Revised Clinical Study Protocol

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A 30 day international, randomized, parallel-group, double-blind, placebo-controlled phase IV study to evaluate efficacy and safety of pre-hospital vs. in-hospital initiation of ticagrelor therapy in STEMI patients planned for PCI

The ATLANTIC study: Administration of Ticagrelor in the Cath Lab or in the Ambulance for New sT elevation myocardial Infarction to open the Coronary artery

Sponsor: **ASTRAZENECA SAS -**

AstraZeneca Research and Development site representative

Date

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The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1:applicable to Canada plus individual centres in other countries- not applicable			
2: applicable to participating sites in France, Netherlands, Italy plus individual centres in other countries.			

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change
1			
2			

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PROTOCOL SYNOPSIS

A 30 day international, randomized, parallel-group, double-blind, placebo-controlled phase IV study to evaluate efficacy and safety of pre-hospital vs. in-hospital initiation of ticagrelor therapy in STEMI patients planned for PCI

International Co-ordinating Investigator

Study centre(s) and number of patients planned

This study will be conducted in approximately 120 investigational centres in 10-15 countries. It is expected that approximately 1770 patients will be randomized to study treatment.

It is expected that the majority of centres will recruit 10 or more patients.

Study period	Phase of development
Estimated date of first patient enrolled	IV
Estimated date of last patient completed	

Objectives

Primary objectives	Outcome variables
To assess the efficacy of pre-hospital vs. in-hospital initiation of ticagrelor therapy by comparing the percentage of patients reaching the co-primary endpoint of TIMI flow grade 3 of MI culprit vessel at initial angiography or a ≥70% ST-segment elevation resolution pre-PCI.	Co-primary endpoint is the percentage of patients reaching TIMI flow grade 3 of MI culprit vessel at initial angiography or a ≥70% ST-segment resolution pre PCI

Secondary objectives	Outcome variables
To compare the efficacy of pre-hospital vs. in-hospital initiation of ticagrelor therapy by assessing the following endpoints:	

1.	Composite of death, MI, stroke, urgent revascularization and acute stent thrombosis during 30 days of study.	Percentage of patients in the following: composite of death, MI, stroke, urgent revascularization and acute stent thrombosis during 30 days of study .
2.	Composite of death, MI, urgent revascularization during 30 days of study	Percentage of patients in the following: composite of death, MI, urgent revascularization during 30 days of study
3.	Acute stent thrombosis during 30 days of study	Percentage of patients presenting an acute stent thrombosis episode during 30 days of study
4.	Thrombotic bail-out with GPIIb/IIIa inhibitors at initial PCI	Percentage of patients receiving thrombotic bail-out with GPIIb/IIIa inhibitors at initial PCI
5.	Complete (≥ 70%) ST-segment elevation resolution at 60 min post-PCI	Complete (≥ 70%) ST-segment elevation resolution at 60 min post-PCI
6.	Corrected TIMI frame count (cTFC) at angiography, pre and post PCI.	Corrected TIMI frame count (cTFC) at angiography, pre and post PCI
7.	TIMI myocardial perfusion grade (TMPG) at angiography, pre and post PCI.	TIMI myocardial perfusion grade (TMPG) at angiography, pre and post PCI
8.	Time–relationship (from symptom onset to 1st dose intake) on each co-primary	Time from symptom onset to 1st dose intake correlated to TIMI flow grade 3 of MI culprit vessel at initial angiography and on ≥70% ST-segment elevation resolution pre-PCI
9.	Time–relationship (from 1st dose intake to ECG/ angiography) on each co-primary	Time from first dose intake to ECG correlated to ≥70% ST-segment elevation resolution pre-PCI and time from randomization to initial angiography correlated to TIMI flow grade 3 of MI culprit vessel
10.	TIMI flow grade 3 at end of procedure.	TIMI flow grade 3 at end of procedure

Safety objectives		Outcome variables
1.	To assess the safety of pre-hospital vs. in-hospital initiation of ticagrelor therapy using PLATO bleeding definition, within the first 48 hours and during 30 days of study	Bleeding events (a) The total number of patients with major life-threatening bleeding events (b) Total number of patients with other major bleeding events, (c) Total number of patients with minor or major bleeding events The above endpoints will be defined according to PLATO bleeding definition (excluded CABG-related bleeding), within the first 48 hours and, , during 30 days of study defined as follows: – major life-threatening bleeding: fatal bleeding, intracranial bleeding, intrapericardial bleeding with cardiac tamponade, hypovolemic shock or severe hypotension due to bleeding and requiring vasopressors or surgery, decline in the hemoglobin concentration of 5.0 g/dL or more, or need for transfusion of at least 4 units of red cells, – other major bleeding: bleeding that led to clinically significant disability (e.g., intraocular bleeding with permanent vision loss) or bleeding associated with a drop in the haemoglobin concentration of at least 3.0 g/dL but less than 5.0 g/dL or requiring transfusion of 2 to 3 units of red cells, – minor bleeding: any bleeding requiring medical intervention but not meeting the criteria for major bleeding.
2.	To assess the safety of pre-hospital vs. in-hospital initiation of ticagrelor therapy in term of adverse events within 30 days of study	Other safety events Adverse events, abnormal laboratory findings, physical examination, vital signs within 30 days of study

Study design

This is a 30 day, international, randomized, parallel-group, double-blind, placebo-controlled phase IV study to evaluate the efficacy and safety of pre-hospital vs. in-hospital initiation of ticagrelor therapy in STEMI patients planned for primary PCI.

Target patient population

Male and female patients aged 18 years and over with documented evidence of acute ST elevation myocardial infarction (STEMI), planned for angioplasty (PCI), who had the onset of cardiac ischemic symptoms within the 6 hours before randomization and who were initially managed by ambulance physician/ personnel in pre-hospital settings; this concerns as well patients (not pre-treated for their STEMI) in emergency rooms of non-PCI hospitals. The qualifying ECG and inclusion into the study are made solely by the ambulance personnel.

Investigational product, dosage and mode of administration

Ticagrelor (AZD6140): 90 mg tablets.

Double blind period:

Pre-hospital ticagrelor arm: Patients will receive a loading dose of 180 mg ticagrelor for the pre-hospital administration and placebo for in-hospital administration.

In-hospital ticagrelor arm: Patients will receive a placebo for pre-hospital administration and 180 mg ticagrelor loading dose for in-hospital administration.

30 days active treatment period

After loading dose, all patients will receive ticagrelor 90 mg (tablet), twice daily, orally during 30 days.

Comparator, dosage and mode of administration

‘Placebo’ (matching the investigational product)

Duration of treatment

Patients will be randomised to treatment no later than 6 hours after the onset of cardiac ischemic symptoms. Approximately 12 hours after the second loading dose the patient will continue on ticagrelor 90 mg BID as maintenance treatment and will be followed in study for 30 days post randomisation.

After this 30 day period, it is up to the investigator to decide whether the patient should be maintained on ticagrelor as a component of dual antiplatelet therapy or other antithrombotic therapy. If the investigator feels it is in the best interest of the patient to continue ticagrelor and ticagrelor is not yet commercially available, AstraZeneca will provide ticagrelor free of charge until such time as it is commercially available in the relevant market or for up to 12 months as recommended in the Summary of Product Characteristics (SmPC). AstraZeneca will not provide ticagrelor free of charge in markets where ticagrelor is commercially available.

The 30 day active treatment period will be followed by an additional safety monitoring period of 7 days.

Concomitant therapy, dosage and mode of administration+

Concomitant ASA: In addition to study medication, patients may receive 150–300 mg per os or 250 (–500) mg bolus i.v., in the double blind phase followed by 75–100 mg daily as recommended by ESC/EACTS guidelines 2010 or up to 150 mg according to ticagrelor Summary of Product Characteristics (SPC).

Parenteral anticoagulants: Short-term treatment with approved parenteral anticoagulants (eg. unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), bivalirudin, fondaparinux) is allowed.

GPIIb/IIIa receptor antagonists: Upstream (ambulance) use of GPIIb/IIIa receptors antagonists is not recommended as a concomitant treatment but will be left to physician's discretion. In lab use of GPIIb/IIIa receptors antagonists after the angiogram is possible and not discouraged. This use will have to be identified as being a strategy of choice or a bail out use during PCI.

Statistical methods

The primary objective of the study is to assess the efficacy of pre-hospital administration of ticagrelor compared to an in-hospital administration.

Two co-primary endpoints are considered relevant to assess this objective:

- The TIMI flow of the culprit artery at first angiography by the evaluation of percentage of patients reaching TIMI flow grade 3
- The ST-segment elevation resolution between pre-hospital assessment and in-hospital assessment pre PCI, by the evaluation of percentage of patients reaching a complete ST elevation resolution according to (Schröder R et al 1994) (ST resolution $\geq$ 70%).

Each endpoint will be analyzed separately using a Chi-Square test. For each endpoint the null hypothesis is one of no difference between the two groups. The alternative hypothesis is that there is a difference. Correction procedure will be used to adjust for multiplicity while maintaining an overall Type I error rate of 5%.

Since, based on multiplicity procedure, the initial significance level is 2.5%, the sample size calculation will be based on a significance level of 2.5% and 80% power. Sample size calculations were derived using nQUERY7.

The sample size for the two co-primary endpoints is derived from the ST Resolution hypothesis. However, the study is enough powered for the 2 criteria when considering the table below.

The ST segment deviation was previously studied in On TIME2 study (Van't Hof Aw et al 2008), where complete ST resolution occurred in 20.7% of patients in the pre-hospital GP IIb/IIIa group versus 15.4% in the non GP IIb/IIIa group, all patients receiving a clopidogrel loading dose. This last number, corresponding to an in-hospital group was confirmed in Assent 4 PCI study where electrocardiographic reperfusion was shown in 14.9% of patients.

Based on this data, it is hypothesized that 15% of patients in the in-hospital group will achieve complete ST resolution versus 21% in the pre-hospital group (absolute difference of 6%). Taking into account a significance level of 2.5%, 779 evaluable patients are required in each treatment group to have 80% power using a two-group chi squared test of equal proportions. Assuming a12% dropout for invaluable or missing ECG criteria, a total of 1770 patients are required to be enrolled in the study to assess the ST segment resolution difference.

TIMI Flow 3 at initial angiography ranges from 15-27% according to various studies. Clinicians agreed that a 30 to 35% relative difference between the 2 groups is clinically relevant. In order to hypothesize on the various degree of angiographic reperfusion expected the following table was created to show a range of hypothesis and the related sample size. A statistical difference can be shown for the highlighted hypothesis (in bold) in the table. Dropout rate at initial angiography is assumed to be low, and less than 8%.

	Assumptions with TIMI flow grade3 = 15% in in-hosp group		**Assumptions with TIMI flow grade3 = 27% in in-hosp group**	
Assumptions of relative difference (%) between the two groups	30	35	30	35
In –hosp group	15%	15%	27%	27%
Pre-hosp group	19,5%	20,3%	35,1%	36,5%
N per group with alpha=0.05	1106	826	512	376
N per group with alpha=0.025	1339	1001	620	456

The efficacy analysis will be based on the modified ITT analysis set.

The safety analysis will include all randomized patients who received at least one dose of study drug.

Safety endpoints will be analyzed using descriptive methods.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ACC	American College of Cardiology
ACS	Acute Coronary Syndromes
AE	Adverse event (see definition in Section 6.4.1)
AHA	American Heart Association
ASA	Acetylsalicylic Acid (Aspirin)
AVB	Atrioventricular Block
BARC	Bleeding Academic Research Consortium
BID	Twice a day
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
Cath Lab	Catheterization Laboratory or catheterization room or coronarography room
CD	Compact Disc
CAD	Coronary artery disease
CHD	Coronary Heart Disease
CI	Confidence Interval
Core Lab	Laboratory for central review for ECG/angiography
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
cTFC	Corrected TIMI Frame Count
CYP3A	Cytochrome P4503A, the most abundant of the P450 enzymes responsible for initial drug metabolism in the liver
DAE	Discontinuation of Investigational Product due to Adverse Event
DB	Double Blind
DSMB	Data Safety Monitoring Board
DUS	Disease under Study
EACTS	European Association for Cardio-Thoracic Surgery
ECG	Electrocardiogram

Abbreviation or special term	Explanation
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
Endpoint	Symptomatic or asymptomatic events that are centrally adjudicated and specifically defined in the protocol as efficacy variables.
EOT	End of treatment (refers to study visit at which patient is discontinued from study medication)
ESC	European Society of Cardiology
FUP	Follow UP
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
GP	Glycoprotein
GUSTO	Global Utilization of Streptokinase and t-PA for occluded coronary arteries
Hb	Hemoglobin
HR	Hazard Ratio
IB	Investigator's Brochure
ICF	Informed Consent Form
ICU	Intensive Care Unit
ICH	International Conference on Harmonization
ICAC	Independent Central Adjudication Committee
IHD	Ischemic Heart Disease
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational Product (same as study medication)
IPA	Inhibition of Platelet Aggregation
ISTH	International Society on Thrombosis and Haemostasis
IVRS/IWRS	Interactive Voice Response System/ Interactive Web Response System
IV	Intravenous
LBBB	Left Bundle Branch Block
LD	Loading Dose
LSLV	Last Subject Last Visit
LVH	Left Ventricular Hypertrophy
MI	Myocardial Infarction

Abbreviation or special term	Explanation
NSAID	Non Steroidal Anti-Inflammatory Drug
NSTEMI	Non ST-Elevation Myocardial Infarction
OAE	Other Significant Adverse Event (see definition in Section 11.2.2)
On-TIME2	The Ongoing Tirofiban in Myocardial Evaluation (study)
OLE	Open label Extension
PCI	Percutaneous Coronary Intervention
PI	Principal Investigator
PLATO	A study of PLATelet inhibition and patient Outcome
PRBCs	Packed Red Blood Cells
S3	S3 gallop (audible extra heart sound by cardiac auscultation)
SAE	Serious adverse event (see definition in Section 6.4.2).
SPC	Summary of Product Characteristics (also known as Core Data Sheet)
SSS	Sick Sinus Syndrome
STEEPLE	Safety & Efficacy of Enoxaparin in Percutaneous coronary intervention (PCI) ; An International Randomised Evaluation
STEMI	ST-Elevation Myocardial Infarction
TIA	Transient Ischemic Attack
TIMI	Thrombolysis in Myocardial Infarction
TMPG	TIMI Myocardial Perfusion Grade
vs.	versus
WBDC	Web Based Data Capture
WHO	World Health Organization

1. INTRODUCTION

1.1 Background

1.1.1 Acute coronary syndromes and ST-elevation myocardial infarction

Ischemic Heart Diseases (IHDs), also named coronary heart diseases (CHDs), make up a major group of cardiovascular diseases that are an important cause of death and morbidity worldwide. In 2002, the World Health Organization (WHO) estimated that 12.6% of worldwide deaths were from IHDs, which were the leading cause of death in developed countries, and third to acquired immunodeficiency syndrome (AIDS) and lower respiratory infections in developing countries (WHO 2002).

