AstraZeneca

PROTOCOL SYNOPSIS

A Randomized, Double-Blind, Placebo Controlled, Parallel Group, Multinational Trial, to Assess the Prevention of Thrombotic Events with Ticagrelor Compared to Placebo on a Background of Acetyl Salicylic Acid (ASA) Therapy in Patients with History of Myocardial Infarction

International Co-ordinating Investigator

Study centre(s) and number of patients planned

This study will be conducted in approximately 1000 investigational centres in approximately 30 countries worldwide. It is expected that approximately 21000 patients will be randomized to study treatment.

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

Objectives

Primary objective

The primary objective of the study is to compare the effect of long-term treatment with ticagrelor vs. placebo on a background of acetyl salicylic acid (ASA) on the event rate of the composite of cardiovascular death, non-fatal myocardial infarction (MI), or non-fatal stroke in patients with history of MI and high risk of developing atherothrombotic events. The primary efficacy variable is time to first occurrence of any event after randomization from the composite of cardiovascular death, non-fatal MI, or non-fatal stroke.

Secondary objectives

The first secondary objective is to compare the effect of long-term treatment with ticagrelor vs. placebo on a background of ASA on the event rate of cardiovascular death in patients with history of MI and high risk of developing atherothrombotic events. The efficacy variable is time to occurrence of cardiovascular death after randomization.

The second secondary objective is to compare the effect of long-term treatment with ticagrelor vs. placebo on a background of ASA on the event rate of all-cause mortality in patients with history of MI and high risk of developing atherothrombotic events. The efficacy variable is time to occurrence of all-cause mortality after randomization.

Other objectives

To compare the effect of long-term treatment with ticagrelor vs. placebo on a background of ASA on the event rate of the composite of cardiovascular death, non-fatal MI, non-fatal stroke, or urgent coronary revascularization. The efficacy variable is time to first occurrence of any event after randomization from the composite of cardiovascular death, non-fatal MI, non-fatal stroke, or urgent coronary revascularization.

To compare the effect of long-term treatment with ticagrelor vs. placebo on a background of ASA on the event rate of the composite of cardiovascular death or coronary or cerebrovascular arterial thrombosis hospitalization (including non-fatal MI, non-fatal stroke, urgent coronary revascularization, unstable angina, or transient ischemia attack). The efficacy variable is time to first occurrence of any event after randomization from the composite of cardiovascular death or coronary or cerebrovascular arterial thrombosis hospitalization. The individual components will also be examined in an analogous manner.

To compare the effect of long-term treatment with ticagrelor vs. placebo on a background of ASA on the event rate of the composite of coronary heart disease death, non-fatal MI, or non-fatal stroke. The efficacy variable is time to first occurrence of any event after randomization from the composite of coronary heart disease death, non-fatal MI, or non-fatal stroke. The individual component of coronary heart disease death will also be examined in an analogous manner.

To evaluate the net clinical benefit of long-term treatment with ticagrelor vs. placebo on a background of ASA. The variable is the time to first occurrence of any event after randomization from the composite of cardiovascular death, non-fatal MI, non-fatal stroke or TIMI major bleeding.

To compare the effect of the long-term treatment with ticagrelor vs. placebo on a background of ASA on the incidence of coronary stent thrombosis. The variable is the time to first occurrence of coronary stent thrombosis after randomization.

To collect health care utilization associated with hospitalizations and utilities assessed by Euro Quality of Life-5 Dimensions (EQ-5D) to support health technology assessment and health economic modeling.

Safety objectives

The safety objective of this study is to assess the safety and tolerability of long-term therapy with ticagrelor compared to placebo on a background of ASA in patients with history of MI and high risk of developing atherothrombotic events. Bleeding events will be analysed using the TIMI, PLATO, GUSTO, and ISTH definitions. Specific focus will be on:

- Time to first TIMI major bleeding event following the first dose of study medication, as well as time to first TIMI major or minor bleeding event and time to first PLATO major bleeding event.
- Time to discontinuation of study medication due to any bleeding event
- Evaluation of Adverse Events (AEs)

Study design

This is an event-driven, randomized, double blind, placebo controlled, parallel group, international multicentre study to assess the prevention of cardiovascular events with ticagrelor given at 2 doses (90 mg bd and 60 mg bd) compared to placebo on a background of ASA in patients with history of MI (1-3 years ago) and additional risk factors for atherothrombosis.

Target patient population

Male and female patients 50 years of age and over with history of MI 1-3 years ago and at least 1 of the following risk factors: age ≥65 years, diabetes, a second prior MI, evidence of multivessel coronary artery disease (CAD), or chronic non-end stage renal dysfunction.

Study Medication, dosage and mode of administration

Ticagrelor: 90 mg and 60 mg tablets. Patients will either receive 90 mg or 60 mg of ticagrelor orally bd or placebo for a minimum of 12 months.

Concomitant therapy, dosage and mode of administration

Concomitant ASA: In addition to the assigned study medication, all patients will take concomitant ASA, at a planned dose of 75 - 150 mg once daily, from randomization through the end of the treatment period. If a patient develops an indication for higher dose ASA during the treatment period (e.g. acute coronary syndrome or percutaneous coronary intervention), higher dosing is allowed for the duration of that indication, after which the dose of ASA should be reduced to between 75 mg and 150 mg once daily.

ADP receptor blockers (eg, clopidogrel, prasugrel, ticlopidine), dipyridamole, and cilostazol: Planned concomitant treatment with any of these drugs is not allowed in the study. For situations where a patient already enrolled in the study develops an indication for use of an ADP receptor blocker according to medical guidelines (eg, acute coronary syndrome or percutaneous coronary intervention), see section 5.5.3. If open-label treatment with one of

these drugs is considered essential during the study, study medication must be discontinued but may be resumed when open-label treatment is stopped.

Duration of treatment

The patients will be followed a minimum of 12 months and up to approximately 38 months. If, however, the number of primary events is not achieved when the last patient has been followed for 12 months, the treatment period may be extended. The expected median duration is 26 months. A study closure plan will be developed to take into account the patient recruitment pattern and number of outcome events experienced (target: 1360). All patients will have a Follow-up Visit approximately 2 weeks after their last dose of study medication. The study may be terminated early if either a clear beneficial or harmful effect of the study treatment is detected during the Independent Data Monitoring Committee (IDMC) review.

Statistical methods

The primary efficacy variable is the time to first occurrence of any event from the primary composite of cardiovascular death, non-fatal MI, or non-fatal stroke. Analysis of the primary variable will be performed using the Cox proportional hazards model with a factor for treatment group. Each ticagrelor dose will be tested separately vs. placebo.

The analysis of the primary composite efficacy variable and the 2 secondary efficacy variables will comprise the confirmatory analysis. The first secondary variable, cardiovascular death, will be tested in the confirmatory sense only if the primary comparison is significant for that dose. Similarly, if the first secondary variable is significant for a given dose, all-cause mortality will be tested as the last confirmatory test for that dose. An independent statistical group will perform analyses of unblinded data for the IDMC.

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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
ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
AE	Adverse event (see definition in Section 6.4.1)
ALT	Alanine aminotransferase
ARR	Absolute risk reduction
ASA	Acetyl salicylic Acid
AST	Aspartate aminotransferase
AV	Atrioventricular
bd	Twice a day dosing
BMI	Body Mass Index
BP	Blood Pressure
CABG	Coronary artery bypass graft
CAD	Coronary Artery Disease
CEC	Clinical Endpoints Committee
CI	Confidence interval
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed Tomography
CV	Cardiovascular
CYP3A	Cytochrome P450 3A
DAE	Discontinuation of Study Medication due to Adverse Event
DNA	Deoxyribonucleic acid
DRG	Diagnosis-related group
ECG	Electrocardiogram
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
EoT	End of Treatment (refers to study visit at which patient is discontinued from study medication)

Abbreviation or special term	Explanation
EQ-5D	European Quality of Life-5 Dimensions questionnaire
FAS	Full analysis set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPIIb/IIIa	Glycoprotein IIB/IIIa receptor
GRand	AstraZeneca Global Randomization system
HR	Hazard Ratio
IB	Investigator's brochure
ICH	International Conference on Harmonization
ID	Identification
IDMC	Independent Data Monitoring Committee
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.
IPA	Inhibition of platelet aggregation
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
Killip Class	Haemodynamic classification of patient with acute MI
LIMS	Laboratory Information Management System
LBBB	Left Bundle Branch Block
LLOQ	Lower Limit of Quantification
LMWH	Low Molecular Weight Heparin
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
NSAID	Non Steroidal Anti Inflammatory Drug
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
od	Once daily dosing
$P2Y_{12}$	A sub-type of P2 receptor found on platelets
PAD	Peripheral artery disease
PCI	Percutaneous Coronary Intervention
Peri-event	In relation to concomitant medications this means all medications taken in the 7 days prior to onset, during, and for the 7 days after the event

Abbreviation or special term	Explanation
PGx	Pharmacogenetic research
PLATO	Study acronym – a study of PLATelet inhibition and patient Outcomes
QD	Administered once daily
PRBCs	Packed Red Blood Cells
RRR	Relative risk reduction
SAE	Serious adverse event (see definition in Section 6.4.2).
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SDV	Source Data Verification
TIA	Transient Ischaemic Attack
TIMI	Thrombolysis in Myocardial Infarction Study Group
UFH	Unfractionated Heparin
URL	Upper Reference Limit
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1. Background

Atherothrombosis is a systemic disease that affects all ethnic groups and is associated with the main causes of mortality on a worldwide scale. Its prevalence will further increase in the future (World Health Organization 2008). Moreover, after the initial manifestation of atherothrombosis, patients remain at high risk for serious complications for years after their initial event (Bhatt et al 2006).

The Clopidogrel versus Acetyl salicylic acid (ASA) in Patients at Risk of Ischaemic Events (CAPRIE) study demonstrated superiority of clopidogrel monotherapy over ASA monotherapy in patients with recent myocardial infarction (MI), stroke, or symptomatic peripheral artery disease (PAD) over the 36-month study duration (CAPRIE Steering Committee 1996). Since then several clinical trials have confirmed greater clinical efficacy of dual antiplatelet therapy with thienopyridine (P2Y12 receptor blocker) and ASA versus ASA alone in patients with acute coronary syndromes (ACS) for up to a year of therapy (Yusuf et al 2001, Sabatine et al 2005, Chen et al 2005). New data have demonstrated a further reduction of thrombotic events in the first year after an acute coronary syndrome using a more potent P2Y12 receptor blocker in combination with ASA as compared to clopidogrel plus ASA (Wiviott et al 2007).

