantage over clopidogrel, with ARR 1.6%, HR 0.84 (95% CI 0.72, 0.98), and nominal p=0.030 for STEMI, and ARR 2.5%, HR 0.83 (95% CI 0.73, 0.94), and nominal p=0.004 for NSTEMI. The continually diverging Kaplan-Meier estimate vs time curves (see Module 5.3.5.1, D5130C05262 CSR, Figure 19 and Module 2.7.3, Figure 10 and Figure 11) show the value of long-term ticagrelor therapy.

Early PCI group (*6 in Figure 2)

A pre-specified exploratory analysis of a subgroup of the 13 408 patients in the intent for invasive procedure group, specifically those who actually underwent PCI within 24 hours of randomisation (N=9254), demonstrated similar benefit of ticagrelor over clopidogrel, with ARR 1.4%, HR 0.85 (95% CI 0.74, 0.99), and nominal p=0.0305 (see Module 2.7.3, Section 3.2.6.3 and Module 5.3.5.1, D5130C05262 CSR, Table 11.2.3.4).

Stent thrombosis prevention (*8 in Figure 2)

More than 60% of patients (N=11 289) received a stent at any time during PLATO. In pre-specified analyses, ticagrelor reduced the risk of definite stent thrombosis by 33%, with ARR 0.6%, HR 0.67 (95% CI 0.50, 0.91), nominal p=0.0091 (see Module 2.7.3, Section 3.2.6.3 and Module 5.3.5.1, D5130C05262 CSR ,Table 11.2.6). Numerical advantages of ticagrelor over clopidogrel exist for all subcategories of stent thrombosis, whether by type of stent, bare metal or drug eluting; or by category of likelihood, definite, probable, or possible, according to the Academic Research Consortium criteria (Cutlip et al 2007).

CABG cohort (*7 in Figure 2)

Of patients undergoing CABG at any time during the study, a post-hoc analysis of the time to first primary efficacy composite event after CABG shows a numerical imbalance in favour of ticagrelor (event rates of 10.7% and 11.9% per year; nominal p=0.6770). Those undergoing early CABG had too few events for analysis. Of 1517 patients undergoing CABG within 2 weeks of taking study drug, the 99 who died displayed a strong imbalance in favour of ticagrelor, 32 deaths (4.3%) vs 67 (8.6%) deaths for those taking clopidogrel within 2 weeks

of CABG (see Module 5.3.5.1, D5130C05262 CSR, Table 11.3.2.3.4.7). Ticagrelor also reduced mortality in patients not undergoing CABG within 5 days of last dose of study drug (379 out of 8888 vs 460 out of 8908, HR 0.83, nominal p=0.0062, see Module 2.7.3, Section 3.2.6.2).

4.2.2.2 Consistency of effect in subgroups

In addition to the consistency seen in subgroups listed in Section 4.2.2.1, the treatment effect of ticagrelor over clopidogrel appears consistent across multiple patient subgroups by demographic characteristics, including age, weight, gender, race, medical history, and concomitant therapy; and, by region, excepting North America (see below and Module 2.7.3, Figure 9).

The benefits associated with ticagrelor across the study as a whole occurred independently of other acute and long-term pre-specified CV therapies, including heparin, low molecular weight heparin, intravenous platelet glycoprotein IIb/IIIa inhibitors, lipid-lowering drugs, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and ASA (see Module 5.3.5.1, D5130C05262 CSR, Figure 11.2.15 or Table 11.2.2).

A post-hoc exploratory analysis showed that ticagrelor benefits those with baseline renal impairment at least as much as those with normal renal function (see Module 2.7.4, Section 3.3.3 and Module 2.7.4, Table 11). Patients with moderate renal impairment at baseline (N=2402) have a substantial reduction in absolute risk: ARR 5.7% and HR 0.72 (95% CI 0.59, 0.88) for the primary efficacy composite endpoint; those with severe renal impairment (N=181) have a numerical ARR of 9.5% and HR 0.73 (95% CI 0.42, 1.27).

Treatment by region interaction effect

Further evaluation of the region by treatment interaction (p=0.0453) showed that the result in North America was driven primarily by results in the United States (HR 1.27 [95% CI 0.92, 1.75]) compared with all other countries, (HR 0.81 [95% CI 0.74, 0.90]). Although the number of subgroup comparisons suggests that this particular observation could occur by chance alone, the extent of this particular effect (HR point estimate 1.27) suggested a need for additional analyses to evaluate other potential explanations. Systematic operational issues were evaluated and ruled out. A multivariate analysis of potential factors revealed that median ASA dose was associated with this observation. A univariate analysis excluding US data suggested a possible ASA dose response for the primary composite efficacy endpoint, with loss of ticagrelor advantage when ASA dose exceeds 150 mg. ASA dose is strongly confounded with region, with most high-dose (≥300 mg) use occurring in the United States. Thus, the efficacy treatment-by-region interaction effect is likely to arise from either the play of chance, an effect of higher dose ASA administration in the United States, or a combination of these two factors (see Module 2.7.3, Section 3.3.2.1).

The apparent decrease in efficacy with increasing ASA dose arises mostly from an increasing event rate in ticagrelor patients; the event rate increases to a much lesser extent in clopidogrel-treated patients. The HR for ticagrelor to clopidogrel, when viewed as a continuous function of median daily ASA dose, crosses from below 1.0 to above 1.0 at 150 mg. If the observed

treatment-by-region interaction is true, rather than due to play of chance, these observations and calculations suggest that concurrent ASA dose may be a strong contributing factor. Ticagrelor dosing recommendations therefore specify concomitant maintenance ASA doses of 75 to 150 mg once daily, unless specifically contraindicated. Additional information on the treatment interactions observed in PLATO can be found in a separate report (see Module 5.3.5.4, 'Exploratory analysis of treatment interactions in PLATO').

4.3 Limitations

4.3.1 Limitation regarding duration of treatment

Many PLATO patients received treatment for less than 12 months. The protocol specified duration, up to 12 months, derived from treatment guidelines for ACS with dual antiplatelet therapy (Anderson et al 2007; Antman et al 2008; King et al 2008; Bassand et al 2007; Van de Werf et al 2008). PLATO was an event-driven study. Ethical considerations required that PLATO not continue beyond the time needed to accrue the required number of primary endpoint events. As a result, patients who could not reach a full 12 months' treatment by that projected time underwent orderly study termination based on their next scheduled visit. These visits occurred at 3-month intervals, so only 9487 patients reached the 12-month visit, compared to 12 938 for the 9-month visit and 16 325 for the 6-month visit (see Module 5.3.5.1, D5130C05262 CSR, Table 11.1.2.4). This design limitation on patient exposure impacts the efficacy results minimally because most events following ACS occur soon after the index event. Also, the PLATO primary efficacy endpoint Kaplan-Meier curve (see Section 1.2 above) indicates widening, rather than any reversal, of ticagrelor superiority to clopidogrel in the latter 6 months of study participation. Thus termination earlier than 12 months may serve only to blunt the measured ticagrelor efficacy advantage.

4.3.2 Clopidogrel loading dose limitation

Based on changing medical practice and evolving science, the PLATO protocol allowed for an additional 300 mg loading dose of clopidogrel, for a total of 600 mg, for patients planned to undergo PCI. Clinicians now frequently employ loading doses >300 mg of clopidogrel in patients undergoing invasive treatment of ACS. Thus ticagrelor may not be superior to clopidogrel as currently dosed. For several reasons, patients in the clopidogrel arm of PLATO should not have received a 600 mg loading dose. First, results of the OASIS-7 trial indicate no outcomes difference between 300 mg and 600 mg loading doses of clopidogrel in ACS patients intended for invasive management (Mehta et al 2009). Full publication of those results had not occurred as of writing of this Clinical Overview. Second, not all patients in PLATO had an intended treatment path of invasive management. Third, ethical committee considerations in some countries dictated that the PLATO protocol could not require 600 mg prior to PCI because that dose was not labelled for use.