Among CHDs, acute coronary syndromes (ACS) encompass a spectrum of diseases from unstable angina to transmural myocardial infarction (MI). All MIs have a common etiology and occur when an atherosclerotic plaque ruptures, leading to thrombus formation within a coronary artery (Fuster et al 2005). The resulting ischemia (restriction in blood supply) and oxygen shortage, if left untreated for a sufficient period of time, can cause damage or death (infarction) of heart muscle tissue.

Patients who develop symptoms consistent with ACS, such as chest pain and diaphoresis, require rapid evaluation to determine the cause and guide therapeutic decision-making (Miller et al 2006). When an ACS is diagnosed, patients are further subdivided into the following two major categories based on the 12-lead electrocardiogram (ECG): those with new ST-elevation on the ECG, that is diagnosis of acute ST-elevation MI (STEMI), and those who present with ST-segment depression, T-wave changes, or no ECG abnormalities (non ST-elevation ACSs). Non ST-elevation ACSs encompass both unstable angina and non ST-elevation MI (NSTEMI) (Wiviott et Braunwald 2004; Morrow et al 2007)

In a STEMI, the most severe type of MI, the coronary artery is completely occluded by blood clot and, as a result, virtually the whole heart muscle being supplied by the culprit artery starts to die. The annual incidence of hospital admission for STEMI in Europe is more than 800 patients per million population, compared to an incidence of acute MI of about 1900 per million, i.e. an incidence rate of STEMI of about 42% of the total incidence of acute MI (Widimsky et al 2010).

1.1.2 Current management of ST-elevation myocardial infarction

The primary aim in the treatment of acute ST elevation myocardial infarction (STEMI) is the effective and rapid reperfusion of the infarct-related artery (Simes RJ et al 1995; Anderson JL et a**l** 1996). This can be achieved by either medical management with thrombolytics or primary percutaneous coronary intervention (PCI) (Smith SC Jr et al 2006; Silber S et al 2005). Randomized controlled trials and meta-analyses comparing primary PCI with in-hospital fibrinolytic therapy in patients within 6–12 h after symptom onset treated in high-volume, experienced centres, have shown more effective restoration of vessel patency, less re-occlusion, improved residual LV function, and better clinical outcome with primary PCI (Keeley EC et al 2003). Cities and countries switching from fibrinolysis to primary PCI have observed a sharp decrease in mortality after STEMI.(Kalla K et al 2006; Zahn R et al 2000) It is essential to make every effort to minimize all time delays, especially within the first 2 h after onset of symptoms, by the implementation of a system of care network. The preferred pathway as recommended by the latest ESC/EACT guidelines on revascularization is immediate transportation of STEMI patients to a PCI-capable centre offering an uninterrupted primary PCI service by a team of high-volume operators. (Wijns W, Kolh P et al 2010).

1.1.2.1 Antiplatelet therapy as an adjunct to reperfusion therapy

Reperfusion therapies are associated with the need to protect the treated vessels against early and late thrombosis and re-occlusion. They may indeed be complicated by adverse cardiac events including re-infarction, stroke, need for urgent revascularization, and particularly in PCI, acute, sub-acute or late stent thrombosis.

Dual antiplatelet therapy consisting traditionally of aspirin plus clopidogrel has therefore been established as an important adjunct to reperfusion therapy, especially PCI. The latest revascularization guidelines incorporates the newer and more potent antiplatelet agents and hence recommend dual antiplatelet treatment consisting of aspirin combined with either prasugrel or ticagrelor in place of clopidogrel in STEMI patients undergoing PCI (Wijns W, Kolh P et al 2010).

1.1.2.2 Ticagrelor

Ticagrelor (AZD6140) is an oral, reversibly binding, direct-acting, non-thienopyridine inhibitor of P2Y12 receptors (Kowalczyk et al 2009; Davies 2010). It is the first of a new chemical class of antiplatelet agents: the cyclopentyltriazolopyrimidines. Unlike thienopyridine derivatives, ticagrelor:

- is orally active and does not require metabolic activation, allowing a more rapid onset of action and a more potent antiplatelet e ffect (Husted et al 2006; Storey et al 2007);

has been associated with less interpatient variability and less drug-drug interaction (Husted et al 2006);

- binds reversibly to the P2Y12 receptors: platelet function fully recovers within 2-3 days after the last dose of ticagrelor (compared to the 5-7 days required for clopidogrel) (Husted et al 2006; Storey et al 2007).

Optimal dosing strategy as determined by ticagrelor's pharmacokinetic and pharmacodynamic profile is a loading dose of 180 mg followed by 90 mg twice daily. Within 30 minutes, a ticagrelor loading dose of 180 mg resulted in roughly the same level of inhibition of platelet aggregation (IPA) as that achieved 8 hours after a clopidogrel loading dose of 600 mg (IPA of 40% for ticagrelor at 30 minutes compared to 50% for clopidogrel at 8 hours) (Gurbel et al 2009).

Ticagrelor safety and efficacy compared with the standard dose clopidogrel have been evaluated recently in ACS patients with or without ST-segment elevation (PLATO study:Wallentin et al 2009, Cannon et al 2010). After 12 months of treatment, the primary endpoint—any event from the composite of cardiovascular death, MI, or stroke—was significantly reduced in patients receiving ticagrelor than in patients receiving clopidogrel (9.8% vs. 11.7%, respectively, hazard ratio [HR]: 0.84; 95% confidence interval [CI]: 0.77 to 0.92; $p<0.001$).

The secondary endpoints showed significant reductions in the ticagrelor group, as compared to the clopidogrel group, with respect to the rates of:

- the composite endpoint of death from any cause, MI, or stroke (10.2% vs. 12.3%, respectively, $p<0.001$),
- the composite endpoint of death from vascular causes, MI, stroke, severe recurrent ischemia, recurrent ischemia, transient ischemic attack, or other thrombotic events (14.6% vs. 16.7%, respectively, $p<0.001$),
- MI alone (5.8% vs. 6.9%, respectively, $p=0.005$),
- death due to vascular causes (4.0% vs. 5.1%, respectively, $p=0.001$),

other events:

- death from any causes (4.5% vs. 5.9%, respectively, $p<0.001$),
- definite stent thrombosis (1.3% vs. 1.9%, respectively, $p=0.009$).

There was no significant difference in the rates of major bleeding in the ticagrelor and clopidogrel groups (11.6% vs. 11.2%, respectively, p=0.43). There was also no significant difference in the rates of major bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) criteria (7.9% with ticagrelor and 7.7% with clopidogrel, P = 0.57) or fatal or life-threatening bleeding (5.8% in both groups, P = 0.70). However, there was an increase in non-CABG-related bleeding in the first week of treatment with ticagrelor. Rates of dyspnea and ventricular pauses on Holter monitoring were also higher in the ticagrelor group. Similar results were found in the subset of patients with STE-ACS undergoing PCI enrolled in PLATO study (Steg et al 2010).

It was thus concluded that ticagrelor was more effective than clopidogrel in preventing MI/stroke/cardiovascular death in STEMI patients undergoing PCI, without an increase in the rate of overall major bleeding.

On 3rd of December 2010, the European Commission has granted marketing authorization to Brilique® (ticagrelor tablets) in co-administration with aspirin for the prevention of atherothrombotic events in adult patients with Acute Coronary Syndromes (unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]); including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

PLATO results: outcomes in patients with STE-ACS and planned PCI (Steg et al 2010)

Endpoint	**ticagrelor (%) n=3752**	**clopidogrel (%) n=3792**	**hazard ratio for ticagrelor**	**P**
Primary endpoint:				
CV death, MI or stroke	9.4	10.8	0.87	0.07*
Secondary endpoints:				
CV Death, MI (excluding silent)	8.4	10.2	0.82	0.01*
All cause mortality/MI (excluding silent)/ stroke	9.8	11.3	0.87	0.05*
MI (excluding silent)	4.7	5.8	0.80	0.03*
Stroke	1.7	1.0	1.63	0.02*
all-cause mortality	5.0	6.1	0.82	0.05*
cardiovascular mortality	4.5	5.5	0.83	0.07*
definite stent thrombosis	1.6	2.4	0.66	0.03*
Primary safety event:				
major bleeding	9.0	9.2	0.98	0.76*
Side effects other than bleeding:				

Endpoint	ticagrelor (%) n=3752	clopidogrel (%) n=3792	hazard ratio for ticagrelor	P
Dyspnea any	12.6	8.4	-	<0.0001†
Bradycardia	4.7	4.8	-	0.83†

MI, myocardial infarction, TIA, transient ischemic attack
The percentages are Kaplan-Meier estimates cumulative incidence of the endpoint at 12 months. Patients could have more than one type of endpoint.
* By univariate Cox model.
† Fisher's exact test.

1.2 Research hypothesis

Results from PLATO study support ticagrelor as a new standard of care for the management of patients with STEMI intended for PCI. Treatment should be initiated with a single 180 mg loading dose (two tablets of 90 mg) and then continued at 90 mg twice daily. However, the optimal timing for the initiation of treatment with ticagrelor has not been determined as in PLATO patients were initiated on treatment if they presented within 24 hours of symptoms onset.

It is hypothesized that earlier (pre-hospital) initiation of ticagrelor could result in rapid restoring of coronary flow and myocardial reperfusion—as assessed by the co-primary endpoint of TIMI flow grade 3 of MI-related vessel at initial angiography or a ≥70% ST-segment resolution pre-PCI—, and thus may facilitate PCI procedure and hence improve clinical outcome

1.3 Rationale for conducting this study

Although significant recent advances have been made in management strategies for STEMI, residual morbidity and mortality are still high. Data suggest that rapid triage, transfer and treatment is essential (Blankenship et Skelding 2008). Delays in initiation of treatment because of transportation of high-risk patients with STEMI are associated with worse clinical outcome.

The use of the ambulance setting to initiate treatment provides an opportunity to dramatically reduce the time between symptom onset and reperfusion, and a growing body of evidence shows that pre-hospital reperfusion therapy is associated with significantly better short-term and long-term outcomes than in-hospital administration of the same treatment (Goldstein et al 2009). In addition to prevent potential complications of PCI, early antithrombotic administration and blood flow improvement are thought to facilitate the PCI procedure itself (Dauerman et Sobel 2003, Huber et al 2005). For those patients undergoing PCI, results of retrospective analyses indeed suggest that outcomes are better if the MI-related vessel is open before the procedure (namely, TIMI flow grade 2 or 3) (Brodie et al 2000, Stone et al 2001).

Regarding P2Y12 receptor inhibitors, a loading dose of clopidogrel before PCI has become relatively common clinical practice, although the data supporting this practice are limited and

sometimes conflicting. Results from the CREDO trial indeed showed that when a 300-mg loading dose of clopidogrel is used, and if treatment duration is less than 12 hours before PCI, little benefit is obtained compared with a clopidogrel dose of 75 mg administered at the time of PCI (Steinhubl et al 2006). Another study consistently showed that patients undergoing PCI who received a 600-mg loading dose of clopidogrel in the Cath Lab after coronary angiography but prior to PCI had similar outcomes to those who were preloaded with clopidogrel 4 to 6 hours before PCI (ARMYDA-5 PRELOAD studyDi Sciascio et al 2010). A more recent study showed that a loading dose of 600 mg clopidogrel given in the pre-hospital phase in patients with STEMI scheduled for primary PCI is safe, did not increase pre-PCI patency significantly but was associated with a trend towards a reduction in clinical events. (Zeymer AHA 2010). Such results may be partly due to the slow onset of action of clopidogrel, a pro-drug that requires metabolic activation.

In contrast, due to its mechanism of action, ticagrelor inhibits 40% of platelet aggregation within the first 30 minutes and 90% after 2 hours; this fast onset of effect could stop and possibly reverse thrombus formation, improving both coronary artery and myocardial reperfusion. This suggests that the earlier the treatment is instituted, the greater the therapeutic benefit is.

The ATLANTIC study is thus conducted in order to determine whether pre-hospital administration of ticagrelor may result in pre-PCI ST-segment resolution as well as angiographic improvement and, if yes, whether it may facilitate PCI procedure and improve clinical outcomes in STEMI patients.

1.4 Benefit/risk and ethical assessment

Refer to the Summary of Product Characteristics (SmPC) or Investigator's Brochure (in countries where it is appropriate) for an overall risk/benefit assessment of ticagrelor.

Clinical benefit of ticagrelor in patients with ACS has been well demonstrated and is now commonly recognized (Kowalczyk et al 2009). Potential risks related to pre-hospital administration of ticagrelor in comparison to in-hospital administration would be the occurrence of bleeding complications that might impair PCI procedure due to an increased platelet inhibition expected with earlier administration. However, ticagrelor was not associated with an increased risk of major procedural bleeding in the STEMI planned for PCI subpopulation in PLATO (Steg et al 2010) even though ticagrelor has a faster onset of action than clopidogrel and a greater platelet inhibition would be expected at PCI procedure (Gurbel et al 2009). It is therefore expected that pre-hospital treatment with ticagrelor will have positive benefit/risk ratio in the treatment of STEMI patients undergoing PCI.