Ticagrelor (AZD6140) is a reversible, potent, oral adenosine diphosphate (ADP) P2Y12 receptor blocker.

Recently, data from an AstraZeneca study of platelet inhibition and patient outcomes (PLATO/D5130C05262), a Phase III pivotal efficacy and safety study with a duration of up to 12 months comparing ticagrelor 90 mg twice daily dosing (bd) to clopidogrel 75 mg once daily dosing (qd) in acute coronary syndrome patients on ASA background, have demonstrated superiority of ticagrelor over clopidogrel in the prevention of fatal and non-fatal cardiovascular events.

In PLATO, ticagrelor was superior to clopidogrel in reducing the rate of the composite efficacy endpoint of CV death, MI, or stroke after ACS events (relative risk reduction [RRR] 16%, ARR 1.9%; HR 0.84 [95% CI 0.77, 0.92]; p=0.0003). Furthermore, ticagrelor, compared to clopidogrel, decreased separately the rates of cardiovascular death (RRR 21%; ARR 1.1%; HR 0.79 [95% CI 0.69, 0.91]; p=0.0013) and of MI (RRR 16%; ARR 1.1%; HR 0.84 [95% CI 0.75, 0.95]; p=0.0045). PLATO-defined Major bleeding (primary safety endpoint) for ticagrelor did not differ significantly from that of clopidogrel (HR 1.04 [95% CI 0.95, 1.13]; p=0.4336).

The current study is being conducted to determine whether long-term dual-antiplatelet therapy with ticagrelor in combination with ASA is beneficial in patients with history of MI (1-3 years ago) and additional risk factors for atherothrombosis compared with monotherapy with ASA alone.

Further information regarding the background, pharmacological class, properties, and mechanism of action of ticagrelor can be found in the Investigator's Brochure (IB).

1.2. Research hypothesis

This study is designed to test the hypothesis that the combination of ticagrelor and ASA will lead to fewer major adverse cardiovascular events compared to ASA alone in patients with history of MI (1-3 years ago) and high risk of developing atherothrombotic events.

1.3. Rationale for conducting this study

Previous studies have demonstrated the utility of low-dose ASA for secondary prevention of atherothrombotic events after appropriate risk stratification (AHA et al 2006). In the CAPRIE study, clopidogrel monotherapy was superior to ASA monotherapy for reducing the composite of cardiovascular death, MI, or stroke, (5.3% per year vs. 5.8% per year, P=0.043) over 1-3 years of therapy in patients with a recent MI, stroke, or PAD (CAPRIE Steering Committee 1996). Since then several studies have demonstrated superiority of the combination clopidogrel plus ASA vs. ASA alone in reducing death and ischemic complications in patients with acute coronary syndromes treated for up to 1 year (Yusuf et al 2001, Sabatine et al 2005, Chen et al 2005). Nevertheless patients with previous myocardial infarction and additional risk factors are still at high risk for recurring atherothrombotic events even beyond the first year after their myocardial infarction (Bhatt et al 2006). Currently, however, there are no data to support dual therapy beyond 12 months.

The Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management, and Avoidance (CHARISMA) study (Bhatt et al 2004) investigated the use of dual antiplatelet therapy with clopidogrel plus ASA vs. ASA alone for a median of 28 months in a broad spectrum of patients at risk for cardiovascular events. A post hoc analysis demonstrated that the overall rate of cardiovascular death, MI, or stroke in the atherothrombotic disease cohort (documented cardiovascular, cerebrovascular, or PAD) was 8.8% in the placebo plus ASA arm and 7.3% in the clopidogrel plus ASA arm (hazard ratio 0.83, 95% confidence interval 0.72 to 0.96, p=0.01) (Bhatt et al 2007). Moreover, patients with prior documented myocardial infarction appeared to have an even more robust benefit (8.3% vs. 6.6%, HR 0.77, 95% CI 0.61-0.98, P=0.03). These data suggest that extended dual antiplatelet therapy targeted to a high-risk population with prior myocardial infarction would likely provide clinical benefit.

Of note, treatment with ASA in combination with a more potent P2Y12 receptor antagonist with higher and more consistent levels of platelet inhibition than standard or high-dose clopidogrel and ASA in patients with ACS resulted in greater reduction in ischemic events than treatment with clopidogrel (prasugrel: 9.9% versus clopidogrel 12.1%; HR, 0.81; p<0.001 [Wiviott et al 2007]).

Ticagrelor 90 mg bd has greater and 60 mg bd is expected to have greater platelet inhibition than clopidogrel, but unlike clopidogrel, ticagrelor does not require metabolic activation. As a result, ticagrelor may provide greater and more consistent inter-patient antiplatelet effect. PLATO demonstrated a 16% RRR of ticagrelor 90 mg bd versus clopidogrel in major adverse

cardiovascular events following ACS and a 21% RRR in cardiovascular mortality and a 22% RRR in all-cause mortality. Ticagrelor's benefits should translate to continued protection of patients with history of MI and risk factors for repeat cardiovascular events. The selection of cardiovascular death and all-cause mortality as secondary endpoints in this study allows further exploration of the effects of ticagrelor on mortality in patients with high cardiovascular risk.

1.4. Benefit/risk and ethical assessment

Current AHA/ACC/ESC guidelines recommend ASA doses between 75 – 162 mg daily long-term in patients following an MI. In the PLATO study ticagrelor 90 mg bd in combination with ASA was shown to reduce cardiovascular mortality in ACS patients and was shown to be effective therapy for the prevention of recurrent events for up to 1 year of treatment. Prolonged dual therapy, beyond 12 months, may offer additional benefit to patients with prior history of MI and high risk of developing atherothrombotic events. Ticagrelor 60 mg bd has not been directly tested before. However, based on pharmacodynamic modeling, is expected to achieve greater platelet inhibition than does clopidogrel. It is being studied to see if a lower dose of ticagrelor in this stable patient population might effectively reduce major cardiac endpoints with an improved safety profile. Having outcomes data for 2 doses of ticagrelor may allow tailoring of dosing to optimize the risk benefit ratio and may provide further guidance on the optimal use of ticagrelor in this setting.

Although dual antiplatelet therapy is likely to yield more bleeding events compared to ASA alone, it is hypothesized that benefit in reduction of major adverse cardiovascular events will outweigh the bleeding risk. As noted above, studying two different doses of ticagrelor may provide additional insights into the optimal dose in this setting.

Bleeding with dual antiplatelet therapy occurs more in the first months of therapy after a cardiovascular event and the patients in this study will be enrolled 1-3 years after having had their event. Patients with known increased risk of bleeding will not be enrolled in the study. Type and frequency of bleedings will be followed closely in the study.

More than 11,000 healthy subjects or patients have been exposed to ticagrelor in the completed phase I, II and III studies and the overall conclusion based on these studies is that ticagrelor has generally been well tolerated. Despite greater inhibition of platelet aggregation with ticagrelor, results from the PLATO study showed that PLATO Major bleeding with ticagrelor did not differ from that with clopidogrel. Adverse events observed in patients given ticagrelor, other than bleeding, include dyspnoea (a feeling of breathlessness), minimal increases in serum creatinine (difference of 1-2 μM or 0.01-0.02 mg/dL in mean creatinine values when comparing with clopidogrel treated patients), increases in serum uric acid concentrations, and ventricular pauses that were largely asymptomatic. None of these events is considered to pose a risk as they can be adequately handled in the clinical situation.

2. STUDY OBJECTIVES

2.1. Primary objective

The primary objective of the study is to compare the effect of long-term treatment with ticagrelor vs. placebo on a background of ASA on the event rate of the composite of cardiovascular death, non-fatal MI, or non-fatal stroke in patients with history of MI and high risk of developing atherothrombotic events.

The primary efficacy variable is time to first occurrence of any event after randomization from the composite of cardiovascular death, non-fatal MI, or non-fatal stroke.

2.2. Secondary objectives

The first secondary objective is to compare the effect of long-term treatment with ticagrelor vs. placebo on a background of ASA on the event rate of cardiovascular death in patients with history of MI and high risk of developing atherothrombotic events.

The efficacy variable is time to occurrence of cardiovascular death after randomization.

The second secondary objective is to compare the effect of long-term treatment with ticagrelor vs. placebo on a background of ASA on the event rate of all-cause mortality in patients with history of MI and high risk of developing atherothrombotic events.

The efficacy variable is time to occurrence of all-cause mortality after randomization.

Other objectives

To compare the effect of long-term treatment with ticagrelor vs. placebo on a background of ASA on the event rate of the composite of cardiovascular death, non-fatal MI, non-fatal stroke, or urgent coronary revascularization. The efficacy variable is time to first occurrence of any event after randomization from the composite of cardiovascular death, non-fatal MI, non-fatal stroke, or urgent coronary revascularization.

To compare the effect of long-term treatment with ticagrelor vs. placebo on a background of ASA on the event rate of the composite of cardiovascular death or coronary or cerebrovascular arterial thrombosis hospitalization (including non-fatal MI, non-fatal stroke, urgent coronary revascularization, unstable angina, or transient ischemia attack). The efficacy variable is time to first occurrence of any event after randomization from the composite of cardiovascular death or coronary or cerebrovascular arterial thrombosis hospitalization. The individual components will also be examined in an analogous manner.

To compare the effect of long-term treatment with ticagrelor vs. placebo on a background of ASA on the event rate of the composite of coronary heart disease death, non-fatal MI, or non-fatal stroke. The efficacy variable is time to first occurrence of any event after randomization from the composite of coronary heart disease death, non-fatal MI, or non-fatal stroke. The

individual component of coronary heart disease death will also be examined in an analogous manner.

To evaluate the net clinical benefit of long-term treatment with ticagrelor vs. placebo on a background of ASA. The variable is the time to first occurrence of any event after randomization from the composite of cardiovascular death, non-fatal MI, non-fatal stroke or TIMI major bleeding.