Fourth, investigators could give it anyway, and did so: 33% of clopidogrel patients received a loading dose of at least 600 mg, as either open label prior to randomisation, blinded study medication, or as both. Furthermore, the subset of patients receiving 600 to 675 mg clopidogrel loading dose demonstrated HR point estimates similar to those of patients receiving 300 to 375 mg loading dose for both the primary efficacy composite (0.79 vs 0.77;

see Module 5.3.5.1, D5130C05262 CSR, Table 11.2.2) as well as for PLATO-defined Major bleeding, the primary safety endpoint (HR 1.14 vs 1.24; see Module 5.3.5.1, D5130C05262 CSR, Table 11.3.2.2.4.5). Thus, PLATO provides sufficient evidence that the benefit of ticagrelor over clopidogrel does not depend on standard loading doses of clopidogrel.

4.3.3 Limitation of enrolling patients taking chronic clopidogrel therapy

Inclusion of patients taking chronic clopidogrel therapy could bias results in favour of ticagrelor by including "clopidogrel failures," ie, patients who suffered an ACS event while taking clopidogrel, and are thus potential clopidogrel non-responders. Those randomised to ticagrelor can respond to ticagrelor, but clopidogrel non-responders randomised to clopidogrel respond poorly to clopidogrel. Actually, only 7.8% of patients randomised to the clopidogrel treatment arm in PLATO had been taking chronic clopidogrel at the time of their ACS event (see Module 5.3.5.1, D5130C05262 CSR, Table 11.1.4.15.1), too small a group to influence the study efficacy results.

Some patients received open-label clopidogrel prior to randomisation

Some patients subsequently randomised to ticagrelor might have an advantage because they received both $P2Y_{12}$-receptor antagonists, whereas the clopidogrel patients received no ticagrelor. PLATO data confirm that initial open label clopidogrel carries minimal clinical impact: HRs for the primary composite efficacy endpoint in PLATO show similarity for 7449 patients receiving clopidogrel loading doses of 300 to 375 mg (HR 0.77); 3104 patients given 600 to 675 mg (HR 0.79); 2036 patients given other loading doses (HR 0.84); and 5031 patients given no clopidogrel loading dose (HR 0.77; see Module 5.3.5.1, D5130C05262 CSR, Table 11.2.2). Actual clopidogrel loading dose on the day of randomisation cannot explain the efficacy advantage of ticagrelor over clopidogrel over 12 months' duration.

4.3.4 Limitation of free use of proton pump inhibitors

PLATO did not restrict use of proton pump inhibitors (PPIs) at any time during the study. Although observational data from some trials associate PPI use with increased risk of CV events (Ho et al 2009), others do not (O'Donoghue et al 2009) and randomised data from the COGENT trial show no causality, with HR 1.02 (95% CI 0.70, 1.51) for composite CV events in patients taking clopidogrel, ASA, and omeprazole vs those taking clopidogrel, ASA, and placebo (Bhatt et al 2009). PLATO data show that the treatment advantage of ticagrelor over clopidogrel occurs whether or not patients take concomitant PPIs. see Section 3.4.2 in Module 2.7.3 for further discussion.

4.3.5 Limitation of adjudication process for endpoints

The adjudication process in PLATO met initial operational challenges owing to accumulation of nearly 10 000 events and too few adjudicators to process them expeditiously. In response, the pool of adjudicators grew to over 50 individuals, potentially affecting the consistency of their judgments. In a validation exercise prior to unblinding, the adjudication committee repeated the adjudication process on a random sample of over 5% of events. Results indicate agreement for efficacy judgments (see Module 5.3.5.1, D5130C05262 CSR, Appendix 12.1.4..3, ICAC Charter 03APR09).

4.3.6 Limitation of a single pivotal Phase III study

Typically, 2 well-conducted pivotal studies provide evidence of efficacy and safety for a new drug. Ticagrelor presents only a single pivotal study, PLATO, raising the type I error concern of possible spurious significance.

Several observations argue that PLATO alone provides sufficient evidence of the efficacy and safety of ticagrelor:

- The significance level achieved for superiority of ticagrelor over clopidogrel for the primary efficacy endpoint, p=0.0003, is more rare than that of 2 independent studies satisfying a 5% level of significance in the same direction, ie, $0.0003 << (0.05)^2/2$. Multiple sensitivity analyses show a robust primary endpoint, as seen by the significance levels in the formal statistical hierarchy of secondary endpoints. The benefit of ticagrelor over clopidogrel in CV death remains robust to substitution by all cause mortality and retains its significance level.

- Ticagrelor shows superiority to the active comparator clopidogrel, previously shown to reduce the risk of the identical composite primary endpoint when compared to placebo (Yusuf et al 2001; Chen et al 2005).

- The primary efficacy endpoint of PLATO contains hard endpoints. The vast majority of MI endpoints were detected clinically, not by biomarkers alone. MI and CV death, a hard endpoint, drove the primary composite endpoint result.

- The safety database of over 18 000 patients offers ample opportunity to detect important safety signals. However, the need for an active comparator in DISPERSE2 and PLATO yields minimal placebo comparator data across the programme, so that determination of ticagrelor adverse drug reactions (ADRs) presents a challenge.

To summarise, AstraZeneca believes that a regulatory submission based on the pivotal Phase III PLATO study satisfies the criteria of in the CHMP 'Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study' guidance document, as well as the FDA Guidance for Industry 'Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products' regarding a single pivotal study: ie, compelling results with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency. The US FDA noted that a single trial could serve as basis for approval if it presented robust and compelling results, considered during review.

4.4 Conclusions: efficacy of ticagrelor in ACS

Over 12 months of treatment, ticagrelor, compared to clopidogrel, decreases the rate of major clinically important thrombotic events after ACS (RRR=16%; ARR=1.9%) regardless of type of ACS and of intended treatment path. This result derives from statistically significant risk reductions in both CV death (RRR=21%; ARR=1.1%) and MI (RRR=16%; ARR=1.1%), but not in stroke.

The benefit of ticagrelor over clopidogrel appears early in the course of therapy and grows throughout 12 months' of treatment. It is robust to multiple sensitivity analyses and consistent across ACS subtypes and patient subgroups, although a possible efficacy interaction with higher doses of ASA has led to the recommendation that patients taking ticagrelor should take 75 to 150 mg ASA once daily on a chronic basis, unless specifically contraindicated.

5. OVERVIEW OF SAFETY

5.1 Methods of safety assessment

Patients with CAD carry a significant disease burden, including hypertension, diabetes, obesity, renal impairment, and systemic atherosclerosis affecting multiple organ systems. ACS patients, in addition, commonly undergo invasive procedures and receive many concomitant medications. Comparison of events occurring with clopidogrel administration aids interpretation of those occurring with ticagrelor.

5.1.1 Special approaches to safety assessment in the clinical studies

The ticagrelor Phase II studies provided a substantial safety database for detection of safety signals (see Section 5.2.1in this Overview for exposure details). The sensitivity for signal detection provided by this amount of Phase II experience allowed the development programme to probe in Phase III, in a more sophisticated manner, into specific safety issues. For example, because Phase II studies identified dyspnoea as an issue, PLATO collected detailed information allowing characterisation of its onset, offset, duration, number of episodes, and relation to other medical conditions. Two substudies in PLATO described more below, one measuring pulmonary function, the other ventricular pauses, were created because of identified safety issues in Phase II.

In addition to conventional methods of clinical safety assessment such as a thorough QT study, AE collection with MedDRA classification, measurement of vital signs and routine laboratory values, and use of independent DSMB and adjudication committees, the ticagrelor programme also featured the following:

- Classification of bleeding events in PLATO according to 2 different sets of rules, to provide multiple views. The adjudication committee utilised PLATO defined bleeding categories; accordingly, the primary safety endpoint is PLATO 'Major' bleeding. In addition, all bleeding events were categorised according to the TIMI classification. Bleeding analyses present results according to both PLATO and TIMI classifications when appropriate.

- Continuous ECG (Holter) monitoring in a subset of DISPERSE2 patients in Phase II that disclosed an imbalance among treatment groups in the incidence of largely asymptomatic ventricular pauses. This led to an extensive Holter monitoring substudy in PLATO in over 2900 patients for in depth safety assessment of this observation. These recordings now constitute the largest prospective database of its kind.

- Multiple studies measuring pulmonary function to probe the safety implications of the sensation of breathlessness, reported as dyspnoea, that sometimes accompanies ticagrelor administration. These include studies of patients with asthma or chronic obstructive pulmonary disease (COPD); patients with stable CAD; and a substudy in PLATO of ACS patients. Taken together, these data provide ample safety insights to guide benefit risk evaluation and prescribing advice.