Some ethical concerns may also arise from pre-hospital placebo use. Latest guidelines recommend the use of standard treatment combining aspirin and thienopyridines or ticagrelor in STEMI patients planned for PCI to prevent clot formation and thus reduce the risk of further MI, stroke, and death (Wijns W, Kolh P et al 2010). These guidelines however are not very specific on the time the P2Y12 inhibitor has to be administered. Ticagrelor is now indicated for the treatment of ACS patients including STEMI patients planned for invasive

treatment in the EU based on the PLATO study as mentioned previously. In PLATO, patients were started with study medication within 24 hours of start of symptoms and specifically in the STEMI planned for PCI patients the study medication was started from 3 to 12 hours after onset of symptoms. In ATLANTIC all patients are expected to be on active treatment within 8 hours of onset of symptoms and within 2 hours of initial medical contact. It should also be noted that pre-hospital antiplatelet treatment is not a systematic practice and different strategies exist in real life.

The present study will be performed in accordance with the ethical principles that have been laid down in the Declaration of Helsinki and that are consistent with International Conference on Harmonization (ICH) /Good Clinical Practice and applicable regulatory requirements and the AstraZeneca policy on Bioethics.

The main ethical issue that could arise from this study is the fact that patient's written informed consent should be quickly obtained in pre-hospital settings so that study treatment can be initiated as soon as possible. This implies that:

- recruitment and randomization in pre-hospital settings will be performed by emergency medical services personnel (according to local regulations)

- the process about Informed Consent Form collection in emergency situation described in section 8.4 of this protocol should be reviewed and approved by the IEC and regulatory authorities (if appropriate) to protect the rights, the safety and well-being of the patient.

  Two versions of the Informed Consent Form (ICF) will be available: a full version and a short form. The short form may be used in pre-hospital settings if locally approved by the Ethics Committee and Regulatory Authorities (if appropriate).

In all cases, the full Informed Consent Form will be signed.

This informed consent process is described in details in section 8.4 of this protocol and follows the recommendations of the ICH-GCP requirements.

2. STUDY OBJECTIVES

2.1 Primary objective

To assess the efficacy of pre-hospital vs. in-hospital initiation of ticagrelor therapy by comparing the percentage of patients reaching the co-primary endpoint of TIMI flow grade 3 of MI culprit vessel at initial angiography or a ≥70% ST-segment elevation resolution pre-PCI.

2.2 Secondary objectives

To compare the efficacy of pre-hospital vs. in-hospital initiation of ticagrelor therapy by assessing the following endpoints:

- Composite of death, MI, stroke, urgent revascularization and acute stent thrombosis during 30 days of study
- Composite of death, MI, urgent revascularization during 30 days of study
- Acute stent thrombosis during 30 days of study
- Thrombotic bail-out with GPIIb/IIIa inhibitors at initial PCI
- Complete (≥ 70%) ST-segment elevation resolution at 60 min post-PCI
- Corrected TIMI frame count (cTFC) at angiography, pre and post PCI.
- TIMI myocardial perfusion grade (TMPG) at angiography, pre and post PCI.
- Time–relationship (from symptom onset to 1st dose intake) on each co-primary
- Time–relationship (from 1st dose intake to ECG/ angiography) on each co-primary
- TIMI flow grade 3 at end of procedure.

2.3 Safety objective

Bleeding events:

To assess the occurrence of non CABG related bleedings major life-threatening bleeding events, other major bleeding events and minor or major bleeding events in pre-hospital vs. in-hospital initiation of ticagrelor therapy according to PLATO bleeding definition, (see section 6.4.6.1), within the first 48 hours and during 30 days of study .

Other safety events:

To assess the occurrence of any other adverse events in pre-hospital vs. in-hospital initiation of ticagrelor therapy within 30 days of study

2.4 Exploratory objectives

Not Applicable

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subjected to a peer review according to AstraZeneca standard procedures

3.1 Overall study design and flow chart

This is a 30 day, international, randomized, parallel-group, double-blind, placebo-controlled phase IV study to evaluate the efficacy and safety of pre-hospital vs. in-hospital initiation of ticagrelor therapy in STEMI patients planned for primary PCI ; this concerns as well patients (not pre-treated for their STEMI) in emergency rooms of non-PCI hospitals. The qualifying ECG and inclusion into the study are made solely by the ambulance personnel.

The 30 day active treatment period will be followed by a safety monitoring period of 7 days.

After validation of eligibility criteria, patients will be randomized to one of two groups:

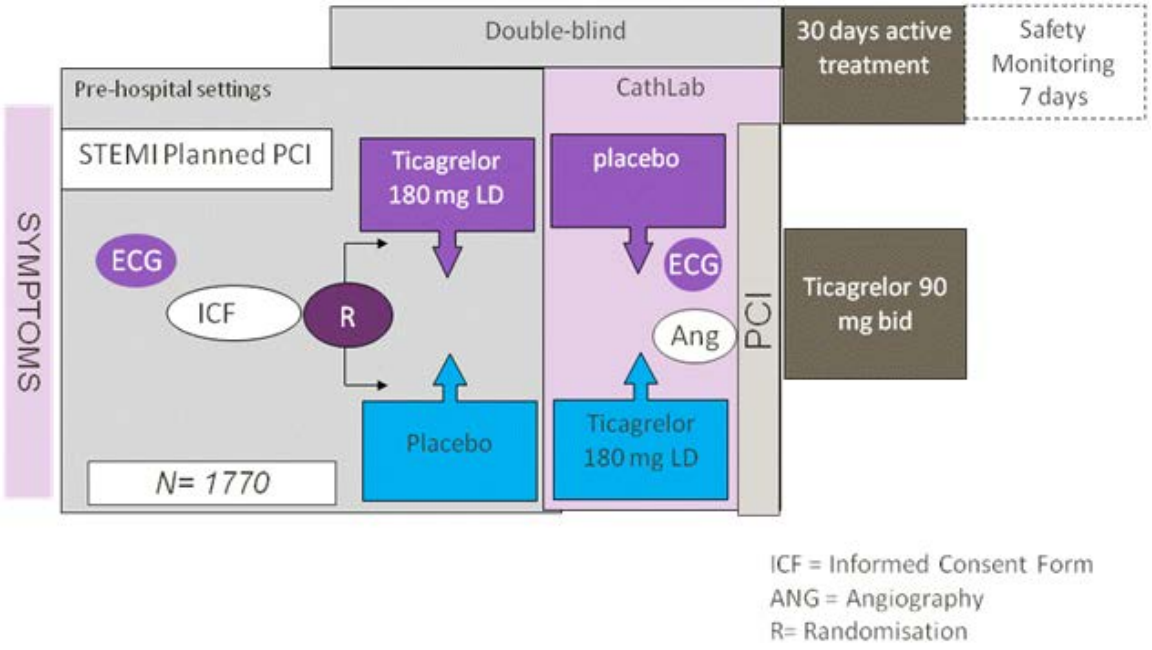
- Pre-hospital ticagrelor arm: patients will receive a loading dose of 180 mg ticagrelor for pre-hospital administration followed by placebo in the hospital before angiography.

- In-hospital ticagrelor arm: patients will receive a placebo in the ambulance followed by loading dose of 180 mg ticagrelor in the hospital before angiography.

Approximately 12 hours after the second loading dose, the patient will continue on ticagrelor 90 mg BID as maintenance treatment and will be followed in study for 30 days post randomisation.

Please refer to the study flow chart (Figure 1)

Figure 1 Study Flow Chart



The Study Plan (Table 1) indicates the number of planned visits.

After this 30 day period, it is up to the investigator to decide whether the patient should be maintained on ticagrelor as a component of dual antiplatelet therapy or continued antithrombotic therapy. If the investigator feels it is in the best interest of the patient to continue ticagrelor and ticagrelor is not yet commercially available, AstraZeneca will provide ticagrelor free of charge until such time as it is commercially available in the relevant market or for up to 12 months as recommended in the Summary of Product Characteristics (SmPC)

A patient receiving ticagrelor provided by AstraZeneca is thus entering an Open Label Extension (OLE) phase until he/she no longer receives it.

AstraZeneca will not provide ticagrelor free of charge in markets where ticagrelor is commercially available.

Table 1 Study Plan

	double blind period		**30 day active treatment period**			**7 days follow up**
	Pre-hospital settings	**Cath Lab**			**End of Treatment (EOT)**	**Safety follow up** (FU)
	D0		**D1**	48 /72 hours post PCI	**D30/EOT**	**D37/**(FU)
Visit number	**1** [a]	**2** [b]	**3**	**4**	**5**	**6**
Informed consent [c]	**X**					
Inclusion/exclusion criteria	**X**					
Demography	**X**					
Specific Relevant Medical/Surgical History	**X**					
Randomization	**X** [d]					
IVRS/IWRS		**X**			**X**[n]	
Brief Physical examination	**X**[a]	**X**	**X**	**X**	**X**	
Vital signs (including weight & height at V2)	**X**	**X**	**X**	**X**	**X**	
Angiography [e] **& PCI**		**X**				
12-lead ECG [f]	**X**	**X**	**X**	**X**	**X**	
Clinical Chemistry (local lab)		**X**	**X**	**X**	**X**	
Haematology (local lab)		**X**	**X**	**X**	**X**	
Additional Blood samples [p]		***X***	***X***			
Troponin I or T (local lab)		**X** [g]	**X** [g]	**X**	**X**	
Collect AEs[h]	**X**	**X**	**X**	**X**	**X**	
Collect SAEs[h]	**X**	**X**	**X**	**X**	**X**	**X**
Collect endpoints[i]	**X**	**X**	**X**	**X**	**X**	**X**[O]
Concomitant medication[j]	**X**	**X**	**X**	**X**	**X**	**X**
Dispense of investigational product,	**X** [k]	**X** [l]	**X** [m]	**X**		
Drug return and accountability of investigational product				**X**	**X**	

(a) Visit 1 will be performed between 30 minutes and 6 hours of onset of symptoms of acute MI.
A brief physical examination will be performed in pre-hospital settings if a physician is present including the Killip class. If not, this brief physical examination will be performed at the arrival in the Cath Lab at visit 2.

(b) Visit 2 will occur in the hospital.

(c) ICF should be obtained in pre-hospital settings (see section 8.4.).
(d) Randomization will be made in pre-hospital settings, just after obtaining the ICF.
(e) The angiography will be performed at the arrival in the Cath Lab. The imaging pre and post PCI will be collected on the same CD /DVD for the central review.
(f) Standard 12-lead ECGs will be performed at all visits. A central review will be done for ECG recordings done in pre-hospital settings, prior PCI and 60 min after PCI. A double print out will systematically be provided for the central review. ECG performed at Visit 3 until the end of the study will be assessed locally and reported in the e CRF.
Only applicable to patient participating in the sub-study presented in appendix C: continuous ECG recording after obtaining informed consent, will be initiated in the ambulance for all eligible patients participating in the sub-study.-not applicable
(g) Blood for Troponin (I or T) values need to be collected prior PCI, at 8, 16 and 24 hours post PCI.
(h) Any AEs occurring after obtaining Informed Consent will be recorded until Visit 5. SAEs will be collected until Visit 6.
(i) Any Endpoints occurring after obtaining Informed Consent will be recorded until the end of the 30 day study period.
(j) All Medications will be recorded from the 7 days prior randomisation until Visit 5, or until V6 in case of new SAE/ endpoints.
(k) The whole investigational products necessary for the study will be dispensed once, at Visit 1. The 1st dose of study medication will be given in pre-hospital settings. Date and time of the administration of the first loading dose will be recorded.
(l) Date and time of the 2nd dose of Study medication will be recorded. This 2nd dose will be given in the Cath Lab, before ECG and initial angiography.
(m) All patients will receive ticagrelor 90 mg twice daily (morning and evening, at approximately 12-hourly intervals) during 30 days.
(n) Only applicable for open label extension enrolment
(o) For prematurely discontinuation of study medication, suspected endpoints are collected until V6
(p) only applicable to patients participating in the sub-study presented in appendix D: PRIVATE-ATLANTIC Sub study (for details, please refer to section 5 and 6 of appendix D):

For details of the visits, please refer to section 6.2

3.2 Rationale for study design, doses and control groups

The objective of ATLANTIC study is to determine whether initiation of ticagrelor, a potent antiplatelet therapy, as early as in the ambulance setting may facilitate PCI, thereby fully optimizing the outcome for the patient.

To this aim, the ATLANTIC study will be conducted in patients with STEMI and onset of the cardiac ischemic symptoms within the 6 hours before randomization and who were initially managed by ambulance physician. These inclusion criteria define a population in which most patients have a coronary occlusion and for whom faster revascularization is a major objective for improving STEMI prognosis (Van de Werf et al 2008, Kushner et al 2009, Wijns W, Kolh P et al 2010).

Double-blind design before and during PCI is necessary as pre-PCI angiography procedure has to be performed without knowing treatment assignment. Use of placebo as comparative treatment is the best choice for demonstrating efficacy of ticagrelor and is considered as ethical in the conditions of ATLANTIC study (see Section 1.4). Knowing also that the PK/PD data of ticagrelor vs clopidogrel show that in both arms of the study the effect will be obtained

more rapidly with ticagrelor than what would be obtained by a pretreatment with high dose clopidogrel.

The primary endpoint of ATLANTIC study is a co-primary endpoint defined as the proportion of patients reaching TIMI flow grade 3 of MI related vessel at initial angiography or a ≥ 70% ST-segment elevation resolution pre-PCI.

Early and complete restoration of blood flow in the MI-related vessel after acute MI is associated with better survival and clinical outcomes (Simes RJ et al 1995, Anderson JL et a**l** 1996, Zeymer et al 1999). For those patients undergoing PCI, results of retrospective analyses suggest that outcomes are better if the MI-related vessel is open before the procedure (namely, TIMI flow grade 2 or 3) (Brodie et al 2000, Stone et al 2001). On the other hand, the ST-segment in the ECG is a good marker of vessel occlusion and closely linked to the outcome of the patients with myocardial infarction (Dong et al 2002, Brodie et al 2005).