To compare the effect of the long-term treatment with ticagrelor vs. placebo on a background of ASA on the incidence of coronary stent thrombosis. The variable is the time to first occurrence of coronary stent thrombosis after randomization.

To collect health care utilization associated with hospitalizations and utilities assessed by Euro Quality of Life-5 Dimensions (EQ-5D) to support health technology assessment and health economic modelling.

2.3. Safety objective

Safety will be monitored closely throughout the study. All adverse events and serious adverse events (AE/SAEs) will be scrutinized and will be added to the earlier safety experience with the drug. The safety objective of this study is to assess the safety and tolerability of long-term therapy with ticagrelor compared to placebo on a background of ASA in patients with history of MI and high risk of developing atherothrombotic events. Bleeding events will be analyzed using the TIMI, PLATO, GUSTO and ISTH definitions. Specific focus will be on:

- Time to first TIMI major bleeding event following the first dose of study medication, as well as time to first TIMI major or minor bleeding event and time to first PLATO major bleeding event
- Time to discontinuation of study medication due to any bleeding event
- Evaluation of AEs

2.4. Exploratory Objective

Cardiovascular Biomarkers (See Appendix D):

- To evaluate the value of biomarkers for predicting ischemic/thrombotic and bleeding events.
- To evaluate whether patients indentified at higher risk on the basis of biomarkers experience a greater absolute and/or relative risk reduction in ischemic/thrombotic events with long-term treatment with ticagrelor vs. placebo.
- To evaluate the correlation between platelet inhibition and ischemic/thrombotic and bleeding outcomes.

- To evaluate whether treatment with ticagrelor reduces levels of biomarkers of inflammation, platelet activation, thrombosis, and endothelial dysfunction.

Pharmacogenetics (see Appendix E):

- The objective of this research is to collect and store DNA for exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to ticagrelor and other cardiovascular medications and/or susceptibility to and/or prognosis of cardiovascular, metabolic and related diseases.

Exposure of ticagrelor and AR-C124910XX

- Blood samples for determination of systemic exposure of ticagrelor and its active metabolite AR-C124910XX will be taken and stored. The samples will only be analyzed if needed for the interpretation of the study results.

- If samples are analyzed population pharmacokinetic (PK) analysis for ticagrelor and AR-C124910XX will be done in order to assess the effect of covariates on the PK and explore the relationship between steady-state exposure of ticagrelor and AR-C124910XX and efficacy and safety variables.

3. STUDY PLAN AND PROCEDURES

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

The study is event driven and the number of randomized patients is estimated to be required to collect 1360 primary events. The study will be running until all patients have been treated for a minimum of 12 months and the pre-estimated number of primary events has been reached. It is intended that all randomized patients will do the End-of-Treatment (EoT) Visit as the last visit on treatment with study medication. A Follow-up Visit off treatment should then be done 14 - 28 days after the EoT Visit. This Follow-up Visit will be the last visit in the study for most of the patients participating in the study.

All randomized patients who are attending study visits when the study is closed should return for the final visit as soon as possible but no later than 2 months after the time point when all patients have been treated for a minimum of 12 months and the pre-estimated number of primary events has been reached. The final visits will be the EoT and Follow-up Visits if the patient is on treatment with study medication at study closure.

For patients who prematurely and permanently discontinue treatment with study medication, it is intended that they will do the EoT at the time treatment is stopped and then a follow-up visit 14-28 days later, then continue attending subsequent study visits according to schedule until study closure, ie, when all patients have been treated for a minimum of 12 months and the pre-

estimated number of primary events has been reached. The final visit will then be done as described in the study plan for the next scheduled visit. Patients that are not attending scheduled visits at study closure will be contacted for assessment of health status or vital status as per agreement, ie, by telephone, by checking medical records or by collecting information from publicly available sources. It is recommended that all patients attend the final visit in person.

3.1. Overall study design and flow chart

Figure 1 Study Flow Chart

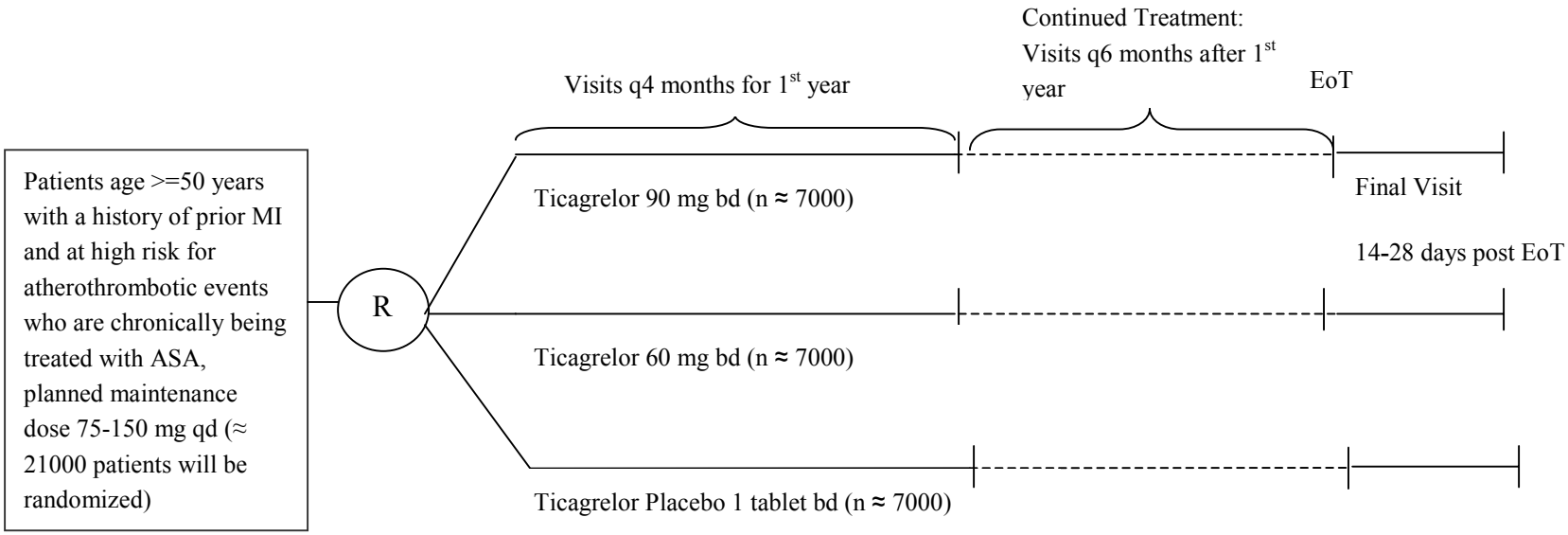


Table 1 Study Plan

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visits 6-9[b]	EoT Visit [c]	Follow-up Visit
Assessment	Enrollment ≤ 14 d prior to rando-mization	Randomization[a] (Day 0)	4 months ± 10d	8 months ±10d	12 months ±10d	18,24,30,36 months ±10d	≈38 months	14 – 28 days after EoT Visit
Signed Informed Consent	√							
Informed consent for genetic research [d]	√							
Inclusion & Exclusion criteria	√							
Relevant medical & surgical history	√							
Demographics	√							
Vital Signs	√						√	
Targeted Physical Examination	√						√	
EQ-5D	√			√	√	√	√	
12-Lead ECG	√[p]						√	
Clinical chemistry & Haematology [e]	√		√[f]	√[f]	√[f]	√[f]	√[g]	√[h]

	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visits 6-9[b]**	**EoT Visit [c]**	**Follow-up Visit**
Assessment	Enrollment ≤ 14 d prior to rando-mization	Randomization[a] (Day 0)	4 months ± 10d	8 months ±10d	12 months ±10d	18,24,30,36 months ±10d	≈38 months	14 – 28 days after EoT Visit
Biomarker sample [i]	√		√					
Genetics sample [j]	√							
PK Sampling [k]			√	√	√			
Serum & urine pregnancy test [l]	√							
Urinalysis	√				√			√
Dispense Study Medication		√	√	√	√	√		
Return Study Medication			√	√	√	√	√	
Compliance/drug accountability			√	√	√	√	√	
Current Medications	√		√	√	√	√	√	√
AEs, SAEs, and Endpoints	√[m]	√[n]	√	√	√	√	√	√

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visits 6-9[b]	EoT Visit [c]	Follow-up Visit
Assessment	Enrollment ≤ 14 d prior to rando-mization	Randomization[a] (Day 0)	4 months ± 10d	8 months ±10d	12 months ±10d	18,24,30,36 months ±10d	≈38 months	14 – 28 days after EoT Visit
Contact verification, retention risk assessment						*To be performed 3 months after each Study Visit after month 12 (eg 15, 21, 27, and 33 months) through study completion[o]		

a Randomization can be done immediately after enrollment or up to 14 days later
b If study continues >38 months, visits will continue every six months
c The study is event driven and number of visits will depend on when the pre-estimated number of primary events has been reached and all patients have been treated for a minimum of 12 months. This visit can occur before a study duration of ≈ 38 months if a randomized patient prematurely and permanently discontinues treatment, see section 3
d Only in participating countries, see appendix E for further details
e Laboratory samples will be analyzed at Central lab
f Serum creatinine only except annual visits (12, 24 and 36 months) which will also include haemoglobin. Only in patients on study drug.
g Analytes same as baseline (except serum ApoB and ApoA, see section 6.4.7)
h Serum creatinine and uric acid only
i Only in participating countries, see Appendix D for further details
j Only in participating countries, see Appendix E for further details. The genetic sample should be taken at visit 1 but can be taken at a later visit if necessary.
k Only in participating countries, see section 6.6 for further details
l Only in women of child-bearing potential, see section 4.1
m SAEs will be recorded from the time of informed consent.
n AEs and endpoints will be collected from time of randomization, see section 6.4.3 for details how to collect AEs in patients that have discontinued treatment.
o Contact verification can be through SMS services for patients who have consented to this form of contact. All patients who are not successfully contacted via SMS services or who have not agreed to SMS contact should be contacted by telephone to verify contact information and continued compliance with study procedures. See section 6.2.1

P A copy of an ECG that has been recorded within 30 days before enrollment can be used provided that the patient's health has remained stable in the timeframe between the ECG assessment and enrollment**.**

3.2. Rationale for study design, doses and control groups

This is a randomized, double blind parallel group endpoint driven study. Treatment duration of a minimum of 12 months has been selected with the goal of demonstrating long-term efficacy and safety. The risk of recurrent events following ACS is highest early but persists chronically so that long-term antiplatelet therapy is required (Wang et al 2007).