5.1.2 Pooling methodology

Safety data in PLATO was kept separate from those in earlier Phase I and II studies. The large PLATO database presents a substantially complete view of ticagrelor safety in the target population. Normally all safety data are pooled to facilitate detection of uncommon events. However, nearly 10-fold more patients (9235 exposed for up to 12 months) received ticagrelor in PLATO than in all Phase II studies (960 exposed for 4 to 12 weeks) combined. PLATO by itself allows for analyses of demographic subgroups by gender, age, ethnic origin, geographical region, relevant concomitant medications, and other clinically relevant characteristics. Augmentation with small numbers of patients with varying diagnoses, treatments, dosing levels and regimens, and clinical settings would serve to degrade, rather than reinforce, safety inferences from the PLATO safety database. PLATO constitutes the primary source for interpretation of safety data. Pooled Phase II data are referenced for comparison to PLATO.

Similarity of patient populations of the 4 Phase II studies in demography and disease state (all have atherosclerosis; most stable CAD, some ACS) enables pooling of their safety data to supplement inferences from PLATO data. Marked variation of study design, dosing, and populations in Phase I data dictated against pooling safety data from those studies. Safety results from Phase I largely support those from Phase II and PLATO (see Module 2.7.4, Section 1.1.1.1 for more details on pooling).

5.1.3 Bleeding definitions

The primary safety endpoint measured the time to first occurrence of any total major bleeding event using PLATO definitions. PLATO definitions evolved from those used in the CURE study (Mehta et al 2000). Compared with either the TIMI (Wiviott et al 2006) or GUSTO definitions (GUSTO Investigators 1993), PLATO definitions feature lower thresholds to capture bleeding events during both acute and chronic phases of ACS. For example, the haemoglobin decrease threshold for PLATO 'Major' bleeding, 30 g/L, is lower than that for TIMI 'Major' bleeding, 50 g/L, and matches that for TIMI 'Minor' bleeding (Table 3). Also, note that TIMI Major criteria resemble PLATO 'Major Fatal or Life-threatening' criteria; TIMI Minor criteria resemble PLATO 'Major Other' criteria; and TIMI Major + Minor resembles PLATO 'Major'.

Table 3 Comparison of definitions between the PLATO and TIMI bleeding severity scales

PLATO scale[a]	TIMI scale[b]
PLATO-defined 'Major Fatal/Life-threatening' Any 1 of the following: • Fatal • Intracranial • Intrapericardial bleed with cardiac tamponade • Hypovolaemic shock or severe hypotension due to bleeding and requiring pressors or surgery • Clinically overt or apparent bleeding associated with a decrease in haemoglobin of more than 50 g/L [c] • Transfusion of 4 or more units (whole blood or PRBCs) for bleeding	**TIMI-defined Major** Intracranial, or Clinically significant overt signs of haemorrhage associated with a drop in haemoglobin of > 5 g/dL (or, when haemoglobin is not available, an absolute drop in haematocrit of > 15%)[d] NOTE: TRITON used ≥5 g/dL NOTE: Not all fatal or life-threatening etc bleeds are included in the TIMI-Major category. **TIMI-Life-threatening** Is fatal; leads to hypotension requiring treatment with intravenous inotropic agents; requires surgical intervention for ongoing bleeding; necessitates the transfusion of 4 or more units of blood (whole blood or packed red blood cells) over a 48-hour period; is a symptomatic intracranial haemorrhage

Table 3 Comparison of definitions between the PLATO and TIMI bleeding severity scales

PLATO scale[a]		TIMI scale[b]
PLATO-defined 'Major Other' Any 1 of the following: • Significantly disabling (eg, intraocular with permanent vision loss) • Clinically overt or apparent bleeding associated with a decrease in haemoglobin of 30 to 50 g/L [c, e] • Transfusion of 2-3 units (whole blood or PRBCs) for bleeding.		**TIMI-defined Minor** Any clinically overt sign of haemorrhage (including imaging) that is associated with a fall in haemoglobin of 3 to ≤5 g/dL (or, when haemoglobin is not available, a fall in haematocrit of 9 to ≤15%)[d] NOTE: TRITON used 3 to <5 g/dL
PLATO-defined 'Minor' Requires medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing).		**TIMI-defined Minimal** Any clinically overt sign of haemorrhage (including imaging) that is associated with a fall in haemoglobin <3 g/dL (or, when hemoglobin is not available, a fall in haematocrit of <9%)[d]
PLATO-defined 'Minimal' All others not requiring intervention or treatment		-

[a] See Module 5.3.5.1, D5130C05262 CSR, Appendix 12.1.1, Protocol Amendment 3, based on Yusuf et al 2001 for PLATO bleeding scale.
[b] TIMI-scale : from "TIMI definitions" at http://www.timi.org/ and Wiviott et al 2006.
[c] Haemoglobin 50 g/L = 3.1 mmol/L monomer or 0.775 mmol/L.
[d] Haemoglobin change adjusted for units of blood transfused.
[e] Haemoglobin 30 g/L = 1.9 mmol/L monomer or 0.465 mmol/L tetramer.

Note: Any PLATO 'Major Fatal/Life-threatening' bleed was considered to be a TIMI Major bleed unless:
1) It did not qualify as a TIMI major bleed, which is to say that the largest drop in hemoglobin, after adjustment for prior transfusion, was ≥ 5 g/L; or
2) The sole criterion for PLATO major fatal/life-threatening was 'Intrapericardial bleed with cardiac tamponade".

PLATO A study of PLATelet inhibition and patient Outcomes; PRBCs Packed red blood cells; TIMI Thrombolysis in Myocardial Infarction; TRITON Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel.

The PLATO adjudication process required judgment against a single set of definitions to maintain consistency and quality. Thus PLATO expresses bleeding results as PLATO-defined

adjudicated events. All adjudicated bleeding events also underwent an algorithmically-driven classification by TIMI criteria. Table 3 provides a full comparison of TIMI and PLATO definitions. Where appropriate, results according to TIMI classifications appear alongside those of PLATO to facilitate additional interpretation of the data. Providing key bleeding data according to both definitions allows a clinically meaningful comparison of ticagrelor and clopidogrel within the study.

The PLATO bleeding results represent well bleeding that occurred during the trial, because (1) the PLATO definitions are sensitive to detect events during both the acute and chronic phases of ACS treatment; (2) they were adjudicated; (3) they were pre-defined; and (4) all CABG patients underwent adjudication for bleeding even if investigators had not initially designated a bleeding event, to minimise bias in identifying potential bleeds.

5.1.4 Safety analysis sets

All presentations of safety data use this definition for data inclusion: all patients who took at least one dose of study medication. Patients are analysed according to treatment actually received, with events and procedures included beginning with the first dose of the treatment and ending 7 days after the last dose. In some instances, a subset of the safety analysis set applies, such as for laboratory measurements or for a particular substudy (see Module 2.7.4, Section 1.1.4.1).

5.1.5 Excluded populations

PLATO did not enrol patients for whom antiplatelet agents are generally contraindicated, such as those with active or pathologic bleeding, a history of previous intracranial bleed, recent GI bleeding, or major surgery within 30 days. Patients actively receiving chronic oral anticoagulant therapy also did not participate. Clinicians should exercise caution when prescribing ticagrelor to these patients.

Ticagrelor has not been studied in patients with moderate or severe hepatic impairment, in those at increased risk of bradycardic events without an implanted pacemaker, in patients requiring dialysis, patients with clinically important thrombocytopenia or anaemia, pregnant or lactating women, patients below the age of 18, and patients on concomitant oral or iv therapy with strong CYP3A inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers.

5.2 Extent of exposure and population exposed

5.2.1 Programme exposure

Long-term exposure to ticagrelor in the clinical program far exceeds the ICH E1A guidance stipulating at least 1500 patients exposed, 300 for at least 6 months, and 100 for at least 1 year. In PLATO alone, 9235 patients received at least 1 dose of ticagrelor, 6762 for >180 days, and 3138 more than 360 days. Mean duration of treatment was 246 days, encompassing 6301 patient-years of ticagrelor exposure (see Module 2.7.4, Section 1.2). PLATO analyses benefit from near-complete collection of endpoint and safety data, with, for example, vital status information known for 18 619 of 18 624 (99.97%) randomised patients.