The secondary objectives of ATLANTIC study are to assess further efficacy differences, as well as safety and tolerability of pre-hospital vs. in-hospital initiation of ticagrelor therapy by means of well-known and well-established endpoints including cTFC, TMPG, bail out use of GPIIb/IIIa antagonists and clinical events (composite endpoint of death, MI, stroke, urgent revascularization, acute stent thrombosis) and bleeding events.

Doses of ticagrelor are consistent with those used in PLATO study (Wallentin et al 2009). Dosing and duration of treatment with aspirin are consistent with current guidelines recommendations (ESC EACT 2010 guidelines).

4. PATIENT SELECTION CRITERIA

No screening period is scheduled as patients enrolment is occurring in the emergency setting.

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

For inclusion in the study patients should fulfill the following criteria:

1. Provision of Informed Consent (short form or full version of the Informed Consent Form) in pre-hospital settings (see section 8.4).

   Due to the nature of the target disease and the study design the qualifying ECG will be performed in pre-hospital settings as normal procedure prior to obtaining patients informed consent. These data will be used for eligibility evaluation for this study.

2. Adult men and women aged 18 years or older. Women must not be of child-bearing potential (1 year post-menopausal or surgically sterile).

3. Symptoms of acute MI of more than 30 minutes but less than 6 hours

4. New persistent ST-segment elevation ≥ 1 mm in two or more contiguous ECG leads.

4.2 Exclusion criteria

Patients should not enter the study (or for exclusion criterion n° 2, not continue in study) if any of the following exclusion criteria are fulfilled:

1. Expected time to 1st PCI balloon inflation in the hospital, from the qualifying ECG is more than 120 minutes.

2. Patient's refusal to sign full version of the Informed Consent Form before first intake of active ticagrelor 90 mg BID

3. Concomitant oral or intravenous therapy with strong cytochrome P450 3A (CYP3A) inhibitors which cannot be stopped for the course of the study.

    - Strong inhibitors: ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin (but not erythromycin or azithromycin), nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atanazavir, over 1 litre daily of grapefruit juice.

4. Contraindication to ticagrelor (e.g. hypersensitivity to the active substance or to any of the excipients, active pathological bleeding, history of previous intracranial bleed, moderate to severe hepatic impairment).

5. Patient who has received a loading dose of clopidogrel, prasugrel or ticagrelor (commercial pack) for the index event or who are on chronic treatment of prasugrel, clopidogrel or ticagrelor (commercial pack)

6. Concomitant medication that may increase the risk of bleeding [e.g non steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulant and / or fibrinolytics, planned or administered 24 hours before randomization]

7. Planned surgery during the study period

8. Any of the following conditions in the absence of a functioning implanted pacemaker: known SSS, second or third degree AVB, or documented syncope of suspected bradycardic origin.

9. Patient requiring dialysis

10. Known clinically important thrombocytopenia

11. Known clinically important anemia

12. Known pregnancy or lactation

13. Condition which may either put the patient at risk or influence the result of the study (e.g., cardiogenic shock or severe hemodynamic instability, active cancer, risk for non-compliance, risk for being lost to follow up)

14. Active involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

15. Previous randomisation in the present study

16. Participation in another clinical study with an investigational product or device study during the last 30 days or during the study.

Other exclusion criteria, applicable only to patients in the centres participating in the sub-study presented in appendix C –not applicable

1. Inability to commence ST-segment monitoring within 30 minutes of study drug initiation

2. Intraventricular conduction defect (including left bundle branch block), or paced rhythm that would obscure the diagnosis of acute STEMI and/or ST segment evaluation.

Procedures for withdrawal of incorrectly randomised patients at entrance into the study or for patients that develop any conditions described above, see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

There are no specific dietary or activity restrictions other than those typical for a patient with this disease.

Patients should not donate blood or bone marrow at any time during the study period.

Restrictions regarding concomitant medications are described in Section 5.6.

5.2 Patient enrolment and randomisation

There will be no enrolment period as in the acute setting, any patient with STEMI planned for PCI, who is willing and eligible to participate, will be randomised on site.

The ambulance medical personnel or paramedics personnel (according to local regulations) justifying of at least 6-month training in pre-hospital or ambulance infarct diagnosis and care, will:

1. Determine patient eligibility. See Sections 4.1 and 4.2

2. Obtain signed Informed Consent Form (for more specific details, refer to section 8.4)

3. Randomise the patient. The randomisation number is indicated on the label of the treatment pack. The patient will be allocated a treatment pack starting with the lowest randomisation number available if more than one pack is available in the ambulance.
   The hospital personnel will:

4. Contact IVRS/IWRS to assign eligible patient a unique enrolment number, beginning with "E#".

If a patient withdraws from participation in the study, then his/her enrolment/ code cannot be reused.

5.2.1 Procedures for randomisation

The randomization will occur at Visit 1 in pre-hospital settings after obtaining the Informed Consent. Visit 1 can be performed between 30 minutes and 6 hours of onset of symptoms of acute MI. Patients who satisfy all the eligibility requirements, will be randomised by the assignation of the randomisation number present on the treatment pack available. The first dose of investigational product will be administered to the patient immediately after opening the patient pack.

The randomization codes will be computer generated by AstraZeneca R&D using GRand (AZ Global Randomization system). A blocked randomization stratified by centre will be produced. The investigational product will be packed according to this randomization list.

5.2.2 IVRS/IWRS

IVRS/IWRS will be used for allocation of enrolment number, management of study medication, open label extension enrolment (where applicable), emergency unblinding; specific IVRS/IWRS functionality will be in the IVRS/IWRS user manual.

The IVRS/IWRS technology will be managed and maintained by Perceptive. The system is accessible by telephone (IVRS) and computer (IWRS) 24 hours a day, 7 days a week. The IVRS/IWRS user manual will be provided to each centre.

5.3 Procedures for handling patients incorrectly randomised

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be randomised. There can be no exceptions to this rule.

Where patients that do not meet the selection criteria are randomised in error or incorrectly started on treatment or where patients subsequently fail to meet the study criteria post initiation or for patients that develop exclusion criteria, the investigator should inform the AstraZeneca Study Delivery Team Physician immediately. A discussion should occur between the AstraZeneca Study Delivery Team Physician and the Investigator regarding whether to continue or discontinue the patient from treatment, unless the investigator decides to stop study drug as it would put the patient at undue risk.

The AstraZeneca Study Delivery Team Physician is to ensure all such contacts are appropriately documented. In situations where an agreement cannot be reached, the patient should have their study therapy stopped.

Randomised patients remain in the trial for follow up visits regardless of whether or not the patient continues study medication unless patient documents his/her refusal to sign full informed consent form before first dose of active ticagrelor.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

Blinding of active and placebo tablets will be maintained by both the active and placebo tablets matching in size, shape, and placebo tablet matching in size, shape and appearance, and all outer packaging of each treatment arm will be identical.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each enrolled patient, will be available to the investigator(s) or pharmacists from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Ticagrelor	tablet, 90 mg	AstraZeneca or designated CRO
Ticagrelor placebo	tablet, placebo to match 90 mg	AstraZeneca or designated CRO

5.5.2 Doses and treatment regimens

At Visit 1 (randomisation), eligible patients will be randomly assigned to one of two treatment groups:

- 2 tablets of ticagrelor (loading dose) taken in the ambulance followed by 2 tablets of matching placebo in the hospital, taken orally.

Or

- 2 tablets of matching placebo taken in the ambulance followed by 2 tablets of ticagrelor (loading dose) in the hospital, taken orally.

After that initial double blind period, all patients will continue on active ticagrelor 90 mg BID and will be followed in study for 30 days post randomisation.

Randomization will be managed by the ambulance personnel by opening the patient pack and administering the first dose of study medication. The second dose will be taken at Visit 2 before undergoing ECG and angiography

Subsequent maintenance doses should be taken morning and evening, at approximately 12-hourly intervals, for the remainder of the treatment period.

Study medication can be taken with or without food. Study medication should not be altered (eg, crushed, put in another vehicle) and should not be given by nasogastric tube or other routes.

The treatment for the entire study will be packaged so that it will follow the patient from the ambulance to the hospital. Individual patient treatment is defined as the double blinded loading dose (2x2 tablets), a bottle of ticagrelor 90 mg containing 64 tablets (30 days of active treatment + 2 days overage), and the Informed Consent Forms will be provided to each ambulance. Each treatment will be clearly identified.

Duration of treatment

Patients will be randomised to treatment no later than 6 hours after the onset of cardiac ischemic symptoms. Approximately 12 hours after the second loading dose, the patient will continue on ticagrelor 90 mg BID as maintenance treatment and will be followed in study for 30 days post randomisation.

Interruptions to study medication

No dose of ticagrelor or placebo blinded study medication should be missed.

In the event of this happening, this would constitute a major deviation to the study.

- If missed 1st loading dose in pre-hospital settings: for patient benefit, it is recommended that all 4 tablets are administered to the patient in hospital.

- If missed 2nd loading dose in the Cath Lab (i.e. loss of the patient bottle): it is up to the investigator to decide the appropriate therapy for the patient during angiography.

Missed dose of ticagrelor active treatment during 30 days post randomisation should not be made up (ie, if a dose is missed the next regularly scheduled dose should be taken and should not be doubled).

A temporary interruption of ticagrelor active treatment is defined as a minimum of 4 missed doses of study medication and should be recorded in the eCRF.

5.5.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling, including the study code and directions for use. Label text will be translated into local language according to local requirements.

5.5.4 Storage

All study medications should be kept in a secure place under appropriate storage conditions. The study medication label on the study supplies specifies the appropriate storage.

5.6 Concomitant treatment(s)

5.6.1 Oral antiplatelet therapies

Concomitant ASA (Acetylsalicylic Acid (Aspirin)) : In addition to study medication, patients may receive 150–300 mg per os or 250 (–500) mg bolus i.v., in the double blind phase, followed by 75–100 mg daily as recommended by ESC/EACTS guidelines 2010 or up to 150 mg according to ticagrelor Summary of Product Characteristics.

The patient will be responsible for the ASA supply throughout the study. The ASA dose should remain constant throughout the study.
ASA for pain relief should, when possible, be discouraged and paracetamol (acetaminophen) given.

Other oral anti-platelets: clopidogrel, prasugrel, ticlopidine, dipyridamole, and cilostazol:

Concomitant treatment with any of these drugs is not allowed in the study.

5.6.2 Non Steroidal Anti-Inflammatory Drugs (NSAIDs)

Concomitant treatment with any of these drugs is not allowed in the study.

5.6.3 GPIIb/IIIa receptor antagonists

Upstream (in ambulance) use of GPIIb/IIIa receptor antagonists is not recommended as a concomitant treatment but will be left to physician's discretion. In lab use of GPIIb/IIIa receptors antagonists after the angiogram is possible and not discouraged. This use will have to be identified as being a strategy of choice or a bail out use during PCI.

Bail-out use of GPIIb/IIIa receptors antagonists is allowed for thrombotic complications (see section 6.3.2.5)

5.6.4 Parenteral anticoagulants

Short-term treatment with approved parenteral anticoagulants (eg. unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), bivalirudin, fondaparinux) is allowed. However, long-term treatment with LMWH in outpatients (at venous thrombosis treatment doses) in combination with study medication is not allowed. Concomitant treatment with venous thrombosis prophylaxis doses is allowed.

5.6.5 Oral anticoagulants

Concomitant treatment with oral anticoagulant drugs is not permitted during the study.

5.6.6 Fibrinolytics

A patient is not eligible for inclusion into the study if fibrinolytic therapy has been given in the 24 hours prior to randomisation or is planned to be administered for STEMI or any other condition.

Fibrinolytic treatment is not permitted during the study.

5.6.7 P-glycoprotein interactions

No data are available on concomitant use of ticagrelor with potent P-glycoprotein (P-gp) inhibitors (e.g. verapamil, quinidine, cyclosporin) that may increase ticagrelor exposure. If the association cannot be avoided, their concomitant use should be made with caution. Ticagrelor modestly increases digoxin levels. Therefore digoxin levels should be monitored closely following initiation of study medication and with any change in study medication. Other p-glycoprotein substrates may be expected to have similar changes in pharmacokinetics. For additional details reference the Summary of Product Characteristics.

5.6.8 CYP3A interactions

5.6.8.1 CYP3A inhibitors

Strong inhibitors of this enzyme (eg, ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin [but not erythromycin or azithromycin], nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atanazavir, or over 1 litre daily of grapefruit juice) should not be coadministered with ticagrelor as plasma levels of ticagrelor would be substantially increased. If treatment with such therapies is necessary, study medication dosing should be interrupted and then resumed if possible when administration of the CYP3A inhibitor is no longer required.

5.6.8.2 CYP3A substrates or inducers

Concomitant therapy with simvastatin or lovastatin at doses higher than 40 mg daily is not recommended. There are no restrictions to other statin therapies (ie, doses of simvastatin or lovastatin ≤40 mg daily or any dose of any other statin is permitted). Standard monitoring of patients for possible statin associated myopathy should be done.

Co-administration of ticagrelor with CYP3A substrates with a narrow therapeutic index (eg, cyclosporine and quinidine) is not recommended.

Co-administration of ticagrelor with strong inducers of CYP3A is discouraged (eg, rifampin/rifampicin, rifabutin, phenytoin, carbamazepine, phenobarbital).

If treatment with such therapies is necessary, study medication dosing should be interrupted and then resumed if possible when administration of the inducer or narrow therapeutic index drug is no longer required.

5.6.9 Surgery and other invasive non-cardiovascular procedures

For urgent major surgery, if a 7 day window off treatment is not feasible, it should be noted that the average half-life of ticagrelor is about 12 hours. The effect on platelet function caused by ticagrelor will have largely dissipated in most individuals by 48 to 72 hours after discontinuation.