Ticagrelor 90 mg twice daily was selected as a dose to be tested in this study based on available data. The dose was well tolerated and showed high and consistent levels of inhibition of platelet aggregation (IPA) in Phase 2 studies with an acceptable safety profile. The phase III study (PLATO) showed a positive benefit risk balance. The 60 mg ticagrelor dose has never been directly tested before. It is predicted to show a positive benefit risk balance based on modeling of IPA response and clinical findings in Phase 2 studies. It is postulated that 60 mg bd will preserve much of the efficacy seen in the PLATO study. With regard to safety it is possible that 60 mg bd will improve the safety profile.

The control arm will receive placebo as currently there are no data to support use of P2Y12 receptor blockers for beyond 12 months after a myocardial infarction or percutaneous coronary intervention with stenting. Moreover, patients will not be enrolled in whom there is felt to be a clinical indication for dual antiplatelet therapy.

For situations where a patient already enrolled in the study develops an indication for use of an ADP receptor blocker according to medical guidelines (eg, acute coronary syndrome or percutaneous coronary intervention) they can get modified blinded study medication (ticagrelor or clopidogrel; see section 5.5.3) which will ensure that a patient will then be taking either ticagrelor + ASA or clopidogrel + ASA. Clopidogrel has been chosen because it is the ADP receptor blocker with the broadest indications and the most frequently used worldwide. This approach allows patients to receive optimal medical care while maintaining the integrity of the blind and allowing long-term safety experience with ticagrelor to be obtained.

Ticagrelor or placebo will be administered on a background of ASA therapy, since ASA is standard therapy for prevention of thrombotic events as recommended by ACC guidelines, and new therapies will be adjunctive. A once daily ASA dose of 75 –150 mg has been recommended since previous clinical studies (Antman et al 2004, Anderson et al 2007, Bassand et al 2007 and King et al 2008) have indicated that this daily dose range for ASA is adequate to protect against thrombotic events.

4. PATIENT SELECTION CRITERIA

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study.

4.1. Inclusion criteria

For inclusion in the study patients must fulfill the following criteria.

1. Men and women ≥50 years of age.

2. Documented history of presumed spontaneous MI (excluding known peri-procedural or definite secondary MI [eg, due to profound hypotension, hypertensive emergency, tachycardia, or profound anemia]) with their most recent MI occurring 1 to 3 years prior to randomization ***and*** have at least 1 of the following risk factors:

   - Age ≥65 years
   - Diabetes mellitus requiring medication
   - Documented history of a second prior presumed spontaneous MI (>1 year ago)
   - Documented history of angiographic evidence of multivessel coronary artery disease (CAD) (stenoses ≥50% in two major coronary artery territories [ie, left anterior descending, ramus intermedius, left circumflex, right coronary artery] involving the main vessel, a major branch, or a bypass graft)[1].
   - Chronic, non-end stage renal dysfunction (creatinine clearance calculated by Cockcroft Gault equation <60 mL/min)[2].

3. Patient currently prescribed and tolerating ASA, and able to be prescribed the protocol mandated dose of 75 - 150 mg once daily for the duration of the study.

4. Females of child-bearing potential (ie, who are not chemically or surgically sterilized or who are not post-menopause) must have a negative urine pregnancy test at enrollment (to be confirmed by blood pregnancy test at the central lab.) Females of child-bearing potential must be willing to use a medically accepted method of contraception that is considered reliable in the judgment of the investigator.

5. Written informed consent prior to any study specific procedures.

4.2. Exclusion criteria

Patients with any of the following conditions are excluded.

[1] Revascularized multivessel disease also qualifies for this inclusion criterion.
[2] Cockcroft - Gault equation for males (for females multiply by 0.85):
CrCL (mL/min) = [(140 – age) x weight (kg)] / [0.814 x serum creatinine (µmol/L)]
CrCL (mg/dL) =[(140 – age) x weight (kg)] / [72 x serum creatinine (mg/dL)]

1. Planned use of ADP receptor blockers (eg, clopidogrel, ticlopidine, prasugrel), dipyridamole, or cilostazol

2. Planned coronary, cerebrovascular, or peripheral arterial revascularization

3. Concomitant oral or intravenous therapy with strong cytochrome P450 3A (CYP3A) inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers 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

   - Substrates with narrow therapeutic index: cyclosporine, quinidine, simvastatin at doses >40 mg daily or lovastatin at doses >40 mg daily[3]

   - Strong inducers: rifampin/rifampicin, rifabutin, phenytoin, carbamazepine, phenobarbital

4. Need for chronic oral anticoagulant therapy or chronic low-molecular-weight heparin (at venous thrombosis treatment not prophylaxis doses)

5. Patients with known bleeding diathesis or coagulation disorder

6. Patients with:

   - A history of intracranial bleed at any time,

   - A central nervous system tumour or intracranial vascular abnormality (eg, aneurysm, arteriovenous malformation) at any time,

   - Intracranial or spinal cord surgery within 5 years, or

   - A gastrointestinal (GI) bleed within the past 6 months, or major surgery within 30 days

7. History of ischemic stroke at any time

8. Patients considered to be at risk of bradycardic events ([eg, known sick sinus syndrome or second or third degree atrioventricular (AV) block]) unless already treated with a permanent pacemaker

9. Coronary-artery bypass grafting in the past 5 years, unless the patient has experienced a spontaneous MI subsequent to the bypass surgery.

[3] (doses of simvastatin or lovastatin ≤40 mg daily or any dose of any other statin is **not** an exclusion)

10. Known severe liver disease (eg, ascites or signs of coagulopathy)

11. Renal failure requiring dialysis or anticipated need for dialysis during the course of the study

12. Pregnancy or lactation

13. Life expectancy < 1 year

14. Any condition which in the opinion of the Investigator would make it unsafe or unsuitable for the patient to participate in this study (eg, active malignancy other than squamous cell or basal cell skin cancer)

15. Concern for inability of the patient to comply with study procedures and/or follow up (eg, alcohol or drug abuse)

16. Participation in previous study with ticagrelor if treated with ticagrelor. Previous randomization in the present study

17. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

18. Participation in another clinical study with an investigational product during the preceding 30 days

Procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

Regarding exclusion criteria for the pharmacogenetic blood sampling (participation optional), see appendix E.

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 history of MI and high thrombotic risk.

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 enrollment and randomization

The Principal Investigator or delegate will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Determine patient eligibility. See Sections 4.1 and 4.2.

3. Assign eligible patient a unique enrollment number, beginning with "E#".

4. Assign enrolled patient unique randomization code (patient number).

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

5.2.1. Procedures for randomization

At Visit 2 (which can be performed immediately after enrollment or up to 14 days later), for patients who will fulfill all the eligibility requirements, the investigator will access the Interactive Voice Response System/ Interactive Web Response System (IVRS/IWRS). The IVRS/IWRS will allocate a randomization code and provide the investigator with unique treatment pack identification (ID) numbers for that patient for the Visit 2 supply of medication. Following randomization, the first dose of study medication will be administered to the patient as soon as possible.

The randomization codes will be computer generated by AstraZeneca R&D using GRand (AZ Global Randomization system) and loaded into the IVRS/IWRS database. A blocked randomization scheduled by site will be produced.

5.3. Procedures for handling patients incorrectly enrolled or randomized

If a patient does not meet the selection criteria but is randomized in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, a discussion should occur between the TIMI Hotline and the Investigator regarding whether to continue or discontinue the patient from treatment based on safety concerns.

The TIMI Hotline will ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have their study therapy stopped, but will continue with study assessments or telephone follow-up.

5.4. Blinding and procedures for unblinding the study

5.4.1. Methods for ensuring blinding

The treatment allocation in this study will be double-blind. The two tablets of ticagrelor (90 mg and 60 mg) to be administered in the study have different sizes. To ensure the blinding of the treatments, matching ticagrelor placebo tablets will be provided (ticagrelor 90 mg placebo and ticagrelor 60 mg placebo). Each treatment group is identical in appearance and has the same number, size, and packaging of tablets. Each pack will be labeled with a unique pack ID number that will be used to assign the treatment to the patient but will not indicate treatment allocation to the investigator or patient.

During the study if a patient has an event that requires ADP receptor blockade, the patient can receive modified study medication to ensure that they receive active ADP receptor blockade. This modification will include the addition of clopidogrel capsules that will either be placebo (in patients already allocated to active ticagrelor) or active (in patients already allocated to placebo ticagrelor). See section 5.5.3 for details. The allocation of modified study medication will be managed by the IVRS/IWRS to ensure study personnel are not unblinded. Each pack will be labeled with a unique pack ID number that will be used to assign the treatment to the patient but will not indicate treatment allocation to the investigator or patient.

5.4.2. Methods for unblinding the study

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the investigator(s) or pharmacists from the IVRS/IWRS. Directions for unblinding 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 randomization. The investigator should first contact the TIMI Hotline for consultation regarding the need for unblinding. If unblinding is deemed necessary, the investigator then should contact the IVRS/IWRS and must document all actions taken. The number of individuals at the study centre who become aware of treatment status should be kept to the absolute minimum (including keeping the patient blinded if possible). Treatment with study medication should also be continued if possible.