Shorter-term exposure, provided by the Phase II trials, was substantial for that level of drug development: 360 patients had mean exposure of 51.9 days to 180 mg bd ticagrelor (51.2 patient-years); 513 patients had 44.4 days mean exposure to 90 mg bd ticagrelor (62.4 patient-years), with much smaller exposures to ticagrelor doses of 50 mg bd (3.1 patient-years) and 400 mg od (3.5 patient-years).

5.2.2 Demography and factors relevant to the safety assessment

The demographic and baseline characteristics of PLATO patients, including medical histories, concomitant medications, and risk factors, match well those of the general ACS population (see Module 2.7.4, Table 3; Fox et al 2002, Peterson et al 2006). The predominantly male population (72%) of median age 62, of whom 15% were at least 75 years old, had an average body weight of 80 kg, with 1312 of 18 624 patients (7%) weighing less than 60 kg (see Module 5.3.5.1, D5130C05262 CSR, Table 11.1.3.1.2). Although Caucasian patients predominated (92%), PLATO did include 222 Black and 1081 Asian patients, evenly divided by treatment.

The distribution of STEMI (38%), NSTEMI (43%), and unstable angina (17%) reflect that seen in contemporary clinical practice (Fox et al 2002, Peterson et al 2006). Both planned and actual ACS treatments in PLATO followed published guidelines (Anderson et al 2007, Antman et al 2008, Bassand et al 2007, Van de Werf et al 2008). At randomisation, investigators planned initial invasive management, defined as angiography and possible further intervention, for three-quarters of patients. Consistent with guidelines, nearly all STEMI patients (94%) had a planned invasive treatment strategy. Nearly every patient with a planned invasive approach underwent coronary angiography, followed by PCI in 72% and early CABG in 5.5% (see Module 5.3.5.1, D5130C05262 CSR, Table 16). In the course of PLATO, 10.2% of patients underwent CABG (see Module 5.3.5.1, D5130C05262 CSR, Section 6.6.2). See Figure 2 in Section 4.2.2.1 of this Overview for treatment pathways.

Many patients in PLATO took multiple concomitant medications such as ASA (96%), lipid lowering agents (93.4%), beta blockers (87%), angiotensin converting enzyme inhibitors (79.3%) and nitrates (74.4%). The dose of ASA did not differ between treatment groups, but did differ by geographical region, with 52% of US patients receiving 325 mg but 86.4% of non-US patients taking 100 mg or less, reflecting local clinical guidelines.

5.2.3 Discontinuation incidence in PLATO

Not only did many patients in PLATO stop taking study medication, but this happened more so in the ticagrelor group: 7.5% of randomised patients because of AEs vs 6.1% of randomised patients in the clopidogrel group, and 10.2% not willing to continue treatment vs 9.4% for clopidogrel (see Module 2.7.3, Figure 4). This decreases confidence that the intention-to-treat analysis compares ticagrelor to clopidogrel.

Complex, long-term outcome studies commonly suffer from high rates of discontinuation from study medication as well as termination from the study. Dyspnoea and epistaxis account for much of the increment in study drug discontinuation rates for ticagrelor over clopidogrel (see Section 5.3.3 of this Overview). Patients remaining in the study contributed outcome

events for analysis; all but 3% of patients remained in PLATO for their specified duration (see Module 5.3.5.1, D5130C05262 CSR, Figure 5). Regardless, the effect of more ticagrelor patients discontinuing study medication and substituting either clopidogrel or nothing would be to blunt the observed efficacy advantage of ticagrelor over clopidogrel. In the face of a striking treatment efficacy difference for hard endpoints, this concern becomes moot. The safety analysis collected events up to 7 days after stopping study medication. Thus most important drug-related safety events would be captured. While some long-term sequelae of ticagrelor could go undetected because of discontinuation, 3138 patients were exposed for at least one year, representing an opportunity for PLATO to detect long-term issues, one matched by a minority of clinical trials.

5.3 Adverse event profile

5.3.1 Adverse events

PLATO investigators reported slightly increased percentages of AEs in ticagrelor vs clopidogrel patients, whether including bleeding events (73% v 70%; Table 4), or excluding them (69% vs 67%; see Module 5.3.5.1, D5130C05262 CSR, Table 11.3.3.1.3). The Phase II pooled AE data provide a similar pattern: 67% for ticagrelor 90 mg bd vs 63% for clopidogrel when including bleeding events; 57% and 55%, respectively, when excluding them (see Module 2.7.4, Table 18 and Table 19).

The most commonly reported AEs in PLATO patients treated with ticagrelor were dyspnoea (12.0%), headache (6.5%), and epistaxis (6.0%); these events occurred at higher rates than with clopidogrel (6.5%, 5.8%, and 3.4%, respectively) (see Module 2.7.4, Table 16). Pooled Phase II AEs show those same 3 preferred terms as most common, with similar frequencies for 90 mg ticagrelor bd, 12.7%, 7.6%, and 8.2% respectively, and for clopidogrel (see Module 2.7.4, Table 20).

The excess of AEs with ticagrelor involves those mild or moderate in nature and does not extend to severe AEs (Table 4). Many of the AEs reported in PLATO, common and uncommon (see Module 2.7.4, Table 16), such as headache; dizziness and vertigo; GI disturbances; epistaxis, post-procedural haemorrhage, urinary tract bleeding, and bruising (subcutaneous or dermal bleeding), reflect ACS, its co-morbidities, and concomitant antithrombotic use. Nevertheless they occur with ticagrelor and thus could reflect ADRs that patients may experience when given ticagrelor. See also Section 5.4.4 and Section 5.4.5 of this Overview regarding AE imbalances for increased uric acid and renal events. The analyses of AEs have identified bleeding and dyspnoea as clinically important safety issues with ticagrelor.

5.3.2 Serious adverse events

Treatment groups in PLATO did not differ in proportions of patients with at least one serious AE, (20% each; see Table 4 of this Overview and also Module 2.7.4, Table 23). Cardiac failure and non-cardiac chest pain were the most frequent preferred terms for each treatment group, at approximately 1% each. For ticagrelor, dyspnoea and cerebrovascular accident each occurred at 0.7% while for clopidogrel, pneumonia (0.9%) and cardiogenic shock (0.7%)

ranked next. The Phase II SAE data show smaller overall frequencies, reflecting the shorter exposures: 9.6% for ticagrelor 90 mg bd and 10.8% for clopidogrel, with MI and chest pain highest ranked for each (see Module 2.7.4, Table 24).

5.3.3 Discontinuation due to adverse events

In PLATO, dyspnoea (N=67) and epistaxis (N=26) accounted for about half of the excess of 187 DAEs for ticagrelor (see Table 4 below and Module 2.7.4, Table 25). Phase II DAE data disclose no imbalances (see Module 2.7.4, Table 26).

5.3.4 Deaths

In PLATO, fewer deaths occurred in ticagrelor-treated patients, no matter how analysed: all known deaths (443 vs 540); all adjudicated deaths (418 vs 520); deaths in the safety analysis set while on treatment (283 vs 339); deaths occurring >7 days after stopping study drug (125 vs 166) (see Module 2.7.4, Section 2.1.3.1); deaths from non-CV causes (46 vs 64; see Module 5.3.5.1, D5130C05262 CSR, Table 11.2.4.1) and those from bleeding (20 vs 23). The entire Phase II program encountered 9 on-treatment deaths, all in DISPERSE2, none treatment-related (see Module 2.7.4, Section 2.1.3.2).

Table 4 Summary of categories of AEs during the treatment period, including bleeding events – PLATO safety analysis set

Number of Patients	Ticagrelor 90 mg bd N = 9235	Clopidogrel 75 mg od N = 9186
Any 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%)
Death[a]	218 (2.4%)	285 (3.1%)
Leading to study drug discontinuation	687 (7.4%)	500 (5.4%)
SAE	259 (2.8%)	218 (2.4%)

Data derived from D5130C05262 CSR, Table 11.3.3.1.12.
Note: Patients may be included in more than 1 AE category.
a This overview summarises SAEs, and within SAEs summarises deaths and non-deaths as subcategories. There are some deaths not coded as SAEs, ie, events that were judged by the investigator as leading to death, but not judged as an SAE. Additionally, fatal events such as cardiac ischaemic events are counted as deaths however, per protocol, were endpoint events and not reported as SAEs.
AE Adverse event; bd Twice daily dosing; od Once daily dosing; SAE Serious adverse event.