It should be noted that all patients in this study are also treated with ASA, an irreversible inhibitor of platelets, and this therapy should be handled according to physician discretion in case of surgery.

5.6.10 Other medications

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator(s) and recorded in the appropriate section of the e CRF.

5.7 Treatment compliance

The administration of all medication (including investigational products) should be recorded in the appropriate sections of the Case Report Form.

5.7.1 Accountability

The study medication provided for this study will be used only as directed in the protocol.

The study personnel will account for all study medication dispensed to and returned from the patient. This record keeping consists of a dispensing record including the identification of the person to whom the drug is dispensed, the quantity, and the date of dispensing.

Patients will be asked to return all unused study medication/ empty bottle to the investigational centre at visit 5 or at discontinuation visit. The Investigator will make an assessment in the eCRF regarding patient treatment compliance. If the patient has taken study medication for more than 80% of the active treatment period, the patient will be regarded as compliant.

Any study medication deliberately or accidentally destroyed must be recorded. Any discrepancy between dispensed and returned study medication should be explained.

The investigator or delegate will retain the returned medication until the trial monitor has checked the records for quantities of returned and unused tablets at a patient level. Following drug accountability, the trial monitor will advise on the appropriate method for destruction of unused study medication. It is preferable that all used and unused medication be destroyed at the site. Destruction of study medication must only be conducted by an authorized site. Signed certificate of destruction will be collected by the trial monitor.

5.8 Discontinuation of investigational product

Patients may be discontinued from investigational product in the following situations:

5.8.1 Temporary discontinuation of a patient from investigational product

Severe thrombocytopenia (platelet count <50,000/uL). Patients may restart study medication once the severe thrombocytopenia resolves.

Major surgery or other non-cardiovascular invasive procedures, see 5.6.9

Major bleeding, see 6.4.6.3

If possible, treatment with study medication should be resumed until the completion of the study (i.e. 30 days post randomisation).

5.8.2 Permanent discontinuation from study medication

- Patient's decision: the patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Incorrectly randomised patient in whom the inclusion/exclusion criteria violation would put the patient at undue risk
- Safety reasons as judged by the investigator (eg, clinically significant ventricular pauses, syncope related to bradycardia, persistent increase in serum creatinine level of clinical relevance, persistent, unexplained anaemia or thrombocytopenia
- Severe non-compliance to study protocol

All patients should remain in the trial and keep all visits whether they continue study medications or not.

5.8.3 Procedures for discontinuation of a patient from investigational product

The patient once randomised is in the study for 30 days. If the patient is permanently discontinued from study medication, the patient should do the End of Treatment visit (V5). A follow-up contact (Visit 6) should be performed in order to collect all AEs/SAEs and suspected endpoints at 30 days post randomisation or 7 days after treatment.

A patient that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); and all study drugs should be returned by the patient.

For premature discontinuation from study medication:

If premature discontinuation occurs at ≤ 23 days (Visit 5), then Visit 6 should be done between 28 and 32 days with SAE and suspected endpoints collected at that visit.

If premature discontinuation occurs between 24 and 27 days (Visit 5), then Visit 6 should be done 7 days following Visit 5 with SAE and suspected endpoints collected at that visit.

If a patient is withdrawn from study, see Section 5.9.

5.9 Withdrawal from study

Randomised patients are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment. Investigators must explain to any such patient so requesting termination of their participation, the importance to the trial and to themselves of their continued participation by keeping study visits. Should the patient insist on not returning for visits, the investigators should attempt to arrange telephone or other acceptable contact at visit times so that adverse events and study endpoints can be assessed. Every effort must be made to collect outcome data on every patient, within the boundaries of each patient's right to privacy and local regulations.

Randomised patient who refuses to sign the full version of the Informed Consent Form before first dose intake of active maintenance ticagrelor 90 mg will be withdrawn from the study. The patient will be asked to document her/his withdrawal on the Informed Consent Form used in the ambulance and the investigator will document this in the patient's medical records. No further efficacy data will be collected from the time of documented refusal. For safety purpose, the patient will be followed by the investigator for a period of 7 days after the last loading dose intake.

If, after having signed the full Informed Consent Form, the patient wished to withdraw from study, this is documented by consent withdrawal on the consent withdrawal page of the Informed Consent Form. The appropriate option should be ticked, and the page signed and dated by both the patient and the investigator, if possible. Such patients will always be asked about the reason(s) and the presence of any adverse events. They will be seen and assessed by an investigator. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4) and all study drugs should be returned by the patient.

Withdrawn patients will not be replaced.

5.10 Patient lost to follow up

No patient should be lost to follow up in this study. In the unlikely event that this does occur, repeated attempts will be made to locate and determine the vital status and occurrence of any MI or stroke for those patients who are considered initially lost to follow up and have not withdrawn consent. A patient will be classified as lost to follow up only if, he/she has failed to return for the required study visits and his/her vital status remains unknown despite multiple attempts to contact him/her via telephone, fax, email, certified letter.

6. COLLECTION OF STUDY VARIABLES

The investigator will ensure that data are recorded in a timely fashion on the eCRF and in accordance with the instructions provided.

6.1 Recording of data

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling and SAE reporting. The electronic Case Report Forms (eCRF) will be completed in the hospital settings. The data collected in the source paper CRF at Visit 1 will be transferred in the electronic Case Report Forms by the hospital Study personnel. The investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement.

Study personnel will be trained and responsible for entering data specified in the protocol into the WBDC system and according to the eCRF Instructions. When data have been entered reviewed, edited and Source Data Verification (SDV) performed by AstraZeneca representative, the data will be frozen to prevent further editing. The principal investigator will be notified to sign the eCRF electronically as per the eCRF instructions. A copy of the eCRF data will be archived at the study site.

6.2 Data collection and enrolment

The visit schedule will be as follows:

- V1 between 30 minutes and 6 hours of onset of symptoms of acute MI: double blind loading dose of study medication will be given in pre-hospital settings/ambulance.
- V2: arrival in the Cath Lab.
- V3: Day 1, first day of active treatment period i.e. ticagrelor 90 mg twice daily.
- V4:48/72 hours post PCI..
- V5:Day 30,(28—32 days) End of Treatment (EOT) Visit.
- V6: Day 37 (for completer patients), follow up contact (telephone).
  In case of premature discontinuation, see section 5.8.3

6.2.1 Visit details

Visit 1 will occur in pre-hospital setting/ambulance

After the inclusion and exclusion have been checked, the eligible patient will sign the full Informed Consent Form. If the patient is not able to give a written consent in pre-hospital settings, please refer to section 8.4.

The following assessments will be performed:

- 12-Lead ECG (collection of 2 print outs for central review), prior 1st study medication intake,
- Brief physical examination if a physician is present.
- Vital signs (heart rate and supine blood pressure (BP)).

The following data will be recorded:

- Date of Visit 1
- Location of care/ 1st medical contact
- Demography (age, date of birth, sex, race).
- Onset date and time of index event
- Date and time of qualifying ECG
- Date and time of 1st dose of study medication administration
- Specific relevant medical and surgical history and Killip class if physician present.
- Any AEs / SAEs or endpoints occurring after obtaining Informed Consent Form.
- Concomitant medication taken within 7 days of randomisation (ex: ASA or oral anti platelet therapy).

Transfer to Cath Lab

The ambulance's personnel will hand over the study medication together with the patient to the Cath Lab's personnel.

Visit 2: will occur in Cath Lab of the hospital

The Cath Lab's personnel will check that the individual patient study medication is present, the Informed Consent Form is signed, the source paper CRF or equivalent is completed and 2 print outs of the ECG done in pre-hospital settings are present.

If only the short form of the Informed Consent Form is signed then the full Informed Consent Form will be obtained as soon as the clinical situation allows it and before first dose intake of active ticagrelor 90 mg. If a patient is unable to read and sign due to critical condition, the full Informed Consent Form will be signed as soon as the clinical situation allows it, please refer to section 8.4.

In-hospital treatment must be given in the Cath Lab, before the ECG and pre-PCI angiography.

Cath Lab admission :

The following assessments will be performed:

- Brief physical examination if not performed in pre-hospital settings,
- Vital signs (heart rate and supine blood pressure (BP)), weight and height,
- 12-lead ECG post 2nd dose of study medication and prior angiography (collection of 2 print outs for central review). If possible, the same electrode patches and the same ECG machine used in pre-hospital settings should be used for this ECG, in order to collect the most accurate data.
- Local laboratory analysis for safety tests (clinical chemistry, haematology)
- Troponin I or T, (local analysis),
- Angiography should be performed at the arrival in the Cath Lab after second drug intake and ECG. The angiography data will be recorded for central review.

The following data will be recorded:

- Date of Visit 2 (i.e arrival in Cath Lab),
- Verify the eligibility criteria performed in pre-hospital settings and complete the full baseline assessments if needed.
- Verify the specific relevant medical and surgical history and complete the full baseline assessments if needed.
- All concomitant medications including use of relevant antiplatelet and anticoagulation medications 7 days prior to 1st dose of study medication intake,
- Date and time of administration of the 2nd dose of study medication.
- Date and time of 12-lead ECG
- Date of angiography and start-time, sheath insertion site (radial or femoral)

PCI:

- PCI: record date and start time (i.e time of 1st balloon inflation), type and number of stent implantation, thrombo-aspiration, bail out of GPIIb/IIIa receptor antagonists.

Post PCI:

- A post PCI angiography will be performed (the same CD/DVD containing both pre and post PCI imaging will be collected for central review)
- 12-lead ECG 60 minutes after PCI (collection of 2 print-outs for central review),
- Troponin (I or T) at 8 hours after PCI (local analysis).

AE/SAE, suspected endpoints and concomitant medication will be collected throughout hospitalisation.

Visit 3: onset of active treatment period

After the loading dose period , all patients will receive active ticagrelor 90 mg BID as maintenance treatment during 30 days. Subsequent maintenance doses should be taken morning and evening, at approximately 12-hourly intervals, for the remainder of the treatment period. The 1st dose of active treatment should be taken 12 hours after blinded LD administrated in Cath Lab.

The following assessments will be performed:

- Brief physical examination,
- Vital signs (heart rate, supine blood pressure (BP)),
- 12-lead ECG
- Local laboratory analysis for safety tests (clinical chemistry, haematology),
- Troponin (I or T) at 16 and 24 hours after PCI (local analysis).

AE/SAE, suspected endpoints and concomitant medication will be collected throughout hospitalisation.

Visit 4: 48/72 hours after PCI

The following assessments will be performed:

- Brief physical examination,
- Vital signs (heart rate and supine blood pressure (BP)),
- 12-lead ECG,
- Local laboratory analysis for safety tests (clinical chemistry, haematology),
- Troponin (I or T), (local analysis).

Suspected endpoint events, AEs/SAEs and all medications will be recorded.

The bottle of active ticagrelor treatment will be given to the patient.

Visit 5: End of Treatment visit (EOT)

This visit should take place at the end of the planned treatment period (30 days) or if the patient discontinues prematurely from the study treatment.

Suspected endpoint events, AE/SAE and current medications will be recorded. For patients reporting suspected endpoint events, SAEs, discontinuing study medication due to an AE, all peri-event medications will be recorded.

All remaining study medication will be returned and drug accountability performed.

The following assessments will be performed: see Visit 4.

After this 30 day period, it is up to the investigator to decide whether the patient should be maintained on ticagrelor as a component of dual antiplatelet therapy or continued antithrombotic therapy.

Visit 6: Safety Follow-up contact

Completer patient will be contacted 7 days after the EOT visit. Any new SAEs will be recorded along with concomitant medication for SAE.

For patient who prematurely withdraws from study medication, a visit should occur at 30 days after randomisation and all suspected endpoints, procedures and new SAE (with its concomitant medications) should be collected. See section 5.8.3

6.3 Efficacy

Clinical efficacy endpoints will be collected in the eCRF. These events will be identified using standard questioning of the patient at each visit, or by information that the investigator may receive as part of standard medical practice.

6.3.1 ECG and angiography

6.3.1.1 ECG

ECGs should be performed according to local clinical practice to diagnose STEMI (Index event) and document the primary variable of the study.

ECGs should be standard 12-lead ECG, with a lead II rhythm strip, in the supine position. Particular attention will be given to the measurement of the ST-segment. Further details can be found in the Core Lab guidelines.

All original ECGs must be stored in the patient’s medical record as source documentation.

ECGs will be recorded at the following time points:

ECG evidence of STEMI: Baseline qualifying ECG will be obtained in pre-hospital settings for the index event and eligibility in the study, prior 1st study medication administration. Due to the study design (randomisation within 6 hours and more than 30 minutes of onset of index event) the ECG assessment for inclusion into the study will be performed prior to obtaining informed consent form. These data will be recorded in the eCRF and utilised for the purposes of the study. This ECG will also be reviewed centrally and a double print-out is required.

ECG performed in the Cath Lab prior angiography and 60 minutes after PCI. These will be reviewed centrally and a double print-out is required. Only the date, hour and overall evaluation of the ECG recording will be captured in the eCRF.

ECG performed at Visit 3 , Visit 4 , Visit 5 : The recordings will be assessed locally and the data reported in the eCRF.

Other ECG recordings: ECG should be performed to document any re-occurrences of MI or recurrent cardiac ischaemia during the study.

If the investigator concludes that new ST elevation of ≥1 mm (0.1 mV) in at least 2 contiguous leads, development of new pathological Q waves on the ECG, new LBBB, ST-segment depression of ≥0.5 mm (≥0.05 mV) in 2 or more contiguous leads, new or presumed new T-wave abnormalities - inversion of ≥1 mm (0.1 mV) in 2 or more contiguous leads indicative of ischaemia are present, then the ECG will be reported in the eCRF and copies of ECG traces will be included in any relevant 'Endpoint Package' sent to WCT endpoint office for central adjudication by the ICAC..

Central reading of ECG

An independent central review of ECGs will be conducted. The ECG print outs at baseline, prior PCI and 60 minutes after PCI will be collected on an ongoing basis and sent to an AstraZeneca appointed Core Lab for central analysis. Results of this independent blind review will not be communicated to investigators, and the management of patients will be based solely upon the assessments conducted by the investigator.