An unblinded person at AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to study medication and that potentially require expedited reporting to regulatory authorities. No information will be provided to the clinical team or the investigators of the trial. 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 study medication(s)

Table 2 Identity of investigational product

Study Medication	Dosage form and strength	Manufacturer	Formulation number
Ticagrelor 60 mg	Plain, round, white, film-coated tablet, 60 mg	AstraZeneca	FDN424
Ticagrelor 60 mg placebo	Plain, round, white, film-coated tablet, placebo to match 60 mg	AstraZeneca	FDN425
Ticagrelor 90 mg	Plain, round, yellow, film-coated tablet, 90 mg	AstraZeneca	FDN334

Ticagrelor 90 mg placebo	Plain, round, yellow, film-coated tablet, placebo to match 90 mg	AstraZeneca	FDN322

Table 3 Identity of secondary ADP receptor blockade

Study Medication	Dosage form and strength	Manufacturer	Formulation number
Clopidogrel	Orange brown capsule, containing one 75 mg clopidogrel tablet (cut into 2 halves)	AstraZeneca	FDN242
Clopidogrel 75 mg placebo	Orange brown capsule, containing placebo to match 75 mg tablet	AstraZeneca	FDN359

5.5.2. Doses and treatment regimens

At Visit 2 (Randomization) eligible patients will be randomly assigned to 1 of 3 treatment groups: ticagrelor 90 mg twice daily, ticagrelor 60 mg twice daily, or placebo twice daily. The two ticagrelor tablets to be administered in the study have different sizes. All patients will therefore need to take two tablets twice daily to guarantee the blinding: (1) ticagrelor 90 mg and ticagrelor 60 mg placebo, (2) ticagrelor 90 mg placebo and ticagrelor 60 mg, or (3) ticagrelor 90 mg placebo and ticagrelor 60 mg placebo.

Randomization and treatment pack assignment will be managed via the IVRS/IWRS and the first dose of study medication should be taken as soon as possible at Visit 2. Subsequent maintenance doses should be taken morning and evening, at approximately 12-hourly intervals, for the remainder of the treatment period.

Study medication should be swallowed whole with water. 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.

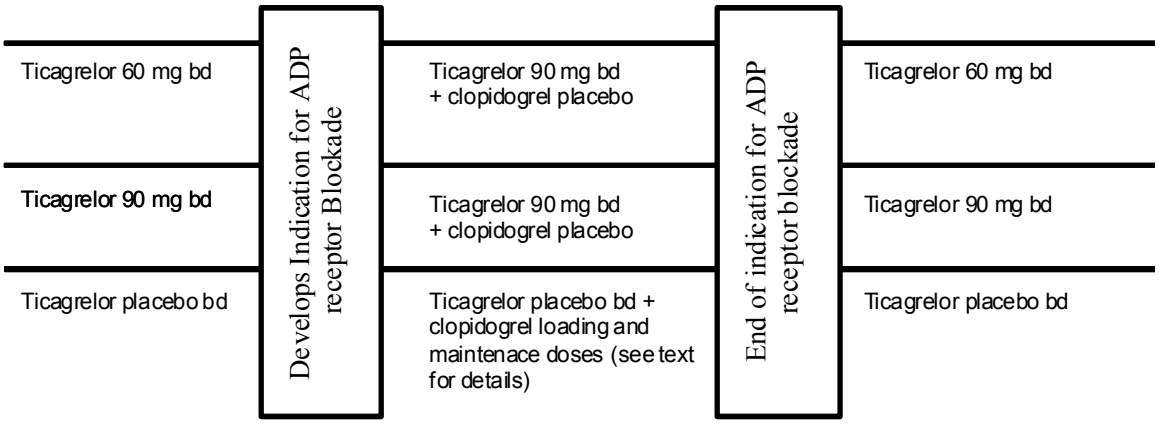
5.5.3. Modified dosing if patient develops an indication for ADP receptor blockade

If a patient already enrolled in the study develops an indication for use of an ADP receptor blocker according to medical guidelines (eg, an acute coronary syndrome or percutaneous coronary intervention), selection of the appropriate agent for individual patients is at the discretion of the local investigator and should be made in accordance with local medical guidelines and standard of care.

If clopidogrel is determined to be suitable then it is recommended that the patient receive ADP receptor blockade therapy using new blinded study medication via the IVRS/IWRS system (replacing their existing study medication). In this case, for patients who were randomized to

the two ticagrelor arms, the study medication will now be: ticagrelor 90 mg and clopidogrel placebo (ie, all patients randomized to ticagrelor will now be receiving ticagrelor 90 mg bd, consistent with the treatment studied in the PLATO trial). For patients who were randomized to placebo, study medication will now be ticagrelor placebo and clopidogrel 75 mg. Patients will take 1 tablet of ticagrelor study medication twice daily and 1 capsule of clopidogrel study medication once daily; patients will also continue to take their ASA (doses greater than 75-150 mg once daily may be used at the discretion of the investigator). Thus, after starting this new study medication a patient will then effectively be taking either ticagrelor 90 mg bid + ASA or clopidogrel 75 mg daily + ASA.

Figure 2 **Treatment in case of an event with indication for dual antiplatelet therapy with ADP receptor blocker**



For recommendations when loading doses and extra doses of ticagrelor/ticagrelor placebo can be administered in case of an event, see below.

For patients in whom a loading dose of ADP receptor blockade is desired (eg, ACS or undergoing PCI), one additional tablet of ticagrelor study medication (ie, 90 mg of ticagrelor) and either 4 capsules (ie, 300 mg) or 8 capsules (ie, 600 mg) of clopidogrel study medication can be taken.

If so desired by the investigator, patients may take 2 capsules of clopidogrel study medication (ie, 150 mg daily) for the first week.

If a patient has an urgent requirement for ADP receptor blockade before modified study medication can be dispensed, patients should be treated with open-label ADP receptor blockade (see section 5.6.1.) and temporarily stop study medication. It is recommended that they should then be switched from open-label ADP receptor blockade to modified study medication as soon as possible.

Alternatively, if the investigator chooses to treat a patient with prasugrel, it may be prescribed as open-label therapy (see section 5.6.1) and the patient must temporarily stop study medication. Once treatment with open-label prasugrel is discontinued, patients may resume

study medication (either ticagrelor/placebo or ticagrelor/clopidogrel at the discretion of the investigator).

When there is no longer an indication for ADP receptor blockade according to medical guidelines, patients should return to randomized treatment and ASA.

Duration of treatment

All patients will be followed a minimum of 12 months and up to approximately 38 months. If, however, the number of primary events is not achieved when the last patient has been followed for 12 months, the treatment period may be extended. The expected median duration is 26 months. A study closure plan will be developed to take into account the patient recruitment pattern and number of outcome events experienced (target: 1360). It is intended that all randomized patients, including patients who discontinue from treatment or study prematurely, will do the EoT Visit followed by a Follow-up Visit off treatment after 2-4 weeks. The study may be terminated early if either a clear beneficial or harmful effect of the study treatment is detected during the IDMC review. It is recommended that patients who have discontinued from treatment and are being followed by telephone or a contact at study closure attend the final visit in the study in person.

5.5.4. Interruptions to study medication

Missed doses of ticagrelor or placebo blinded study medication should not be made up (ie, if a dose is missed the next regularly scheduled dose should be taken and should not be doubled).

An exception to this approach is if a patient has been off study medication and then has an acute coronary syndrome or needs to undergo urgent percutaneous coronary intervention. In this case, patients should be dispensed modified study medication as outlined in section 5.5.3 and take loading doses as also outlined above.

All planned prescribed stops and unplanned non-prescribed temporary stops (>48 hours) should be recorded in the eCRF.

5.5.5. Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local language.

5.5.6. Storage

All study medications should be kept in a secure place under appropriate storage conditions. The study medication label on the study supplies and the Investigator Brochure specifies the appropriate storage (excursions permitted between 15C° and 30C°).

5.6. Concomitant and post-study treatment(s)

Recording of current prescription medications will be made at each visit. All individual medications, prescription and over-the-counter, will be recorded peri-event for any SAE, discontinuation due to AE, or suspected clinical endpoint event.

5.6.1. Oral antiplatelet therapies

ASA: All patients should take open label ASA at a dose of 75 – 150 mg once daily throughout the study. The patient will be responsible for the ASA supply throughout the study. The ASA dose should remain constant throughout the study. However, temporary use of higher doses (>150 mg daily) is allowed in the event that a patient develops a medical indication (e.g. ACS or PCI) for the duration of that indication, with subsequent reduction to a dose between 75-150 mg once daily. ASA for pain relief should, when possible, be discouraged and paracetamol (acetaminophen) given.

ADP receptor blockers (eg, clopidogrel, prasugrel, ticlopidine), dipyridamole, and cilostazol: Concomitant treatment with any of these drugs is not allowed in the study. For situations where a patient already enrolled in the study develops an indication for use of an ADP receptor blocker according to medical guidelines (eg, acute coronary syndrome or percutaneous coronary intervention), see section 5.5.3. If open label treatment with any of these drugs is considered essential during the study, study medication must be discontinued but should be resumed when open label treatment with these drugs is stopped.

5.6.2. Non Steroidal Anti-Inflammatory Drugs (NSAIDs)

Clinical experience with NSAIDS in combination with ticagrelor is limited at this time. Treatment with NSAIDS is allowed during the study at the investigator's discretion. However, chronic daily dosing with non-selective NSAIDS (eg, patients with rheumatoid arthritis) may increase the potential for GI bleeding so either alternative therapy or concomitant acid suppression therapy is recommended. Treatment with selective cycloxygenase-2 inhibitors is permitted, although use is cautioned (Antman et al 2007).

5.6.3. Parenteral anticoagulants

Short-term (< 1 week) 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.

5.6.4. GPIIb/IIIa receptor antagonists

Treatment with GPIIb/IIIa receptor antagonists is allowed during the study.

5.6.5. Oral anticoagulants

Concomitant treatment with oral anticoagulant drugs is not permitted during the study. If treatment with oral anticoagulant drugs is considered essential during the study, study medication must be discontinued, but may be resumed if anticoagulant therapy is stopped.

5.6.6. Fibrinolytics

Clinical experience with fibrinolytics in combination with ticagrelor is limited and caution should be used. If a patient is to be treated with fibrinolytic therapy, study medication should be stopped and restarted no earlier than 24 hours after completion of fibrinolytic therapy and when the risk of bleeding is deemed low in the judgment of the investigator.

5.6.7. P-glycoprotein interactions

Ticagrelor is a weak inhibitor of P-glycoprotein (P-gp), a drug efflux transporter. Digoxin is a substrate of P-gp and concurrent treatment with ticagrelor modestly increases digoxin levels. Therefore digoxin levels should be monitored closely following initiation of study medication and with any change in study medication.