5.4 Key safety topics

5.4.1 Bleeding

Bleeding constitutes the most recognized AE of antiplatelet therapy. Given its higher degree of platelet inhibition compared to clopidogrel, ticagrelor could cause more bleeding Neither 'Total Major' nor 'Major Fatal/Life-threatening' bleeding differed in PLATO, nor did the analogues TIMI-defined Major + Minor or TIMI-defined Major bleeding (see Table 5). Bleeding in DISPERSE2 did not differ among the clopidogrel and 2 ticagrelor treatment groups (see Module 2.7.4, Section 2.1.1.2).

Table 5 Analysis of overall bleeding events – PLATO safety analysis set

	Ticagrelor 90 mg bd KM (%) N=9235	Clopidogrel 75 mg od KM (%) N=9186	p-Value
Primary Safety Endpoint			
Total Major	11.6	11.2	0.4336
Secondary Endpoints			
Fatal/Life-Threatening	5.8	5.8	0.6988
Combined Total Major + Minor bleeding	16.1	14.6	0.0084
Non-CABG 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
TIMI-defined bleeding category			
TIMI-defined Major	7.9	7.7	0.5669
TIMI-defined Major + Minor	11.4	10.9	0.3272

Data derived from Module 5.3.5.1, D5130C05262 CSR, Table 11.3.2.2.4.2 and Table 11.3.2.2.4.3.
Patients may be counted in >1 bleeding event category.
bd Twice daily dosing; CABG Coronary artery bypass graft; CI Confidence interval; HR Hazard ratio; KM Kaplan-Meier; od Once daily dosing; TIMI Thrombolysis in Myocardial Infarction – a cardiology clinical trials study group.

However, 'Combined Total Major + Minor' bleeding occurred more with ticagrelor, 16.1% per year, than with clopidogrel, 14.6% per year, HR 1.11 (95% CI 1.03, 1.20), p=0.0084. This difference arose from more 'Minor' bleeding with ticagrelor. The less severe bleeding events expected with antiplatelet therapy, such as epistaxis, subcutaneous, GI-, and urinary tract-related bleeds, and those accompanying procedures, did not occur very frequently (2.8%). Ticagrelor treatment also associated with more 'Minimal' bleeding, that not needing medical attention, 17.2% of ticagrelor vs 10.6% of clopidogrel patients (see Module 2.7.4, Table 17).

CABG-related bleeding did not differ between treatment groups by PLATO or TIMI definitions (see Module 5.3.5.1, D5130C05262 CSR, Table 40). Patients who stopped ticagrelor 5 or more days before CABG showed visually a reduced incidence of CABG-related 'Major Fatal / Life-threatening' bleeding compared to those stopping closer to CABG surgery (see Module 5.3.5.1, D5130C05262 CSR, Figure 26). Regarding median chest tube drainage and transfusions, ticagrelor patients undergoing CABG in PLATO had a similar peri-operative bleeding profile to that of clopidogrel patients, except when study drug was stopped within 1 day of CABG; in that instance, ticagrelor patients had more peri-operative bleeding (see Module 5.3.5.1, D5130C05262 CSR, Table 11.3.2.3.4.5 and Table 11.3.2.3.4.6). The peri-operative CABG bleeding data, along with ticagrelor's PD faster offset (see Section 3.2.2 of this Overview), suggest that if a patient is to undergo elective surgery and antiplatelet effect is not desired, ticagrelor should be discontinued 5 days prior to surgery. 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 and if discontinuation of ticagrelor treatment should occur.

Ticagrelor has an excess of non-procedural bleeding over clopidogrel. However, treatments do not differ in non-procedural fatal bleeding or major life-threatening/fatal bleeding. Despite numerically more non-procedural intracranial haemorrhages with ticagrelor (27 [0.29%] vs 14 [0.15%]), and more fatal intracranial bleeds (11 vs 1), fewer fatal bleeds occurred overall (20 vs 23). Note that fatal intracranial haemorrhages count not only as bleeding events, but also in the primary efficacy endpoint, for which ticagrelor demonstrated a significant benefit. The incidence of 'Major Fatal/Life-threatening' intracranial bleeding was low in both treatment groups (0.29% and 0.15%) compared to rates of CV death (4.0% and 5.1%) and of MI (5.8% and 6.9%). Given the lack of consistent pattern for these important events, no clear clinical inferences emerge. Analyses failed to identify any subgroup at increased risk of bleeding, either overall, or for intracranial bleeding.

Bleeding and subsequent transfusion, regardless of whether related to CABG, PCI, other procedures, or not related to procedures, impacts patient well-being. For that reason, the clinical impact of bleeding associated with antiplatelet therapy should consider all bleeds of a given magnitude, regardless of the clinical setting. The pre-specified comparison of ticagrelor to clopidogrel, the primary safety endpoint of total 'Major' bleeding, demonstrates no difference between the treatment groups (11.6% vs 11.2%, p=0.4336).

Exposure-response analyses demonstrate a shallow relationship between ticagrelor exposure and non-CABG major bleeding: the rate increases from 2.8% to only 3.4% per year between the 10^{th} and 90^{th} percentiles of exposure (see Module 5.3.4.2 Exposure-Response Technical Report – Safety). Data from across the ticagrelor development programme suggest that ticagrelor is contraindicated only in patients with active pathological bleeding and that dose adjustments are not required. When bleeding occurs, supportive care suffices, possibly with temporary interruption of ticagrelor treatment, depending upon the severity of the bleeding event.

5.4.2 Dyspnoea

Ticagrelor causes a feeling of breathlessness, mapped to dyspnoea by preferred term in MedDRA. Volunteers and patients often describe an "air hunger" similar to the effect when giving intravenous adenosine to patients. Pre-clinical study reveals an increase in respiratory rate in rats (see Module 2.6.2, Section 2.6.2.4), but this does not occur clinically (see Module 2.7.4, Section 2.1.6.1). Ticagrelor is not an adenosine analogue and does not stimulate adenosine receptors. It does block the uptake of adenosine into red cells, potentially prolonging the action of endogenous adenosine, which can then stimulate bronchial receptors that signal the respiratory centre. The AE profiles for intravenous adenosine and for dipyridamole mention dyspnoea, in support of adenosine as a potential mechanism of action for this ticagrelor effect. Multiple attempts to create an animal model for ticagrelor-induced dyspnoea have proved unsuccessful to date. Adenosine is evanescent in blood and difficult to measure directly (Eltzschig HK 2009). As a result, the development programme provides no mechanistic data to support the hypothesis of adenosine-mediated effects.

In PLATO, which included many patients with congestive heart failure (CHF), COPD, and asthma, investigators reported dyspnoea more frequently overall during treatment with ticagrelor, 13.8%, than with clopidogrel, 7.8%. Dyspnoea occurs in ACS patients treated with ASA alone (4.7%), clopidogrel and ASA (4.5%; Clopidogrel US Package Insert 2008), and with prasugrel and ASA (Prasugrel US Package Insert 2009). In the pooled Phase II data, dyspnoea occurred in 4 of 41 (9.8%) ticagrelor patients taking 50 mg bd, 14.6% of those taking 90 mg bd, 15.6% of those taking 180 mg bd, and 8 of 46 taking 400 mg od (17.4%) compared to 5.8% of clopidogrel patients (see Module 2.7.4, Section 2.1.6.1). PLATO data appear to indicate slightly higher values compared to both the Phase II pooled data and those from comparator studies. This may arise because PLATO focussed specifically on reporting dyspnoea, so that more complete reporting occurred.

PLATO investigators more often reported dyspnoea AEs in older patients and those with baseline dyspnoea, COPD, asthma, or CHF (see Module 2.7.4, Section 2.1.6.1). Dyspnoea observed in patients treated with ticagrelor was usually mild to moderate in intensity and often resolved during continued ticagrelor treatment. Most dyspnoea occurred within 30 days of treatment; it occurred earlier with ticagrelor than with clopidogrel. The duration was similar between treatment groups; approximately 30% resolved within 1 week, with median durations of 56 days for ticagrelor vs 62 days for clopidogrel. For some patients in both treatment groups, dyspnoea lasts throughout treatment. Of all patients taking ticagrelor, 0.85% discontinued study medication because of dyspnoea.