6.3.1.2 Angiography

Angiography should be done immediately after arrival in Cath Lab, according to local clinical practice to document the co-primary flow variable of the study. Data acquisition: filming should be done for a sufficient duration (at least 10 seconds from the time of the contrast injection); 25 frames per second and 2 projections are preferred. Further details can be found in the core lab guidelines. The pre and post PCI angiography will be assessed locally and centrally. Only the date, time of the day and thrombus localization will be recorded in the eCRF.

Central reading of angiography

An independent Central review of all coronary angiograms will be conducted. The imaging data pre and post PCI will be anonymised and transferred on the same CD/DVD. The

CD/DVD will be sent to an AstraZeneca appointed Core Lab for central analysis. The following will be measured:

- TIMI flow of MI culprit vessel at angiography, pre and post PCI
- Corrected TIMI frame count pre and post PCI angiography
- TIMI Myocardial Perfusion Grade pre and post PCI angiography

Results of this independent blind review will not be communicated to investigators, and the management of patients will be based solely upon the assessments conducted by the investigators.

6.3.2 Definition and follow up procedures for Suspected Clinical Endpoints

For each suspected clinical endpoint, the investigator will complete information specific to that type of endpoint on the eCRF and compile relevant additional source information into an 'Endpoint Package', as described in the Endpoint and Bleeding Manual for Investigators. The Endpoint Package will be sent to the Independent Central Adjudication Committee (ICAC) for central adjudication except for death and bail out. The investigator should use the following definitions in assessing possible endpoint events.

6.3.2.1 Myocardial Infarction

Definition:

(a) Recurrent MI within 18 hours of onset of the index MI New ST elevation of ≥1 mm (0.1 mV) in at least 2 contiguous leads and recurrent cardiac ischaemic symptoms[a] ≥ 20 minutes at rest[b].

(b) Recurrent MI after 18 hours of onset of the index MI but before myocardial necrosis biomarkers have returned to normal Myocardial necrosis biomarker re-elevation (Troponin) defined as an increase of at least 50% over a previous value that was decreasing **and at least one of the following**:

- Recurrent cardiac ischaemic symptoms[a] ≥20 minutes at rest[b]

or

- One of the following ECG changes
  - New ST elevation of ≥1 mm (0.1 mV) in at least 2 contiguous leads
  - Development of new pathological Q waves[c] on the ECG
  - New LBBB.

(c) Patients with recurrent MI after myocardial necrosis biomarkers have returned to normal (excluding MI in patients undergoing PCI or CABG in the previous 24 hours). Elevation of myocardial necrosis biomarkers typical of acute MI[d] with **at least 1 of the following:**

- Recurrent cardiac ischaemic symptoms[a] ≥20 minutes at rest[b]
- Development of new pathological Q waves[c] on the ECG
- ECG changes indicative of ischaemia[e]

or

- Pathological findings of an acute MI.

(d) MI within 24 hours after PCI:

- Troponin ≥3x local laboratory upper normal limit[f], and, if the pre-PCI Troponin was >ULN, both an increase by at least 50% over the previous value and documentation that Troponin was decreasing prior to the suspected recurrent MI (no symptoms are required)

or

- Development of new pathological Q waves[c] on the ECG (no symptoms are required).

(e) MI within 24 hours after CABG:

- Troponin ≥5x local laboratory upper normal limit[f], and, if the pre-CABG Troponin was >ULN, both an increase by at least 50% over the previous value and documentation that Troponin was decreasing prior to the suspected recurrent MI and development of new pathological Q waves[c] on the ECG (no symptoms are required)

or

- Troponin ≥10x local laboratory upper normal limit[f] and, if the pre-CABG Troponin was >ULN, both an increase by at least 50% over the previous value and documentation that Troponin was decreasing prior to the suspected recurrent MI (no Q waves and no symptoms are required).

(f) For patients who die of suspected MI and for whom no myocardial necrosis biomarkers were obtained:

- The presence of new ST-segment elevation[e] and new cardiac ischaemic symptoms[a]

or

- Pathological evidence of an acute MI.

Definition of terms

[a] **Cardiac ischaemic symptoms**: chest pain or discomfort or equivalent (eg, neck or jaw symptoms, dyspnoea believed to represent an angina pectoris equivalent) believed due to impaired coronary flow secondary to atherosclerotic disease.

[b] **At rest**: started with exercise or spontaneously and did not resolve with rest.

[c] **Development of pathological Q waves**: development of any new or presumed new Q waves that are ≥0.03 sec in width and ≥1 mm (0.1 mV) in depth in at least 2 contiguous leads.

[d] **Myocardial necrosis biomarker evidence of acute MI - any of the following**: maximal concentration of Troponin exceeding the 99th percentile of the values for a reference control group. Elevations should be seen on at least one occasion but preferably with a rising or falling pattern during the first 24 hours following the index clinical event. The coefficient of variation (CV; imprecision) at the 99th percentile should be lower or equal to 10%. Otherwise, the concentration at the 10% CV should be regarded as the diagnostic cut-off. For cardiac troponin T the diagnostic cut-off is equal to or greater than 0.03 µg/L. Cut-offs for cardiac Troponin I assays vary among different manufacturers and should be read-off from approved tabulations.

[e] **ECG changes indicative of ischaemia - any of the following:** ST-segment elevation: new or presumed new ST-segment elevation ≥1.0 mm (0.1 mV) in 2 or more contiguous leads.

New or presumed new ST-segment depression of ≥0.5 mm (≥0.05 mV) in 2 or more contiguous leads.

New or presumed new T-wave abnormalities - inversion of ≥1 mm (0.1 mV) in 2 or more contiguous leads.

[f] **Laboratory upper normal limit**: This is the value that is considered abnormal. For institutions that report an intermediate or indeterminate range for Troponin I or T, these values are considered abnormal for this study.

Procedure in case of recurrent cardiac ischemic symptoms: If the patient experiences cardiac ischemic symptoms ≥20 minutes at rest, he/she will be treated in accordance with local practice and the following procedures will be performed:

- Cardiac biomarkers of necrosis (troponin) should be measured locally approximately every 8 hours for at least 24 hours
- A standard 12-lead electrocardiogram should be obtained during or as soon after the episode of ischemia as possible and 24 hours after resolution of symptoms.

6.3.2.2 Stroke/TIA

Definition:

A stroke is defined as a neurological deficit caused by an ischaemic or haemorrhagic central nervous system event with residual symptoms at least 24 hours after onset or leading to death, confirmed by imaging.

Stroke will be further sub-classified as:

- **Haemorrhagic**: a stroke with documentation of intracranial haemorrhage on imaging (eg, computed tomography (CT) scan or magnetic resonance imaging (MRI) scan) either in the cerebral parenchyma, or a subdural, epidural or subarachnoid haemorrhage. Evidence of haemorrhagic stroke obtained from lumbar puncture, neurosurgery, or autopsy can also confirm the diagnosis.

- **Ischaemic**: a stroke that results from a thrombus or embolus impairing central nervous system perfusion (and not due to haemorrhage). Haemorrhagic conversion of an ischaemic stroke that becomes symptomatic should be recorded as a new haemorrhagic stroke event.

- **Unknown/No imaging performed**: if the type of stroke could not be determined by imaging or other means (from lumbar puncture, neurosurgery, or autopsy).

A TIA is defined as a focal neurological deficit that resolves spontaneously without any evidence of residual deficit by 24 hours. For inclusion in the first secondary composite efficacy endpoint the TIA must either require hospitalisation if an outpatient or prolong hospitalisation if an inpatient or have objective confirmation of cerebrovascular disease.

Procedures in case of focal neurological symptoms (ie, potentially representing stroke or transient ischemic attack). If the patient experiences focal neurological symptoms , he/she will be treated in accordance with local practice and the following procedures will be performed:

- Complete neurologic exam

- Brain imaging [computed tomography (CT) or magnetic resonance imaging (MRI)]

6.3.2.3 Urgent Coronary Revascularization

Definition:

Urgent Coronary Revascularization is defined as repeated PCI or CABG within 24 hrs after a new ischemic event of the culprit vessel of the index event.

Procedures in case of Coronary Revascularization (ie, percutaneous coronary intervention or coronary-artery-bypass grafting): If the patient experiences urgent coronary revascularization, he/she will be treated in accordance with local practice and the following procedures will be performed:

- Cardiac biomarker of necrosis (Troponin) should be measured locally immediately before the procedure and approximately every 8 hours for at least 24 hours after the procedure

- A standard 12-lead electrocardiogram should be obtained before the procedure and in the morning following the procedure.

- For patients undergoing CABG, the number of packed red blood cell or whole blood transfusions and the chest tube output in the first 24 hours should be noted

6.3.2.4 Stent Thrombosis

Definition according to Academic Research Consortium - Mauri et al 2007

- Definite stent thrombosis required the presence of an acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion.

- Probable stent thrombosis included unexplained deaths within 30 days after the procedure or acute myocardial infarction involving the target-vessel territory without angiographic confirmation.

- Possible stent thrombosis included all unexplained deaths occurring at least 30 days after the procedure.

6.3.2.5 Bail-out use of GPIIb/IIIa receptor antagonists

Definition

Bail-out treatment is to provide GPIIb/IIIa inhibition with IIb/IIIa inhibitors urgently during the course of an interventional procedure in the event of abrupt closure, no reflow, side branch closure, or other bail-out situations.

6.3.2.6 Death

Definition

All cause deaths reported until 30 days post-randomisation will be recorded as clinical endpoints. They will not be adjudicated. The cause of death will be reported in the SAE form or in bleeding/stroke or cardiac-ischemic event form of the eCRF, according to the definition of Adverse Event (see section 6.4.1).

In the eCRF, death will be further sub-classified by vascular or non-vascular primary cause. Death from vascular causes includes cardiovascular deaths, cerebrovascular deaths, deaths from any other vascular abnormality or deaths for which there was no clearly documented nonvascular cause. Some specific examples are given below:

Vascular death: sudden death, MI, other CAD, stroke, arterial embolism, pulmonary embolism, ruptured aortic aneurysm, aortic dissection, heart failure, cardiac arrhythmia or death from bleeding (not related to trauma).

Non-vascular death: cause of death was respiratory failure, pneumonia, cancer, trauma, suicide, sepsis, multi-organ failure or any other clearly defined cause (eg, liver failure or renal failure).

For Drug Safety reporting purposes any death with unknown/uncertain cause should be reported as death, if the cause of death becomes known, then the cause is reported as the SAE.

6.4 Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

6.4.1 Definition of adverse events

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

Suspected cardiac ischaemic events including MI, severe recurrent cardiac ischaemia which lead to stent thrombosis and / or urgent revascularization should not be reported as AE/SAE (see section 6.4.5).

6.4.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

Results in death

Is immediately life-threatening

Requires in-patient hospitalisation or prolongation of existing hospitalisation

Results in persistent or significant disability or incapacity

Is a congenital abnormality or birth defect

Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.4.3 Recording of adverse events

Time period for collection of adverse events

Non Serious Adverse Events will be collected from the time when informed consent is obtained until the end of the treatment period.

Serious Adverse Events will be collected from the time when informed consent is obtained until the end of the follow up period (maximum 30 plus 7 days).

AE/SAE collected in the Open Label Extension (OLE): After visit 6, for patients participating in the Open Label Extension phase, the Adverse Events/ Serious Adverse Events will be collected on a specific paper report form until 7 days after the end of the OLE treatment.

For patient who refused to sign full Informed Consent Form, the SAE will be collected from the last loading dose intake until the end of the 7 day follow up.

Follow-up of unresolved adverse events

Any AE/SAEs that are unresolved at the patient's end of treatment visit or safety follow up period during the study period are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collected for each AE:

- AE (verbatim)
- the date and time when the AE started and stopped
- maximum intensity
- whether the AE is serious or not
- whether the AE is a suspected endpoint or not
- investigator causality rating against the Investigational Product (yes or no)
- action taken with regard to investigational product
- outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to (see definition in 6.4.2)
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE.

The following definitions for intensity rating are:

1. mild (awareness of sign or symptom, but easily tolerated)
2. moderate (discomfort sufficient to cause interference with normal activities)
3. severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?’

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as ‘yes’.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit/you were last asked?", or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Since ticagrelor is an anti-platelet agent, surveillance for possible bleeding events will be undertaken as follows:

All bleeding events that fulfil the criteria of an AE as judged by the investigator should be reported using the standard procedures for assessing severity, causality and seriousness. Some bleeding events may not be considered as AEs if the situation is not different from that expected by the investigator (eg, usual blood loss during CABG).

Bleeding AEs will be further classified as described in section 6.4.6.3.

6.4.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF during the study period plus 7 day follow up. SAEs occurring in patients in the OLE or for unresolved SAE will be reported on a specific paper form and sent by fax to the AZ Patient Safety Data Entry Site.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives within one day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site within one calendar day of initial receipt for fatal and life threatening events and within five calendar days of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but no later than the end of the next business day of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel should fax a paper back-up SAE report to the AstraZeneca representative immediately, recognizing that the same reporting time frames still apply. The Investigator or other study site personnel is responsible for completing the eCRF as soon as the system becomes available again.

The reference document for definition of expectedness/listedness is the SmPC or the Investigators Brochure (IB) for ticagrelor (AZD6140) in countries where it is appropriate.

6.4.5 Reporting of suspected cardiac ischaemic events as adverse events

Suspected cardiac ischaemic events should not be reported as AEs/SAEs. They are part of the natural history of the condition under investigation and therefore may be expected. All other events, with the exception of expected procedural-related bleeding events, will be reported as AEs/SAEs as detailed in Sections 6.4.3 and 6.4.4.

Once an event has been identified, using their clinical judgment, investigators must determine if the event could be classified as MI or recurrent cardiac ischaemia which lead to a stent thrombosis and/or an urgent revascularization.