5.6.8. CYP450 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 co-administered 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

Concomitant therapy with simvastatin or lovastatin at doses higher than 40 mg daily is not permitted. There are no restrictions to other statin therapies (ie, doses of simvastatin or lovastatin $\leq$ 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) should be avoided. If treatment with such therapies is necessary, study medication dosing should be interrupted and then resumed if possible when administration of the drug that is a CYP3A substrate with a narrow therapeutic index is no longer required.

5.6.8.3. CYP3A inducers

Co-administration of ticagrelor with strong inducers of CYP3A also should be avoided (eg, rifampin/rifampicin, rifabutin, phenytoin, carbamazepine, phenobarbital): however, if treatment with a strong inducer is necessary during the study period, the study medication may be continued.

5.6.8.4. CYP2C19 inhibitors

Ticagrelor is not metabolized via CYP2C19. In contrast, clopidogrel is a prodrug that needs to be metabolized to its active metabolite in part by CYP2C19. Concomitant use of drugs that inhibit the activity of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. Thus, for patients who are being treated with modified study medication (see section 5.5.3), which could include clopidogrel, or open-label clopidogrel, it is recommended to avoid concomitant use of drugs that inhibit CYP2C19, according to the clopidogrel label.

5.6.9. Surgery and other invasive non-cardiovascular procedures

It is recommended that elective major surgery (ie, surgery that in the opinion of the Investigator poses a risk for clinically major bleeding, which typically includes cardiothoracic, abdominal, pelvic, spinal, and cranial surgery) not be performed until more than 5 days after stopping study medication to avoid excessive bleeding. There is a trade-off between stopping study medication too early and risking thrombotic events versus continuing treatment too close to surgery and risking haemorrhage. Thus it is also recommended that study medication not be discontinued for significantly longer than 5 days so as to minimize the risk of thrombotic complications while off study medication.

For elective minor surgery or other invasive procedures, study medication may be continued or interrupted temporarily at the discretion of the investigator.

For urgent major surgery that needs to be performed within 5 days, it should be noted that the effect on platelet function caused by ticagrelor will have largely dissipated in most individuals by approximately 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.

Patients taking modified study medication (see section 5.5.3) may also be receiving clopidogrel 75 mg daily, which is recommended to be stopped 5-7 days prior to surgery.

After surgery, study medications should be restarted when the risk of bleeding is deemed low in the judgment of the investigator.

5.7. Treatment compliance

The administration of all medication (including study medications) should be recorded in the appropriate sections of the electronic Case Report Form (eCRF).

Patients will be asked to return all unused study medications and empty packages to the clinic at each visit. The patient's compliance will be assessed by the investigator and recorded in the

eCRF. A pill count should be done at a patient level and recorded in the eCRF and a dispensing log by the study site personnel.

5.7.1. Accountability

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

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

Patients will be asked to return all unused study medication to the investigational centre at each visit. The investigator or delegate will enter the amount of returned tablets on the eCRF and make an assessment regarding patient treatment compliance. In addition, the investigator or delegate will enter the amount of returned tablets on the dispensing log or similar log according to local practice at site. Any patient found to be non compliant will be counseled on the importance of taking their investigational product as prescribed.

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

The investigator will retain the returned medication until the trial monitor or delegate collects it, along with any medication not dispensed. The monitor is responsible for checking the quantities of returned and unused tablets at a patient level before medication is returned to the sponsor and/or destroyed. Following drug accountability, the trial monitor or delegate will advise on the appropriate method for destruction of unused study medication. Destruction of study medication must only be conducted by an authorized site.

Certificates of delivery and return must be signed.

5.8. Discontinuation of Study Medication

Patients should be discontinued from study medication in the following situations:

5.8.1. Temporary discontinuation from Study Medication

- Severe thrombocytopenia (platelet count <50,000/uL). Patients may restart study medication once the severe thrombocytopenia resolves.
- Major surgery, see 5.6.9 (NB, For elective minor surgery or other invasive procedures, study medication may be continued or interrupted temporarily at the discretion of the investigator, see 5.6.9)
- Major bleeding, see 6.4.6.2
- Development of a reversible bleeding diathesis or coagulation disorder

- Need of treatment with prohibited concomitant medications, see 5.6
- Development of significant conduction system disease (eg sick sinus syndrome or second or third degree atrioventricular (AV) block) until treated with a pacemaker
- Severe hepatic impairment

5.8.2. Permanent discontinuation from Study Medication

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Investigator's decision:

1. Incorrectly enrolled patient in whom the inclusion/exclusion criteria violation would put the patient at undue risk
2. Development of a condition during the study that would subject the patient to undue risk:
    - Ischemic stroke or intracranial bleeding of any kind; intracranial or spinal cord surgery; discovery of a central nervous system tumour or intracranial vascular abnormality (eg, aneurysm, arteriovenous malformation)
    - Development of chronic bleeding diathesis or coagulation disorder
    - Renal failure requiring dialysis
    - Pregnancy
    - Development of significant conduction system disease (eg sick sinus syndrome or second or third degree atrioventricular (AV) block) not treated with a permanent pacemaker
3. Adverse Event felt to be related to the study medication for which the Investigator feels continued treatment would put the patient at undue risk
4. Severe non-compliance to study protocol

All such decisions should be made in consultation with the TIMI Hotline.

Discontinuation of study medication does not mean discontinuation of follow-up. Study assessments or telephone follow-up should be continued in all cases.

5.8.3. Procedures for discontinuation of a patient from study medication

If the patient is permanently discontinued from study medication, the patient should do the End of Treatment Visit and Follow-up Visit off treatment (2-4 weeks after discontinuation)

and then the regularly scheduled study visits (every 4 to 6 months). Data collection and procedures should continue according to the study protocol (with the exception of clinical chemistry & haematology blood draws, which are not required for patients off study drug) until study closure. If the patient does not agree to this option (which must be documented), a modified follow-up (eg, regular telephone contacts or a contact at study closure) should be arranged, if agreed to by the patient and in compliance with local data privacy laws/practices. It is recommended that anyone being followed by regular telephone contacts or a contact at study closure attend the final visit in person. The approach taken should be registered in the eCRF, medical records and ICF.

A patient that decides to discontinue study medication 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); devices for patient reported outcomes and study medication should be returned by the patient.

5.8.4. End of Treatment

At the End of Treatment visit physicians caring for the patient will decide which antiplatelet medication the patient should receive as part of his/her ongoing clinical care. This medication(s) will be open label and obtained locally.

5.9. Withdrawal from study (withdrawal of consent)

Patients are at any time free to withdraw from study (study medication and assessments), without prejudice to further treatment. Withdrawal of consent must be ascertained and documented by the Investigator who must inform the TIMI Hotline and document the withdrawal of consent in the eCRF as well as in the ICF and medical records. The ICF should be resigned 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.

At the time of withdrawal, patients should, if possible do the End of Treatment visit. The patient should return study medication. To ensure validity of study data, it is very important to collect as much data as possible throughout the study and especially vital status (dead or alive) at study closure. AstraZeneca or delegate will therefore attempt to collect information on all patients' vital status from publicly available sources at study closure, even if informed consent has been withdrawn completely.

For information about medical treatment after end of treatment with study medication, see 5.8.4.

6. COLLECTION OF STUDY VARIABLES

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

6.1. Recording of data

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. Data will be entered in the eCRF using a Web Based Data Capture (WBDC) system at the study site. 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 AZ 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 enrollment

Each patient will undergo enrollment procedures during Visit 1. The following data will be collected in the eCRF:

- Demographics (including sex, date of birth, race, ethnic group)
- Relevant medical and surgical history
- Safety laboratory blood and urinalysis (clinical chemistry, haematology and dipstick testing for proteinuria and hematuria)
- Serum pregnancy test (for females of child bearing potential)
- Current concomitant medications (within 7 days of enrollment)
- Targeted physical examination including vital signs (supine heart rate and BP), weight and height, and hip & waist circumference
- 12-lead ECG (A copy of an ECG that has been recorded within 30 days before enrollment can be used provided that the patient's health has remained stable in the timeframe between the ECG assessment and enrollment)
- Biomarker and Genetic Samples, if applicable

6.2.1. Follow-up procedures

Patients will have routine Follow-up Visits and procedures as outlined in section 3.1. Any new suspected endpoint events, AEs, SAEs and current medications will be recorded in the eCRF. It will be the responsibility of the Investigator to obtain all necessary source documents.

In addition to the follow-up study visits, patients will be monitored for contact information verification and undergo retention risk assessment. These assessment will be performed 3 months after each Study Visit after month 12 (eg, 15, 21, 27, and 33 months) through study completion. Contact verification can be through SMS services for patients who have consented to this form of contact. All patients who are not successfully contacted via SMS

services or who have not agreed to SMS contact should be contacted by telephone to verify contact information and continued compliance with study procedures.

If the patient experiences a suspected clinical efficacy endpoint event or a bleeding event, the following actions should be taken whenever possible and in accordance with local practice:

Symptoms of cardiac ischemia (ie, potentially representing unstable angina or myocardial infarction):

- Cardiac biomarkers of necrosis (troponin and/or CK-MB) should be measured locally serially according to local standards 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 serially according to local standards until resolution of symptoms.

Coronary Revascularization (ie, percuatenous coronary intervention or coronary-artery-bypass grafting):

- Cardiac biomarkers of necrosis (troponin and/or CK-MB) should be measured locally immediately before the procedure and serially after the procedure according to local standards.
- A standard 12-lead electrocardiogram should be obtained before the procedure, immediately post-procedure, and, if possible, 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.

Focal neurological symptoms (ie, potentially representing stroke or transient ischemic attack):

- Complete neurologic exam.
- Brain imaging [computed tomography (CT) or magnetic resonance imaging (MRI)].
- Assessment using modified Rankin scale at time of discharge and at 30 days.

Bleeding (either unexpected or of unanticipated quantity):

- Record 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.
- Record the date, time and number of packed red blood cell or whole blood transfusions.

The patient will have a visit off treatment approximately 2-4 weeks after the End of Treatment visit. For patients who complete the scheduled study treatment this visit will be at the end of the study. For patients who discontinue study treatment prematurely the scheduled visit plan should be followed after the Follow-up Visit until the study is closed. The patients should follow all planned study assessments with the exception of clinical chemistry & haematology blood draws, which are not required for patients off study drug. It is recommended that patients who have discontinued from treatment and are being followed by telephone or a contact at study closure attend the final visit in the study in person.