The excess dyspnoea with ticagrelor does not associate with heart failure or lung disease: despite more dyspnoea AEs overall, AEs for heart failure (4.4% vs 4.6%), COPD (0.6% vs 0.4%), and asthma (0.2% vs 0.3%) do not occur more frequently in ticagrelor patients. Multiple studies throughout the programme measured pulmonary function while patients took ticagrelor or clopidogrel. They found no measurable differences between treatment groups or from baseline, when available, in spirometry, lung volumes, diffusion, flow rates, or oxygenation in volunteers with asthma or COPD, in patients with stable CAD, and in ACS patients. These findings held for those experiencing dyspnoea close to or during testing.

If a patient develops new or worsened dyspnoea during treatment with ticagrelor, the healthcare professional should rule out other potential causes of dyspnoea, such as CHF, asthma, or COPD, prior to ascribing a patient's dyspnoea to ticagrelor. If ticagrelor-related, no specific treatment is required; ticagrelor may be continued without interruption or dose adjustment.

5.4.3 Ventricular pauses

Continuous ECG (Holter monitors), employed in DISPERSE2 to detect silent ischaemia, instead revealed ventricular pauses after ACS events that occurred numerically more often with ticagrelor than with clopidogrel. This may represent another effect of adenosine reuptake inhibition, as adenosine depresses sinoatrial node activity, AV nodal conduction, and ventricular automaticity. PLATO included a properly powered substudy of Holter monitoring to probe safety aspects of the DISPERSE2 observation.

The PLATO Holter of 2908 patients substudy showed that ventricular pauses of at least 5 seconds occurred more frequently with ticagrelor than with clopidogrel, more so in the first week after the index ACS event (2.1% vs 1.0%) than a month later (0.8% vs 0.5%). However, they infrequently occurred even on the same date with related clinical AEs: 9 ticagrelor and 12 clopidogrel patients (see Module 2.7.4, Table 30). Many patients had at least 1 bradyarrhythmia during Holter monitoring: 59% and 54% respectively in the first week (see Module 2.7.4, Table 29). Sudden cardiac death occurred in 10 ticagrelor and 21 clopidogrel patients, by adjudication. Treatment groups did not differ with respect to the number of patients receiving pacemakers: 82 (0.9%) vs 79 (0.9%) (see Module 2.7.4, Table 28). Patients at risk for bradycardic events not already protected by a pacemaking device did not participate in PLATO and have not been studied. Aggregate data on cardiac arrhythmia-related AEs, SAEs, DAEs, and from the Holter substudy demonstrate no clinical important safety concerns related to bradyarrhythmias for ticagrelor (see Module 2.7.4, Section 2.1.6.2).

5.4.4 Increased serum uric acid

All phases of the development programme revealed elevation in serum uric acid concentration with ticagrelor. In PLATO, both treatment groups demonstrated increased mean serum uric acid, approximately 15% from baseline for ticagrelor and 7.5% for clopidogrel (see Module 2.7.4, Table 45). Mean serum uric acid decreased after stopping ticagrelor, but not after stopping clopidogrel, so that 30 days after stopping therapy, both treatment groups showed similar increases in uric acid concentrations, about 7% over baseline. Mean serum uric acid concentrations generally increased 5% to 10% with ticagrelor treatment in clinical pharmacology studies; this effect reversed in about 60 hours after stopping ticagrelor (see Module 5.3.4.1, D5130C00050 CSR).

In PLATO, the treatment groups had similar percentages of patients whose serum uric acid concentration exceeded 6 (females) or 7 (males) mg/dL and who developed potential uric acid-related AEs while on treatment: 33/1296 (2.5%) for ticagrelor and 19/852 (2.2%) for clopidogrel (see Module 2.7.4, Section 2.1.6.4). Using a diuretic more than 50% of the time while taking study drug does not appear to increase the likelihood of having an episode of gout with ticagrelor compared with clopidogrel. The pooled Phase II data do not reflect

PLATO data well, perhaps because they arise from small numbers: 1.2% of ticagrelor 90 mg bd patients, 1.9% of ticagrelor 180 mg bd patients, and 0.2% of clopidogrel patients had uric acid-related adverse events (see Module 5.3.5.3, Appendix 2.7.4.7, Table 2.6.1).

Increased uric acid, a laboratory finding, is neither a reliable surrogate for, nor predictor of, gout or gout-related events (Logan et al 1997). While increases in serum uric acid occurred with ticagrelor, relatively few patients (2.1% of ticagrelor treated patients in PLATO) experienced potential uric acid-related AEs, and even fewer (0.8%) experienced gout, gouty arthritis, or podagra (see Module 2.7.4, Table 47). Diuretics, known to increase serum uric acid, did not increase the likelihood of a potential uric acid related event. PLATO data do not support an association between ticagrelor and gout-related events. In addition, the results demonstrate that serum uric acid does not predict reliably clinical AEs, so routine measurement of serum uric acid during ticagrelor treatment is not indicated. Increased uric acid should not lead to discontinuation of ticagrelor.

5.4.5 Serum creatinine increases and renal AEs

Renal impairment is a co-morbid condition in patients with CV disease; it occurs frequently in ACS patients (Parikh et al 2008; Walsh et al 2002; Bellomo et al 2004; Zoffoli et al 2005). Both PLATO treatment groups displayed increases in serum creatinine of <10% above baseline. Slightly greater creatinine increases (about 1 to 2 μM, or 0.01 to 0.02 mg/dL mean), as well as more renal-related AEs, were observed with ticagrelor. Treatment groups showed similar numbers of patients whose creatinine concentration more than doubled (35 vs 34), although more ticagrelor patients had increases between 30% and 100% (992 vs 825; see Module 2.7.4, Table 33).

Urinalysis data from the Phase I and II program do not provide any evidence for drug induced kidney injury. In PLATO, which did not perform urinalyses, the vast majority of renal-related AEs contain terms relating to alteration of renal function, such as renal insufficiency, impairment, or failure. Patients with mild or moderate renal dysfunction at baseline and the elderly show imbalances of renal-related non-serious AEs with more reports in ticagrelor patients (see Module 2.7.4, Table 39 and Table 41). This difference however did not translate into an imbalance of renal-related SAEs and associated clinically meaningful outcomes including, death, dialysis, renal transplantation and permanent discontinuation of treatment (see Module 2.7.4, Table 40 and Table 42).

Patients with baseline renal impairment benefit from ticagrelor at least as much as those with normal renal function (see Section 4.2.2.2 of this Overview). Thus withholding ticagrelor from patients with renal impairment for fear of a potential renal AE stands to deprive a population who can benefit from its administration.

Studies to date have not provided mechanistic evidence as to the cause of the renal events. Based on these data there is insufficient evidence to suggest that the increases in creatinine observed with ticagrelor treatment result in clinically significant outcomes requiring specific intervention and/or discontinuation of ticagrelor. Monitoring of creatinine beyond standard

practice in this ACS population is therefore unlikely to be of value in the management of these patients. Renal impairment remains a potential risk, for further evaluation.

5.4.6 Hepatic function

Although liver function test abnormalities were observed in patients who received ticagrelor across the clinical development programme, the frequency of these liver function test abnormalities was low. In the Phase III PLATO study, patterns of potential concern for liver injury occurred similarly in the ticagrelor (1.4%) and clopidogrel (1.5%; see Module 2.7.4, Table 51) treatment groups. Transaminase elevations that occurred soon after index event likely reflect the enzymatic response to acute myocardial injury occurring in ACS. The pattern of hepatic AEs with ticagrelor provides no evidence of drug-induced liver injury during treatment with the drug (see Module 2.7.4, Table 51). Results of the Phase I study conducted in mild hepatically impaired patients confirm that no dose adjustment is warranted (see Module 5.3.3.3, Study D5130C00016 CSR). Phase II pooled hepatic-related AEs are too sparse to contribute to this topic. Patients with moderate and severe hepatic impairment have not been studied. Routine monitoring of hepatic function is not indicated for patients receiving ticagrelor treatment.