6.4.6 Definition and follow up procedures for Suspected Safety Endpoints:

6.4.6.1 Bleeding events: definition (according to PLATO)

In this study bleeding events will be classified as shown below:

For patients experiencing a bleeding event that fulfils criteria in more than one category, the bleed will be assigned to the most severe category. This classification is a modification of the CURE definitions (Yusuf S et al 2001).

Major bleed – fatal/life-threatening

Any one 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 Hb of more than 50 g/L[a] (3.1 mmol/L [b]; 0.775 mmol/L[c])[d]
- Transfusion of 4 or more units (whole blood or packed red blood cells (PRBCs)) for bleeding.

Major bleed – other

Any one of the following:

- Significantly disabling (eg, intraocular with permanent vision loss)
- Clinically overt or apparent bleeding associated with a decrease in Hb of 30 g/L[a] (1.9 mmol/L[b]; 0.465 mmol/L[c])d to 50 g/L[a] (3.1 mmol/L[b]; 0.775 mmol/L[c])[d]
- Transfusion of 2-3 units (whole blood or PRBCs) for bleeding.

Minor bleed

- Requires medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing).

Minimal bleed

All others (eg, bruising, bleeding gums, oozing from injection sites, etc) not requiring intervention or treatment.

Definitions of Terms

[a] Reference range 130 to 180 g/L (males); 120 to 160 g/L (females)

[b] Reference range Hb tetramer 8.1 to 11.2 mmol/L (males); 7.4 to 9.9 mmol/L (females)

[c] Reference range Hb monomer 2.02 to 2.80 mmol/L (males); 1.85 to 2.47 mmol/L (females)

[d] To account for transfusions, Hb measurements will be adjusted for any PRBCs or whole blood given between 2 blood measurements. A transfusion of one unit of blood will be assumed to result in an increase of 10 g/L[a]; 0.62 mmol/L[b]; 0.155 mmol/L[c] in Hb. Therefore, to calculate the true change in Hb if there has been an intervening transfusion between 2 blood measurements, the following calculations should be performed:
Δ Hb = [baseline Hb – post transfusion Hb] + [number of transfused units x conversion factor in Hb[e]]

[e] Conversion factor = 10 g/L[a]; 0.62 mmol/L[b]; 0.155 mmol/L[c]

Bleeding (either unexpected or of unanticipated quantity). If the patient experiences bleeding, he/she will be treated in accordance with local practice and the following data will be recorded:

- Last stable haemoglobin before start of bleeding (or hematocrit if hemoglobin unavailable). Hemoglobin (or hematocrit if hemoglobin unavailable) should be measured locally serially until resolution of the bleeding.

- Date, time and number of packed red blood cell or whole blood transfusions.

6.4.6.2 Procedures for study medication in case of bleeding

In case of a major bleed, study medication must be stopped immediately, but may be reinstated when the risk of bleeding is deemed low in the judgment of the Investigator. Major bleeding events should be managed according to need with general support and blood. The study medication administration need not be stopped in case of a minor bleeding. All bleedings should be treated and followed up according to local clinical practice. It should be noted that platelet transfusion may not reverse bleeding in a patient receiving ticagrelor as the new platelets may be inhibited by ticagrelor as long as it remains circulating in the blood.

There is no antidote to ticagrelor and treatment of bleedings should therefore be symptomatic and handled according to the clinical routines at the investigational site. For further details, refer to section 13.2.

6.4.6.3 Bleeding assessment

For all bleeding events the investigator will complete information on the eCRF specific to that bleeding event. For all bleeding events (excluding minimal) relevant additional source information will be compiled into a “Bleeding Package” as described in the Endpoint Reporting Manual for Investigators. The package will be sent to the ICAC for central adjudication.

Bleeding event data will be collected in sufficient detail so that categorisation according to other previously published definitions (eg, TIMI, ISTH, GUSTO, STEEPLE, BARC) will be possible. The ICAC will adjudicate and evaluate bleeding events (excluding minimal) according to the above bleeding definitions.

Bleeding endpoints will be assessed by investigator according to PLATO definitions.

6.4.6.4 Bleeding associated with procedures

Information regarding the relationship of any bleed to coronary (CABG, PCI or coronary angiography) will be recorded on the eCRF. The ICAC will adjudicate if bleeding associated with procedures is related to that procedure or not.

Bleeding associated with a procedure should be reported as an AE if the amount of bleeding exceeds the quantity expected by the investigator for this corresponding procedure.

6.4.7 Laboratory safety assessment

Blood samples for determination of clinical chemistry, haematology will be taken at the times indicated in the Study Plan (see on Table 1). No fasting is required.

The following laboratory variables will be measured and analyzed locally for all patients:

6.4.7.1 Haematology and Clinical chemistry

Clinical chemistry (S denotes serum)	**Haematology (B denotes whole blood)**
S-Creatinine	B-Haemoglobin
S-Alkaline phosphatase	B-Haematocrit
S-Aspartate aminotransferase (AST)	B-Platelets
S-Alanine aminotransferase (ALT)	B-White blood cells
S-Total Bilirubin	B-White blood cells (differential)
	B-Haemoglobin A1c (only diabetics)

6.4.7.2 Myocardial necrosis biomarkers

The myocardial necrosis biomarkers (Troponin I or T) are required to document the index event and should be obtained to evaluate any recurrences of cardiac ischaemia. They will be analyzed locally for all patients to and will be collected at the following time points:

- In the Cath Lab (V2-pre PCI)
- And then at 8, 16 and 24 hours after PCI

Blood samples for Troponin measurement will also be collected whenever a patient is experiencing chest pain or cardiac event. The result will be part of the endpoint package for ICAC.

All local laboratory results and relevant reference ranges must be stored in the patient's medical record as source documentation.

For blood volume see Section 7.1

6.4.8 Physical examination

A physical examination will be performed by medically qualified individuals. The targeted examination should include general appearance, cardiovascular, respiratory, abdomen and neurological evaluations. Results will be recorded as an overall normal or abnormal with a listing of abnormalities.

Please refer to the Study Plan (Table 1) in Section 3.1.

Killip classification will be assessed as:

Killip class I: Absence of rales over the lung fields and absence of an S3

Killip class II: Rales over 50% or less of the lung fields or the presence of an S3

Killip class III: Rales over more than 50% of the lung fields

Killip class IV: Cardiogenic shock: signs include hypotension (systolic pressure of 90 mmHg or less) and evidence of peripheral vasoconstriction such as oliguria, cyanosis and diaphoresis.

6.4.9 Vital signs

Heart rate, systolic blood pressure (BP) and diastolic BP will be assessed after the patient has been at rest for 5 minutes.

Please refer to the Study Plan in Section 3.1

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each patient in this study is as follows:

Table 2 Volume of blood to be drawn from each patient

For patients participating in the sub study presented in appendix D: an additional volume of 40 ml will be drawn (see details in appendix D).

Assessment		**Sample volume (mL)**	**No. of samples**	**Total volume (mL)**
Baseline (V2)	Clinical chemistry	5	1	5
	Haematology	2	1	2
	Troponin I or T	2	1	2
Safety	Clinical chemistry	5	3	15
	Haematology	2	3	6
	Troponin I or T	2	5	10
Total			14	40

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses.

7.3 Labelling and shipment of biohazard samples

Not Applicable.

For patients participating in the sub study presented in appendix D, see details in appendix D.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle according to the local practice.

For patients participating in the sub study presented in appendix D, see details in appendix D and E.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. Distribution of these documents to the applicable Ethics Committee will either be done by the investigator or by AstraZeneca, according to the national guidelines. Investigator will ensure distribution of these documents to the study site staff.

The opinion of the Ethics Committee should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before randomisation of any patient into the study, the final study protocol, including the final version of the Informed Consent Forms, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

8.4 Informed consent

The ambulance medical personnel or paramedics personnel (according to local regulations), will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study,
- Ensure each patient is notified that they are free to discontinue from the study at any time,
- Ensure that each patient is given the opportunity to ask questions.

In emergency situation:

In emergency situation it might be impossible to take enough time to provide informed consent by the full version of the Informed Consent Form. If locally approved by the Ethics Committee and Regulatory Authorities (if appropriate), a short form of the Informed Consent Form will be provided. It can be used in pre-hospital settings to collect consent of the patient or its legally acceptable representative to confirm that the ambulance personnel/physician (according to local law) has discussed the study with the patient.

When prior consent of the patient or its legally acceptable representative is not possible, the patient may be randomised if the ambulance personnel/physician (according to local law) has attested on the Informed Consent Form that the information about the study has been discussed with the patient.

In all cases, the patient's signature or that of the patient's legally acceptable representative will be obtained on the full version of the Informed Consent Form. If only the short form of the Informed Consent Form is signed then the full Informed Consent Form will be obtained before first dose intake of active ticagrelor 90 mg tablet to document the patient's willingness to continue. If a patient is unable to read and sign due to critical condition, the full Informed Consent Form will be signed as soon as the clinical situation allows it.

If the patient or legally acceptable representative subsequently refuses to complete the consent process, the patient is terminated from the trial, following full discussion with the patient regarding the risks associated with trial termination, and no additional data from the patient is collected. The data collected up to the refusal will be used.

The Principal Investigator (s) at each centre will:

- Ensure that each patient has signed the full Informed Consent Form prior to be given the first dose of active ticagrelor (90 mg tablet)
- Ensure all original, signed Informed Consent Form(s) are stored in the Investigator's Study File,

- Ensure a copy of the signed Informed Consent Form(s) is given to the patient,

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 8.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the ambulance organisation and the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator.

In certain countries, the investigational study sites will involve the ambulance organisation and the hospital cardiology unit.

Prior to centre validation, a centre qualification process will take place. The independent Core Labs identified for the review and analysis of ECG and angiograms, will conduct a survey in order to check the quality of the documentation supporting the primary variables of the study and its transfer to the Core Lab. Preselected centers will have to submit at least 2 ECG recordings of the same patient with STEMI diagnosis. Recordings of two or more contiguous leads should be done in the pre-hospital and in-hospital (pre-PCI) setting and sent to Core lab along with the CD of the pre-PCI angiography imaging, for quality and variability assessment. The result of the survey will enable to confirm or not the centre participation to the study.

9.2 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff. The AstraZeneca representative will also train the site personnel in any study specific procedures and the WBDC system utilised (wherever it is appropriate).

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.3 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, ECGs and angiogram's for central review are handled in accordance with the Core Lab Manual and that study drug accountability checks are being performed
- Perform Source Data Verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital and other records relevant to the study) including verification of informed consent(s) of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)

The AstraZeneca representative will be available between visits if the investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.3.1 Source data

Refer to the Clinical Study Agreement (CSA) for location of source data.

9.4 Study agreements

The Principal Investigator at each centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are randomised.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.5 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The study is expected to start in and to end by .

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with ticagrelor.

If AstraZeneca decides to prematurely terminate or suspend the study, the Principal Investigator, sub investigator, the head of the institution, and regulatory authorities should receive written notification of the reasons for the premature termination or suspension.

The Principal Investigator/sub-investigator will immediately notify the decision to the patients, give appropriate medical treatment; take necessary measures, and record treatment or measures provided on the source documents.

10. DATA MANAGEMENT

Data management will be performed by staff and database set-up by the Data Management Centre of AstraZeneca.

Data queries will be raised for inconsistent, impossible or missing data and will be updated by the study site personnel as needed. All entries to the study database will be immediately saved to a central database and changes tracked to provide an audit trail

Data management will determine the format of the data to be collected through core laboratory and will produce ongoing reconciliation with clinical database as applicable.

Serious Adverse events Reconciliation reports will be produced and reconciled with Patient Safety database. Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by

All data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of efficacy variables

ECG and angiographic assessments will be centrally measured.

The co-primary endpoint from ECG, complete ST –segment elevation resolution will evaluate the percentage of patients with an ST-segment elevation resolution ≥ 70% derived from percentage change in ST- segment elevation between ambulance assessment and in-hospital assessment pre-PCI.

The co-primary endpoint from angiography, TIMI flow grade 3 will evaluate the percentage of patients reaching TIMI flow grade 3 at initial angiography, issued from TIMI flow data, all grades.

Binary (yes/no) variables patients will be created and classified according to whether the specified event occurred.

Events related to secondary binary endpoints including complete (≥ 70%) ST-segment elevation resolution at 60 minutes post PCI, TIMI flow grade 3 at end of procedure, Thrombotic bail-out with GPIIb/IIIa inhibitors at initial PCI will be classified in the same way.

Length of time variables will be derived as the number of minutes from the onset to the end of the time interval considered. These intervals include time from symptom onset to first study medication administration and time from first study drug administration to time of ECG/angiography.

For the other endpoints, in each case patients will be classified (yes/no) according to whether one or more the events considered occurred during the 30 days of study. This includes the composite of death, MI, stroke, urgent revascularization, acute stent thrombosis and a similar composite including death, MI, and urgent revascularization.

Continuous variables measured by core lab include the correct TIMI frame count (cTFC) at angioplasty pre and post PCI and the ordinal TIMI myocardial perfusion grade (TMPG) at angioplasty pre and post PCI.

11.2 Calculation or derivation of safety variable(s)

11.2.1 Bleeding Events

Each patient will be classified (yes/no) according to whether there were one or more bleeding events according to the PLATO bleeding definition. This includes first, major life-threatening, second, other major bleeding events, and third, minor or major bleeding events. Two periods will be considered: the first 48 hours after first administration of study medication and during the 30 days of study. Thus each patient will have 6 classifications of “yes” or “no.”

11.2.2 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert’s judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory, ECG and vital sign data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

12. STATISTICAL METHODS AND SAMPLE SIZE

Statistical analyses will be performed by Statistic Department, using Statistical Analysis System (SAS). Statistical Analyses will be performed in accordance with the study protocol. The Statistical Analysis Plan will provide further details of the analyses and presentation of data. The statistical analysis plan will be finalised before the database lock.

12.1 Description of analysis sets

12.1.1 Efficacy analysis set

The Modified Intent to Treat Population (mITT) will include all randomized patients who received a dose of study medication. Patients will be classified according to the treatment group they were randomized to. All efficacy endpoints will be analyzed using the mITT population.