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. Safety endpoint events will be identified similarly.

For each suspected 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 Reporting Manual for Investigators. The Endpoint Package will be sent to the Clinical Endpoints Committee (CEC) for central adjudication. The investigator should use the following definitions in assessing possible endpoint events. Additional details about the evaluations of endpoint events will be contained in the CEC charter.

6.3.1. Death

All deaths reported post-enrollment will be recorded and adjudicated.

Deaths will be sub-classified by cardiovascular and non-cardiovascular primary cause. Cardiovascular death includes sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to a cerebrovascular event, death due to other cardiovascular causes (eg, pulmonary embolism, aortic disease, cardiovascular intervention), and deaths for which there was no clearly documented non-cardiovascular cause (presumed CV death).

Additionally, deaths will be sub-classified by coronary heart diseases death (CHD death) and non-CHD death. CHD death includes Sudden Cardiac Death, Death due to Acute MI, and the subset of Death due to other Cardiovascular Causes that are secondary to a coronary revascularization procedure.

6.3.2. Definition of Myocardial Infarction

MI is diagnosed based on the Universal MI definition (Thygesen K et al 2007):

- For a spontaneous MI, detection of rise and/or fall of cardiac biomarkers, preferably troponin, with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

  - Symptoms of myocardial ischemia
  - ECG changes (ST segment, T waves, or new left bundle branch block) indicative of new ischemia
  - Development of pathologic Q waves on the ECG
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

- Sudden unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

- PCI-related MI: Elevation of cardiac biomarkers >3x 99th percentile of the URL within 48 hours after PCI.

- CABG-related MI: Elevation of cardiac biomarkers >5x 99th percentile of the URL within 72 hours after CABG, plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary occlusion, or imaging evidence of loss of viable myocardium.

- Silent MI based on ECG or imaging findings.

- Pathological findings of an acute MI not otherwise meeting above definitions.

6.3.3. Definition of Stroke

Stroke is defined as an acute episode of neurologic dysfunction attributed to a central nervous system vascular cause. Stroke should be documented by imaging (eg, CT scan or magnetic resonance imaging [MRI] scan). Evidence obtained from autopsy can also confirm the diagnosis. Stroke will be sub classified, when possible, as either:

<u>Primary ischaemic stroke</u>
Primary ischaemic stroke is defined as an acute episode of focal brain, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue and documented by imaging. A primary ischemic stroke may also undergo hemorrhagic transformation (i.e., no evidence of hemorrhage on an initial imaging study, but appearance on a subsequent scan).

<u>Primary haemorrhagic stroke</u>
Primary haemorrhagic stroke is defined as an acute episode of focal or global brain, spinal, or retinal dysfunction caused by non-traumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage as documented by neuroimaging or autopsy. Microhemorrhages (<10 mm) evident only on MRI are not considered to be a hemorrhagic stroke. Subdural and epidural bleeding will be considered intracranial hemorrhage, but not strokes.

A stroke with unknown aetiology will be classified as an unclassified stroke if the type of stroke could not be determined by imaging or other means.

6.3.4. Definition of Urgent Coronary Revascularization

The diagnosis of urgent coronary revascularization requires both of the two following criteria are met:

1. Ischemic chest pain (or equivalent) at rest ≥10 minutes in duration or repeated episodes at rest lasting ≥5 minutes considered to be myocardial ischemia upon final diagnosis, and

2. Prompting hospitalization and percutaneous coronary revascularization within 7 days of the symptoms or surgical coronary revascularization within 14 days of symptoms.

6.3.5. Definition of Unstable Angina

The diagnosis of unstable angina will require ischemic chest pain (or equivalent) at rest ≥10 minutes in duration considered to be myocardial ischemia upon final diagnosis *and* prompting hospitalization within 24 hours of the most recent symptoms, *and* without elevation in cardiac biomarkers of necrosis, *and* the presence of objective evidence of ischemia as defined by at least 1 of the following criteria:

1. New or worsening ST or T wave changes in ≥2 anatomically contiguous leads on a resting ECG (in the absence of LVH and LBBB):
   a) transient (<20 minutes) ST elevation at the J point ≥ 0.2 mV in men (> 0.25 mV in men < 40 years old) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads, or
   b) horizontal or down-sloping ST depression ≥ 0.10 mV, or
   c) T-wave inversion ≥ 0.2 mV

2. Definite evidence of myocardial ischemia on myocardial scintigraphy (clear reversible perfusion defect), stress echocardiography (reversible wall motion abnormality), or MRI (myocardial perfusion deficit under pharmacologic stress) that is believed to be responsible for the myocardial ischemic symptoms/signs.

3. Angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs.

6.3.6. Definition of Transient Ischaemic Attack

TIA is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction (Easton et al 2009). Patients are required to be hospitalized within 48 hours of their most recent neurologic symptoms.

6.3.7. Definition of Stent Thrombosis

Stent thrombosis will be classified as per the Academic Research Consortium Definition (Mauri et al 2007).

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. See section 6.4.5 for details on reporting of serious adverse events that are also endpoints in the study.

6.4.1. Definition of adverse events

An adverse event 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.

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 fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

For reporting purposes, any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and is reported in an expedited manner. Any organism, virus or infectious particle (for example prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

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

Adverse Events will be collected from time of Randomization throughout the treatment period and including the follow-up period.

SAEs will be recorded from the time of informed consent.

SAEs will be recorded at all visits in patients who prematurely discontinue treatment with IP. AEs will in these patients be recorded until the first scheduled visit after the Follow-up Visit off treatment.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last visit in the study 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 collect for each **AE:**

- AE (verbatim)
- the date 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 Study Medication (yes or no)
- action taken with regard to study medication
- 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
- Date of hospitalization

- 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
- Date and time of last dose of study drug before AE

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.

The following definitions for intensity rating are:

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

Causality collection

The Investigator will assess causal relationship between Study Medication 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 study medication?”

Causal relationship in cases where the disease under study has deteriorated due to lack of effect will be classified as no reasonable possibility.

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 eCRF. 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 summarized 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 fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the study medication.

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).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

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.

6.4.4. Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the study medication, or to the study procedure(s). All SAEs will be recorded in the eCRF.

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 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 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 AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

6.4.5. Reporting of serious adverse events that are also endpoints in the study

Non-fatal components of the primary efficacy endpoint in the study (ie, non-fatal MI and non-fatal stroke) will not be reported to health authorities as SAEs to avoid unnecessary unblinding of efficacy endpoints that are also SAEs. Clinical data for suspected endpoints will be collected as AEs/SAEs as well as on separate event forms in the eCRF to support central adjudication. The initial notification of a suspected efficacy endpoint should be sent within the same time frames as defined for SAEs, see above. All other events, with the exception of procedural related bleeding if expected for the procedure, will be reported as AE/SAEs.

In addition to the normal monitoring of the study, an IDMC will review all endpoint data and all other AEs/SAEs. Information will be sent to the executive committee and regulatory authorities if the IDMC expresses safety concerns that suggest that study conduct should be amended.

6.4.6. Bleeding assessments

For all bleeding events that are unexpected or of unanticipated quantity, the investigator will complete information on the eCRF specific to that bleeding event. In addition, for all reported bleeding events (excluding those which are self-limited and do not prompt medical evaluation or intervention) 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 CEC for central adjudication.

The CEC will adjudicate and evaluate bleeding events (excluding minimal) according to the following bleeding definitions: TIMI, PLATO, GUSTO, and ISTH. Additional details can be found in the CEC Charter.

6.4.6.1. Bleeding associated with procedures

Bleeding associated with procedures should **only** be reported as a bleeding event and AE/SAE if it exceeds what can be expected for the procedure.

6.4.6.2. Procedures for Study Medication in case of bleeding

Study medication must be stopped immediately in case of a bleed deemed to be clinically significant in the judgment of the investigator (eg, a significant fall in hemoglobin, need for transfusion, hemodynamically significant, or in a critical location such as intracranial, intraspinal, intraocular, or pericardial). In the case of any intracranial bleeding then the study drug should be stopped permanently, otherwise the study drug, may be reinstated when the risk of bleeding is deemed low in the judgment of the Investigator. 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. Major bleeding events should be managed according to need with general support and blood. It should be noted that platelet transfusion is unlikely to reverse bleeding in a patient receiving ticagrelor as the new platelets are likely to be inhibited by ticagrelor as long as it is 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.

6.4.7. Laboratory safety assessment

The following laboratory variables will be analyzed at the central laboratory for all patients:

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)
(Elevated values to be fractionated)	B-Haemoglobin A1c (only diabetics)
S-Uric acid	
S-glucose	
S-pregnancy test (females of child bearing potential only at visit 1)	
S-ApoB & ApoA (to be taken only at visit 1)	

Proteinuria and hematuria measured with urine dipstick.

A urine pregnancy test will be performed at the investigational site during the enrollment visit for all females of child-bearing potential.

Follow-up testing for abnormal laboratory results should be performed using the central laboratory according to instructions on the laboratory reports from the central laboratory or according to local practice.

Details of all blood variable units will be found in the Laboratory Manual.

For blood volume see Section 7.

No safety laboratory samples should be taken in patients who prematurely discontinue treatment with IP that are attending planned study visits scheduled after the Follow-up Visit off treatment.

6.4.8. Physical examination

A targeted physical examination will be performed by medically qualified individuals and include an assessment of the following: lungs, cardiovascular, and neurological evaluations. Results will be recorded as an overall normal or abnormal with a listing of abnormalities.

6.4.9. ECG

ECG should be performed according to local clinical practice to document any occurrences of MI or recurrent cardiac ischaemia during the study, see 6.2.1 for further details.

6.4.9.1. Resting 12-lead ECG

Standard 12-lead ECGs will be recorded and assessed locally.

ECGs should be standard 12-lead ECG with a lead II rhythm strip, covering at least 5 complexes in the supine position after the patient has rested in this position for 5 minutes.

6.4.10. Vital signs

6.4.10.1. Heart Rate and blood pressure

Heart rate, systolic BP and diastolic BP will be assessed using non-invasive equipment after the patient has been at rest for 5 minutes.