5.4.7 Cancer

Pre-clinical work demonstrated uterine adenocarcinoma and hepatocellular adenoma and carcinoma in female rats after lifelong ticagrelor feeding of 180 mg/kg/day. Similar dosing in mice did not show these tumours. Follow-up investigations identified an effect in rat but not human of ticagrelor on testosterone metabolism leading to chronic hormonal imbalance that might explain the tumour data. For this reason, a PLATO amendment, halfway through the trial, specified that women with non-menstrual vaginal bleeding undergo a complete gynaecologic evaluation. Treatment groups did not differ in abnormal vaginal bleeding, whether menstrual or non-menstrual: 23 AEs and 1 SAE for ticagrelor vs 18 AEs and 2 SAEs for clopidogrel (see Module 2.7.4, Section 2.1.6.6). One patient, taking ticagrelor for 14 days, reported an endometrial adenocarcinoma. Given the latency needed for tumour growth, a causal relationship with ticagrelor is unlikely. Data do not support a safety concern for abnormal vaginal bleeding; however, the relatively short, 12 month duration of therapy limits inference on lack of an association with endometrial cancer in humans.

In PLATO, treatment groups displayed similar number of patients with benign neoplasms and with non-benign neoplasms, both on and off study treatment (see Module 5.3.5.1, D5130C05262 CSR, Table 11.3.7.7.3). Fewer ticagrelor patients (23 of 402, 5.7%) than clopidogrel patients (31 of 397, 7.8%) with a baseline history of non-benign neoplasm developed a treatment-emergent neoplasm during treatment. Similar numbers of patients, 1.6% and 1.7% respectively, without that baseline history developed treatment-emergent neoplasms (see Module 5.3.5.1. D5130C05262, Table 11.3.7.7.4). Deaths due to cancer did not differ between treatment groups, with 15 ticagrelor (0.2%) and 17 clopidogrel (0.2%) (see Module 5.3.5.1, D5130C05262 CSR, Table 11.3.7.7.5). No safety concerns exist related to neoplasms with ticagrelor compared to clopidogrel based on the limited duration of treatment and follow-up in the development programme.

5.5 Special populations

5.5.1 Populations potentially at increased risk with antiplatelet therapy

Subgroup analysis for the primary safety endpoint, PLATO 'Major' bleeding, discloses no meaningful treatment interactions, and no particular population at risk for more bleeding with ticagrelor compared to clopidogrel. This includes the elderly, whether considered ≥65 years old or ≥75 years old; women; patients of different body weight, whether split by gender-specific median or at 60 kg; and those with prior a history of stroke or transient ischaemic attack (see Module 5.3.5.1, D5130C05262 CSR, Table 11.3.2.2.4.5). Adverse event frequencies displayed no consistent pattern for patients with BMI ≥30. For none of these groups is there a specific safety concern with ticagrelor; no dosage adjustment is indicated.

5.5.2 Use in pregnancy or during lactation

No clinical study has been conducted in pregnant or lactating women. Very limited clinical data exist (N=1) on exposure to ticagrelor during pregnancy.

Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal or foetal development, parturition, or postnatal development. Ticagrelor had no effect on male or female fertility. Because animal reproduction studies cannot reliably predict human response, ticagrelor should be used during pregnancy only if the potential benefit to the mother justifies any potential risks to the foetus.

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 ticagrelor during breastfeeding is not recommended.

5.5.3 Intrinsic factors

Demographic factors

For both ticagrelor and clopidogrel treatment groups, the frequency of AE reports increases with age, probably reflecting underlying background morbidity. Women have more AE reports than men, a pattern seen frequently in clinical trial AE reporting. Caucasians and non-Caucasians report AEs with similar frequencies.

Diabetes mellitus

Subgroup analysis demonstrates no treatment difference in PLATO Total 'Major' bleeding for diabetics (HR 0.95) and for non-diabetics (HR 1.08) (see Module 5.3.5.1, D5130C05262 CSR, Figure 29). Although overall AE reporting did not differ between diabetics and non-diabetics, diabetics more often reported SAEs, DAEs, and had higher mortality in PLATO. For diabetics and non-diabetics alike, fewer ticagrelor patients died than clopidogrel patients (3.6% and 1.9%) and (4.4% and 2.6%), respectively; see Module 5.3.5.3, Appendix 2.7.4.7, Table 1.2.5.1). Diabetics and non-diabetics alike benefit from ticagrelor with similar safety profiles.

Renal and hepatic impairment

The development programme studied patients with all degrees of renal impairment except those requiring dialysis. A comprehensive review of renal function and renal AEs (see Module 2.7.4, Section 2.1.6.3) found insufficient evidence to suggest that increases in creatinine with ticagrelor result in clinically significant outcomes. Renal impairment remains an important potential risk of ticagrelor administration. A similar review for hepatic impairment (see Module 2.7.4, Section 2.1.6.5) supports no safety concerns in patients with mild hepatic impairment. Patients with moderate or severe hepatic impairment have not been studied. No dose adjustment is indicated for renal impairment or for mild hepatic impairment.

5.5.4 Extrinsic factors

Analysis of AEs by geographic region disclosed no safety concerns for ticagrelor. Despite the known adverse effects of smoking, habitual smokers in PLATO had a similar AE frequency to non-habitual smokers and fewer SAEs and DAEs, as well as fewer deaths. Even cough was reported less frequently, although exertional dyspnoea was more frequent. Both treatment groups displayed these patterns, and ticagrelor patients had fewer deaths than clopidogrel for both those who smoked habitually and those who did not (see Module 2.7.4, Section 5.2.2.1). Food has a small effect on ticagrelor PK, so that ticagrelor can be administered with or without food. The effect of alcohol specifically has not been studied.

A comparison of AE frequencies by PT for patients taking a specific concomitant medication more than 20% of the time they received ticagrelor, compared to those taking that medicine not more than 20% of the time, did not identify any extrinsic effect for the following selected drugs: simvastatin, atorvastatin, diltiazem; angiotensin-converting enzyme inhibitors as a class; and angiotensin receptor blockers as a class. Similar findings occurred for digoxin and for statins as a class; however, only 141 patients took digoxin and >90% of patients took statins, making each within group comparison very imbalanced, and the results more subject to variation (see Module 2.7.4, Section 5.2.4.1).

5.6 Overdose and abuse potential

PLATO recorded 27 patients taking greater than the prescribed dose, 16 randomised to ticagrelor and 11 to clopidogrel, but only 1 case involved intentional overdosage. No case had an associated AE (see Module 5.3.5.1, D5130C05262 CSR, Section 8.7.3). In human volunteer studies, the maximum tolerated single dose was 900 mg.

No known antidote exists to reverse the effects of ticagrelor; no data indicate whether or not it can be dialysed. Treatment of overdose should follow local standard medical practice. Bleeding, the expected pharmacologic effect of excessive dosing, should be treated with appropriate supportive measures.

There is no indication that ticagrelor has any potential for abuse.

5.7 Withdrawal and rebound

In a 30-day post-study drug observation period in PLATO, 0.9% of patients in each randomised treatment group developed an event in the primary efficacy composite (see Module 5.3.5.1, D5130C05262 CSR, Table 11.2.11.1). Few events occur in these 30 days, reflecting an absence of pharmacologic rebound. Although events after stopping ticagrelor appear to occur slightly earlier than after stopping clopidogrel, over 30 days, the Kaplan-Meier rate estimates do not differ. Thus, despite more intense antiplatelet effect with ticagrelor, an exaggerated response does not accompany withdrawal of therapy. No special withdrawal precautions are required for ticagrelor. In patients with ACS, premature discontinuation with any antiplatelet therapy, including ticagrelor, could result in an increased risk of CV death or MI due to the patient's underlying disease.

5.8 Effects on ability to drive or operate machinery

No studies on the effects of ticagrelor on the ability to drive and use machines have been performed. Ticagrelor has no or negligible influence on the ability to drive and use machinery. During treatment for ACS, dizziness and confusion have been reported. Therefore, patients who experience these symptoms should be cautious while driving or using machines.

5.9 Post-marketing safety reports

There are no post-marketing data for ticagrelor at the time of this application.