12.1.2 Safety analysis set

All patients who received at least one dose of the study medical product will be included in the safety population. Throughout the safety results sections, erroneously treated patients (eg, those randomised to group A but actually treated as group B) will be accounted for in the actual treatment group. Patients who did not receive a dose of study medical product will not be considered.

12.2 Methods of statistical analyses

Continuous variables will be summarized using mean, standard deviations and extreme values (minimum, maximum). Confidence intervals, when included, will be two-sided 95% intervals except otherwise specified. Categorical variables will be summarized in frequency tables including counts and percents. Values will be summarized by treatment group and overall.

12.2.1 Primary Efficacy Endpoints

Each of the co-primary endpoint will be analyzed separately using a Chi-Square test.

The Holm multiple correction procedure will be used to maintain an overall Type I error rate of 5%. Specifically the two derived p-values will be compared. If the smaller p-value is greater than 0.025 then neither null hypothesis is rejected. Alternatively, if it is less than 0.025 then the associated null hypothesis is rejected and the null hypothesis associated with larger p-value is rejected if the p-value is less than 0.05.

12.2.2 Other Efficacy Endpoints

The effect of the length of time (minutes) between key events on the primary endpoints will analyzed using logistic regression with time as the explanatory variable. The time intervals considered are time from onset of symptoms to first dose of investigational product and time from first dose of investigational product to ECG/angiography. Separate analyses will be conducted for each time interval and each primary endpoint.

Categorical endpoints will be compared using Chi-Square tests. This includes complete (≥ 70%) ST-segment elevation resolution at 60 minutes post PCI, TIMI flow grade 3 at end of procedure, Thrombotic bail-out with GPIIb/IIIa inhibitors at initial PCI and both composite endpoints.

The ordinal TIMI myocardial perfusion grade at angiography will be compared using the Cochran-Mantel-Haenszel test with modified ridit scores.

Corrected TIMI frame counts will be compared using analysis of variance (ANOVA).

12.2.3 Bleeding Events

Endpoints will be compared between treatment groups in the Safety Population using Chi-Square testing.

Statistical testing of bleeding events will not be considered confirmatory as no pre-specified hypothesis has been made.

12.2.4 Other safety data

Adverse events (AEs) will be summarized by system organ class and preferred term using MedDRA. Summaries will be presented by treatment groups using descriptive statistics. Specific more detailed analyses of dyspnoea and bradycardic events will be performed. All AEs related to bleeding events will be summarized separately.

Safety laboratory parameters and transfusion of blood products will be displayed by descriptive statistics with the change from baseline when appropriate.

12.2.5 Interim analyses

No interim analyses are planned for this study.

12.3 Determination of sample size

Since, based on multiplicity procedure, the initial significance level is 2.5%, the sample size calculation will be based on a significance level of 2.5% and 80% power. Sample size calculations were derived using nQUERY7.

The sample size for the two co-primary endpoints is derived from the ST Resolution hypothesis. However, the study is enough powered for the 2 criteria when considering the table below.

The ST segment deviation was previously studied in On Time2 study (Van't Hof Aw et al 2008), where complete ST resolution occurred in 20.7% of patients in the pre-hospital GP IIb/IIIa group versus 15.4% in the non GP IIb/IIIa group, all patients receiving a clopidogrel loading dose. This last number, corresponding to an in-hospital group was confirmed in Assent 4 PCI study where electrocardiographic reperfusion was shown in 14.9% of patients.

Based on this data, it is hypothesized that 15% of patients in the in-hospital group will achieve complete ST elevation resolution versus 21% in the pre-hospital group (absolute difference of 6%). Taking into account a significance level of 2.5%, 779 evaluable patients are required in each treatment group to have 80% power using a two group chi squared test of equal proportions. Assuming a 12% dropout for invaluable or missing ECG criteria, a total of 1770 patients are required to be enrolled in the study to assess the ST segment elevation resolution difference.

To insure the sample size is adequate for the analysis of the co-primary endpoint TIMI Grade at initial angiography, values ranging from 15-27% were reported in various studies. Clinicians agreed that a 30 to 35% relative difference between the 2 groups is clinically relevant. In order to hypothesize on the various degree of angiographic reperfusion expected the following table was created to show a range of hypothesis and the related sample size. A statistical difference can be shown for the highlighted hypothesis (in bold) in the table. Dropout rate at initial angiography is assumed to be low, and less than 8%. These values indicate the sample size of 1770 patients is adequate for this endpoint.

	Assumptions with TIMI flow grade3 = 15% in in-hosp group		**Assumptions with TIMI flow grade3 = 27% in in-hosp group**	
Assumptions of relative difference (%) between the two groups	30	35	30	35
In–hosp group	15%	15%	27%	27%
Pre-hosp group	19,5%	20.3%	35.1%	36.5%
N per group with alpha=0.05	1106	826	512	376
N per group with alpha=0.025	1339	1001	620	456

12.4 Study Committees

All committees will operate according to written charters outlining roles and responsibilities.

1. A Data Safety Monitoring Board (DSMB) will be appointed by AstraZeneca independently from the investigators and the Executive Committee. The DSMB will review interim data to detect evidence of adverse effects and will provide recommendation to Executive Committee and AstraZeneca with respect to trial conduct. The safety of all AstraZeneca clinical studies is also closely monitored on an on-going basis by AstraZeneca representatives in consultation with the Patient Safety Department

2. An Independent Central Adjudication Committee (ICAC) will be established for the review of clinical endpoints events during 30 days. Those clinical endpoints will include also any major life threatening, other major bleeding, minor bleeding events (according to PLATO, TIMI, ISTH, GUSTO, STEEPLE, BARC definitions) within the first 48 hours and during the 30 days of the study.

3. An Executive Committee will be set up. It will involve 5 experts with the relevant knowledge and experience required for the study and who will have an active role in coordinating the study at the study level. In addition, 3 non-voting representatives from AstraZeneca will be appointed. This Executive Committee will have the executive oversight and supervision of the study. It will also be involved in the publication strategy of the study.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4**

In the case of a medical emergency the investigator may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician at AstraZeneca.

Name	**Role in the study**	**Address & telephone number**
	Study Delivery Team Leader	
	SDT Physician	
Drug Safety at local R&D site		
Outside working hours*, please call		

*Monday to Friday 9 am to 6.30pm (CET)

Each Marketing Company will manage Drug Safety issue and clinical questions locally.

13.2 Overdose

An overdose is defined as any intake of study medication greater than 900 mg/day.

In the event of an overdose with ticagrelor ascertain the time and extent of the overdose regardless of severity. Determine the causative circumstance and whether haemorrhagic or toxic complications have occurred or are likely to do so. Depending on these facts it has to be decided if the patient should be hospitalized for observation or not. Bleeding is one of the most likely pharmacological effect of excessive ticagrelor dosing, and appropriate supportive measures such as volume replacement, local haemostatic measures, and decompression or drainage may be required depending on the extent of bleeding or volume of blood lost. Patients with overdose-related bleeding should be cautioned to avoid unnecessary activity, mechanical tissue stress, and minor trauma for at least 24 hours after the bleeding has stopped. For other symptoms that can be expected after an overdose of ticagrelor and additional information see SmPC or the IB in countries where it is appropriate.

An overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the eCRF.

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.

An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study medication occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day**, ie, immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply, see Sections 6.4.3 & 6.4.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

If a patient becomes pregnant during the course of the study, study medication should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the study medication under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day** i.e., immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.4.4 and within 30 days for all other pregnancies

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

13.3.2 Paternal exposure

There are no restrictions against fathering a child when treated with ticagrelor. If paternal exposure pregnancy occurs in the course of the study, then investigators or other site personnel should inform appropriate AstraZeneca representatives **within one day** as described in the maternal exposure section 13.3.1.

14. LIST OF REFERENCES

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Clinical Study Protocol Administrative Change Number 3 – Edition 2

Drug Substance	AZD6140
Study Code	D5130L00006
Date	
Protocol Dated	

A 30 day international, randomized, parallel-group, double-blind, placebo-controlled phase IV study to evaluate efficacy and safety of pre-hospital vs. in-hospital initiation of ticagrelor therapy in STEMI patients planned for PCI

Sponsor:

ASTRAZENECA

Centres affected by the Administrative Change:

All centres participating in the study

The protocol for the study is to be changed as follows:

Section of protocol affected:

6.4.7.1 Haematology and Clinical chemistry

Previous text:

Clinical chemistry (S denotes serum)	**Haematology (B denotes whole blood)**
S-Creatinine	B-Haemoglobin
S-Alkaline phosphatase	B-Haematocrit
S-Aspartate aminotransferase (AST)	B-Platelets
S-Alanine aminotransferase (ALT)	B-White blood cells
S-Total Bilirubin	B-White blood cells (differential)
	B-Haemoglobin A1c (only diabetics)

Revised text:

Clinical chemistry (S denotes serum)	**Haematology (B denotes whole blood)**
S-Creatinine	B-Haemoglobin
S-Alkaline phosphatase	B-Haematocrit
S-Aspartate aminotransferase (AST)	B-Platelets
S-Alanine aminotransferase (ALT)	B-White blood cells
S-Total Bilirubin	~~B-White blood cells (differential)~~
	B-Haemoglobin A1c (only diabetics **at visit 2)**

Reason for Administrative Change:

In this context and patient population, the collection of white blood cells and differential cells is not considered pertinent nor critical for the management and treatment of the patients in this study. The repetition of Haemoglobin A1C collection in diabetics patients after visit 2 is not considered pertinent.

Explanation for replacement of Administrative Change n°3 by this edition 2. In the first edition of administrative change n°3, there was a typo error : first sample of Haemoglobin A1c is collected at visit 2 not at visit 1 as previously indicated.

Persons who initiated the Administrative Change:

Signed agreement to the Administrative Change:

I hereby approve the Administrative Change to the Clinical Study Protocol.

Study Code: D5130L00006

. . . . .	. . . . .
Date	AstraZeneca Study Delivery Team Leader

(Day Month, Year)

Clinical Study Protocol Administrative Change Number 4

Drug Substance	AZD6140
Study Code	D5130L00006
Date	
Edition n°	2.0
Protocol Dated	

A 30 day international, randomized, parallel-group, double-blind, placebo-controlled phase IV study to evaluate efficacy and safety of pre-hospital vs. in-hospital initiation of ticagrelor therapy in STEMI patients planned for PCI

Sponsor:

ASTRAZENECA

Centres affected by the Administrative Change:

All centres participating in the study

The protocol for the study is to be changed as follows:

Section of protocol affected:

Protocol Synopsis

Previous text:

Study period:

Estimated date of last patient completed

Revised text:

Study period:

Estimated date of last patient completed

Reason for Change:

Due to slow recruitment, the study period is extended.

Section of protocol affected:

5.4.2. Methods for unblinding the study

Previous text:

The investigator documents and reports the action to AstraZeneca without revealing the treatment given to patient to the AstraZeneca staff.

Revised text:

The investigator documents and reports the action to AstraZeneca without revealing the treatment given to patient to the AstraZeneca staff. **The patient is then withdrawn from study treatment.**

Reason for Change:

Clarification has been added in order to be consistent with the instructions in the IVRS/IWRS.

Section of protocol affected:

5.8.2 Permanent discontinuation from study medication

Previous text:

All patients should remain in the trial and keep all visits whether they continue study medications or not.

Revised text:

All patients should remain in the trial **and a follow up will be performed according to section 5.8.3 below, unless full Informed Consent is not signed** ~~and keep all visits whether they continue the study medication or not~~.

Reason for Change:

Emphasize the pre requisite of obtaining the full version of the Informed Consent to continue in study even if study medication is stopped and add reference to section 5.8.3 for clarity on follow up procedures.

Section of protocol affected:

6.4.5 Reporting of suspected cardiac ischaemic events as adverse events

Previous text:

Suspected cardiac ischaemic events should not be reported as AEs/SAEs. They are part of the natural history of the condition under investigation and therefore may be expected. All other events, with the exception of expected procedural-related bleeding events, will be reported as AEs/SAEs as detailed in Sections Sections 6.4.3 and 6.4.4.

Once an event has been identified, using their clinical judgment, investigators must determine if the event could be classified as MI or recurrent cardiac ischaemia which lead to a stent thrombosis and/or an urgent revascularization.

Revised text:

~~Suspected cardiac ischaemic events should not be reported as AEs/SAEs. They are part of the natural history of the condition under investigation and therefore may be expected. All other events, with the exception of expected procedural-related bleeding events, will be reported as AEs/SAEs as detailed in Sections Sections 6.4.3 and 6.4.4.~~

Except in some clinical situations, suspected cardiac ischaemic events should not be reported as AEs/SAEs.

Once a **suspected cardiac ischaemic** event has been identified, using their clinical judgment, investigators must determine if the event could be classified as MI or recurrent cardiac ischaemia which lead to a stent thrombosis and/or an urgent **coronary** revascularization. **Those will be recorded as endpoints and reported to the ICAC for central adjudication (see Section 6.3.2).**

All other **suspected cardiac ischaemic** events, **not meeting endpoint definitions**, will be reported as AEs/SAEs as detailed in Sections Sections 6.4.3 and 6.4.4.

Reason for Change:

The previous wording was causing some confusion in the management of cardiac ischemic event not meeting the endpoints definitions as defined in section 6.3.2. The clarification added provides clarity in the management of these events consistent with eCRF data entry instructions provided by the Study team.

Reason for Administrative Change:

To document the study period extension, be consistent with IVRS/IWRS instructions and add clarity in the follow-up process in case of discontinuation from study medication and management of suspected cardiac ischaemic events not meeting endpoint definitions.

Persons who initiated the Administrative Change:

Signed agreement to the Administrative Change:

I hereby approve the Administrative Change to the Clinical Study Protocol.

Study Code: D5130L00006

…… ……

Date AstraZeneca Study Delivery Team Leader

(Day Month, Year)