5.10 Safety conclusions

Ticagrelor was evaluated in a patient population with significant disease burden, interventions, and concomitant medications. Both dyspnoea and an increased risk of bleeding constitute important identified risks. Increased serum uric acid and creatinine levels are mentioned in the prescribing information, and renal impairment has been designated an important potential risk. Detailed investigations of liver function tests, cancer incidences, and ventricular pauses lead to no specific safety concerns with ticagrelor for these issues. A host of GI disturbances, types of bleeding, and various other symptoms also occur with ticagrelor and thus could reflect adverse drug reactions that patients may experience when given ticagrelor.

Considering the totality of safety data, ticagrelor does not substantially add to the background morbidity in the ACS population or pose a safety concern considerably different from that of clopidogrel, the current standard of care for patients with ACS.

6. BENEFITS AND RISK CONCLUSIONS

ACS, a serious, life-threatening medical condition, contributes substantially to worldwide morbidity and mortality. Ticagrelor prevents more major adverse cardiac events after ACS, most notably reducing CV mortality, compared with the current standard of care, clopidogrel, without adding clinically important safety concerns.

6.1 Benefits of ticagrelor

Against the active comparator and standard of care, clopidogrel, ticagrelor reduced the rate of the composite efficacy endpoint of CV death, MI, or stroke after ACS events, with ARR 1.9%, RRR 16%, and NNT of 54. This result derives strongly from both CV death and MI, with no contribution from stroke. Analysis of all-cause mortality (ARR 1.4%, RRR 22%, nominal p=0.0003) confirms the CV death benefit (ARR 1.1%, RRR 21%CV, p=0.0013). This compelling effect, preventing 1 CV death for every 91 patients treated with ticagrelor instead of clopidogrel for 12 months, represents a noteworthy therapeutic advance in the treatment of ACS.

Superiority of ticagrelor over clopidogrel for the primary composite endpoint shows consistency across age, gender, and body weight. Based on a higher rate of events for the primary efficacy composite with ticagrelor in the United States, possibly the result of a combination of the play of chance and common use there of higher doses of aspirin, ticagrelor should be given with chronic ASA doses of 75 to 150 mg daily.

PLATO tested ticagrelor in clinically relevant settings. Ticagrelor's advantage to clopidogrel applies to the broad, inclusive population of ACS patients with or without ST-segment elevation on the ECG, whether or not intended for invasive management. The benefit appears early in the course of treatment and continues to grow throughout the 12 month treatment period, suggesting that it is appropriate to treat patients with ticagrelor for at least 12 months.

6.2 Risks of ticagrelor

The important identified clinical risks related to ticagrelor are bleeding and dyspnoea.

Bleeding constitutes the most important safety issue for all antiplatelet medications. Despite greater inhibition of platelet aggregation with ticagrelor, PLATO 'Major' bleeding with ticagrelor did not differ from that with clopidogrel. Whether evaluated overall, or restricted to CABG-related bleeds, or restricted to non-procedural bleeds, ticagrelor and clopidogrel did not differ in fatal bleeding, or fatal/life-threatening bleeding. Ticagrelor had numerically fewer fatal bleeds than clopidogrel, although fatal intracranial bleeds occurred more frequently with ticagrelor. No particular patient subgroup presents an increased risk for bleeding as a whole or for intracranial haemorrhage whilst taking ticagrelor. As a result, clinicians cannot identify such patients in advance, making risk mitigation difficult for bleeding. Nevertheless, bleeding can occur more frequently with ticagrelor. This must be considered against the survival benefits of ticagrelor, so patients may require encouragement to continue taking ticagrelor after recovery from a bleeding event. No ticagrelor dose adjustment need be made for most conditions potentially altering drug exposure.

Dyspnoea, a feeling of breathlessness, occurs commonly in patients with ACS, more so with ticagrelor treatment, 13.8% v. 7.8% with clopidogrel. In PLATO, dyspnoea was usually rated mild in severity, and did not associate with heart failure or lung disease. It led 9 in 1000 ticagrelor treated patients to discontinue therapy. Older patients and those with dyspnoea, heart failure, asthma, or COPD at baseline were more likely to develop dyspnoea

during the trial. Because early discontinuation of ticagrelor after ACS may remove its risk reduction benefit, the clinician should rule out other potential causes of dyspnoea, such as CHF, asthma, or COPD, prior to ascribing a patient's dyspnoea to ticagrelor. If ticagrelor-related, no particular treatment or dose adjustment is necessary.

Other clinical events observed in patients given ticagrelor, include ventricular pauses, largely asymptomatic; increases in serum uric acid concentrations; and increases in serum creatinine. Each of these has lesser clinical impact and/or is readily managed in the context of ACS therapy.

Routine risk management activities focus on product labelling and pharmacovigilance to note the need to rule out medically important causes of dyspnoea, and the relative risks and benefits of continuing ticagrelor therapy when bleeding or dyspnoea arises from drug use. In addition, AstraZeneca will explore in the early post-launch period the feasibility of studies to clarify the clinical impact of changes in renal function with ticagrelor after an ACS event.

Ticagrelor was evaluated in a patient population with significant disease burden, interventions, and concomitant medications. Both dyspnoea and increased risk of bleeding have been designated as important identified risks and renal impairment as an important potential risk. Still, ticagrelor's safety and tolerability profile demonstrated that ticagrelor does not substantially add to the background morbidity in the target population or pose a safety concern considerably different from clopidogrel, the current standard of care for patients with ACS.

6.3 Special populations

The elderly, women, and patients of low body weight obtain the same efficacy benefit as others do from ticagrelor, with no increased risk of major bleeding or of other identifiable clinically important safety event. Preservation of the primary efficacy and primary safety results applies in the elderly to the category of patients at least 65 years old and also to those at least 75 years old; these results apply by body weight whether it is split at 60 kg or at 80 kg. Patients with prior stroke or transient ischaemic attack, those with renal impairment, and those with mild hepatic impairment each benefit from ticagrelor at least as much as those with normal organ function, and entail no clinically important additional safety risks.

6.4 Benefit risk evaluation

Quanititative methods for combining risk and benefit easily suffer the criticism of absent or flawed weighting of individual components. However, multiple approaches to the assessment of benefit-risk, if consistent, afford a more convincing view. Viewed in multiple ways, ticagrelor's benefits outweigh its risks.

The pre-specified combined safety-efficacy composite endpoint in PLATO, consisting of the primary composite, CABG-related PLATO Fatal/Life-threatening Bleeding, and non-CABG-related PLATO Major bleeding, demonstrated statistically significant superiority for ticagrelor over clopidogrel, with ARR 1.4%, RRR 8%, NNT=71, and p=0.0257 (see Module 2.7.3, Table 10). Sensitivity analyses, substituting in this composite (1) all cause mortality for CV

death; (2) all CABG 'Major' bleeding for only those fatal or life-threatening bleeds; and, (3) both of these substitutions, all support the pre-specified analysis results.

Another assessment of the benefit-risk balance views important events predicted to occur in 1000 ACS patients given ticagrelor instead of clopidogrel over 12 months. Based on the ARR found in PLATO for the primary efficacy endpoint (1.9%) and for CV death (1.1%); on the differential incidence for dyspnoea (13.8%-7.8% = 6.0%); and on the incidence of 0.85% DAE due to dyspnoea, one expects: 19 fewer major adverse cardiac events (CV death or MI) of which 11 represent lives saved, without additional major bleeding, but with 60 additional complaints of dyspnoea leading 9 patients to stop therapy.

6.5 Overall conclusions

The last 50 years have witnessed few major treatment advances in ACS associated with decreases in mortality:

- The establishment of cardiac care units with continuous electrocardiogram monitoring to detect and treat sudden cardiac death
- The recognition of the role of platelets in acute MI, leading to widespread use of ASA
- Introduction of intracoronary and intravenous thrombolytic therapy

Each of these advances came with costs and risks that were overshadowed by survival benefits. Ticagrelor presents the next chapter in this story of improved survival in ACS, a benefit that outweighs attendant increases in minor bleeding and other readily managed risks. The compelling data from PLATO, supported by strong data from the rest of the programme, provide clear evidence of a substantially improved benefit to risk balance vs clopidogrel to support registration of ticagrelor for superior risk reduction in patients with ACS.

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