6.5. Patient reported outcomes (PRO)

Patients will be asked to complete the EQ-5D quality of life questionnaire at Visits 1, 4, 5 and EOT. For patients continuing in the study after visit 5 the EQ-5D will be administered every 6 months until the EoT Visit. The EQ-5D will only be administered in countries where an official language version is available. Descriptive analysis and reporting of the data will be carried out in the Clinical Study Report (CSR).

6.6. Pharmacokinetics

A blood sample for determination of ticagrelor and its active metabolite AR-C124910XX in plasma will be collected at Visit 3 (4 months), Visit 4 (8 months) and Visit 5 (12 months) in approximately 7500 patients.

Instructions for collection, labelling, storage and shipment of samples are provided in the Laboratory Manual. The date and time of sample collection will be recorded in the eCRF as well as the date and time of last intake of study medication.

6.6.1. Drug concentration measurements, and derivation or calculation of pharmacokinetic parameters

A decision will be taken at the end of the study if the PK samples will be analyzed or not. If samples are analyzed population pharmacokinetic (PK) analysis for ticagrelor and AR-C124910XX will be done in order to assess the effect of covariates on the PK and explore the relationship between steady-state exposure of ticagrelor and AR-C124910XX and efficacy and safety variables.

6.7. Pharmacodynamics (Not Applicable)

6.8. Pharmacogenetics

Pharmacogenetics (PGx) to be explored, see Appendix E.

6.9. Health economics

Information on hospitalizations admissions as well as health related quality of life (EQ-5D) will be collected to enable Health Technology Assessment, health economic analysis, and health economic modelling. Reason for hospitalization and length of stay for all hospitalizations occurring during the study period will be recorded. Within the scope of the health economic analysis, each hospitalization will be assigned a diagnosis-related group (DRG) based on the information collected.

The variables collected to support health economic evaluation are EQ-5D Questionnaire at baseline, at 8 months, 12 months, 18 months, every 6 months thereafter, and at the end of treatment visit as well as information on all hospitalization, during the course of the study. Descriptive reporting of the hospitalization data and EQ-5D data will be carried out in the CSR. The hospitalization data and utility data based on the EQ-5D will be combined with economic data and life expectancy data collected independently of the study to construct comparative health economic analyses between treatment groups. This analysis will be reported separate from the main study report.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1. Volume of blood

The maximum total volume of blood that will be drawn from a patient during 38 months treatment (including the Follow-up Visit off drug) in this study is as follows:

Table 4 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Baseline	Clinical chemistry	5	1	5
	Haematology	3	1	3
Safety	Clinical chemistry[a]	5	9	45
	Haematology	2	4	8
Total			15	61[b]

[a] Samples will be collected every 4 months within the first 12 months and every 6 months beyond the first 12 months.

[b] Biomarker sub study is an additional up to approximately 35 mL, the Genetic Sub study is an additional approximately 10 mL and the Pharmacokinetic study is an additional approximately 6 mL.

7.2. Handling, storage and destruction of biological samples

The safety samples will be used up or disposed of after analyses. Samples taken for analysis of genetics and biomarkers will be stored for up to 20 years and then destroyed.

7.3. Labeling and shipment of biohazard samples

The Principal Investigator ensures that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labeling, shipment and containment provisions are approved.

7.4. Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system or that of a contracted third-party during the entire life cycle.

7.5. Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an optional part of the study, an enrolled patient may withdraw consent for the use of biological samples, but still continue with further study treatment.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca.
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented.
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site.
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

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. The investigator will ensure the distribution of these documents to the applicable Ethics Committee, and 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 enrollment of any patient into the study.

The Ethics Committee should approve all advertising used to recruit patients for 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 enrollment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, 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.

Each Principal Investigator is responsible for providing the Ethics Committees/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the study medication. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

8.4. Informed consent

The Principal Investigator(s) at each centre 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 and allowed time to consider the information provided.
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File.

- Ensure a copy of the signed Informed Consent Form is given to the patient.

- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

8.5. Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the 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 should be approved by each Ethics Committee and if applicable, also the national regulatory authority, before implementation. Local requirements should 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 center's Informed Consent Form, AstraZeneca and the center's Ethics Committee should 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

Authorized 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, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (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 may be necessary for a representative of AstraZeneca to visit 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.

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 and also train them in any study specific procedures and the WBDC system(s) utilized.

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, that biological samples are handled in accordance with the Laboratory Manual and that study medication 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 or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts).
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

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 for location of source data.

9.4. Study agreements

The Principal Investigator at each/the 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 enrolled.

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 entire study is defined as “the last visit of the last patient undergoing the trial”.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. The Executive Committee may terminate enrolment in a country in order to ensure a reasonable international distribution of patients. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with ticagrelor.

10. DATA MANAGEMENT BY ASTRAZENECA

Data management will be performed by AstraZeneca Data Management Centre staff.

The data collected through third party sources will be obtained and reconciled against study data.

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 the Medical Coding Team at the AstraZeneca Data Management Centre.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The 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.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1. Calculation or derivation of efficacy variable(s) (Not Applicable)

11.2. Calculation or derivation of safety variable(s)

11.2.1. 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 judgment, significant adverse events of particular clinical importance may, after consultation with the Global Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of other safety 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.

11.3. Calculation or derivation of patient reported outcome variables

The EQ-5D data will be used to calculate utility based on the local tariffs as part of subsequent health economic analyses outside the CSR. If no local tariff is available the UK tariff will be used.

11.4. Calculation or derivation of pharmacokinetic variables (Not Applicable)

11.5. Calculation or derivation of pharmacodynamic variable(s) (Not Applicable)

11.6. Calculation or derivation of pharmacogenetic variables (Not Applicable)

11.7. Calculation or derivation of health economic variables

For the purpose of the Clinical Study Report the EQ-5D data and the hospitalization data will be presented as tabulation only.

Outside the CSR in a separate Health Economic Report the EQ-5D date will be used to calculate the utility based on the availability of validated tariffs; for countries where there is a validated EQ-5D questionnaire without a corresponding tariffs the UK tariff will be used. The health economic consequences of using ticagrelor will be assessed combining the information about hospitalizations data collected in the study and cost data collected independently. Long-term cost-effectiveness will be assessed by Health Economic modelling combining the hospitalization date, external cost data, the utility calculated in the study, and relevant survival statistics.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1. Description of analysis sets

12.1.1. Full analysis set (FAS)

All patients who have been randomized to study treatment will be included irrespective of their protocol adherence and continued participation in the study. Patients will be analyzed according to their randomized study medication irrespective of whether the event occurred before or following discontinuation of study medication. Patients who withdraw consent to participate in the study will be included up to the date of their study termination except for vital status known through public records (for use in the analysis of all cause mortality). All efficacy variables will be analyzed using the FAS.

12.1.2. Safety analysis set

All patients who received at least 1 dose of randomized ticagrelor or placebo and for whom post-dose data are available will be included in the safety population. Throughout the safety results sections, erroneously treated patients (eg, those randomized to ticagrelor but actually given placebo) will be accounted for in the actual treatment group. Patients will be censored 7 days after their last dose of study medication.

12.2. Methods of statistical analyses

12.2.1. Analysis of primary variable

The primary efficacy variable is time to first occurrence of any event from the composite of cardiovascular death, non-fatal MI or non-fatal stroke. The primary analysis will compare the time from randomization to the first occurrence of any event in the composite endpoint using the Cox proportional hazards model with a factor for treatment group. Each ticagrelor dose will be tested separately vs placebo. The null hypothesis will be that the risk/hazard of an event on ticagrelor is equal to the corresponding risk/hazard on placebo i.e.:

H_0: hazard ratio (ticagrelor divided by placebo) = 1

The alternative hypothesis will be that the hazard ratio is greater, or less than 1, i.e.:

H_1: hazard ratio $\neq$ 1

To control the overall type I error at 5%, the alpha apportioned to each ticagrelor dose-placebo comparison is 0.0269 (2-sided), utilizing the correlation (0.5) between the test statistics. At least one interim analysis is planned at 50% events in this trial (section 12.2.6), with the possibility of further interim analyses as considered necessary by the IDMC. In order to control the type 1 error at 0.0269 (2-sided) per dose comparison, the Haybittle-Peto alpha-spending function will govern interim and final statistical testing using the software East (version 5.2 Copyright © 2008 Cytel Inc). A one-sided significance level of 0.001 will be applied to each interim dose-placebo comparison. For example, if only the interim analysis planned when half of the events have occurred is performed, then the significance level applicable to each dose at final analysis is 0.0261(2-sided). With two interims, eg, one at 50% and another at 75% of the events, the significance level applicable to each dose at the final analysis would be 0.0259(2-sided). Should more than two interims be performed, the one-sided significance level 0.001 will continue to be applied to the interim dose-placebo comparisons, and the significance level applicable to each dose at the final analysis would be determined using the Haybittle-Peto spending function via East.

An explorative analysis of the primary endpoint with the 2 doses combined vs. placebo will also be performed.

The primary analysis will be performed on the FAS. Patients who fail to record any event in the primary composite efficacy endpoint will be censored at the time of study closure, death from non-cardiovascular causes, or at the timepoint after which the occurrence of all components of the primary endpoint could not be assessed.

The hazard ratio and 95% confidence interval will be reported for each dose. Kaplan Meier estimates of the cumulative incidence to the first occurrence of any event in the composite endpoint will be calculated and plotted, as will the cumulative risk to the first occurrence of each component separately.

The assumption of proportional hazards for the factor for treatment groups will be assessed visually using log-cumulative hazard plots. The effect of any departures from proportional hazards will be discussed as part of the presentation of results of the analyses.

The contribution of each component of the primary composite efficacy endpoint to the overall treatment effect will be examined for each dose. An additional explorative analysis with cardiovascular death replaced by all-cause mortality in the composite endpoint will also be performed. Methods similar to those described for the primary analysis will be used to separately analyze the time from Randomization to the first occurrence of each component of the primary efficacy composite endpoint.

Subgroup analyses to evaluate variation in treatment effect will be performed on the basis of tests for interaction using the Cox model. The p-values for the subgroup analyses will not be adjusted for multiple comparisons as the tests are exploratory and will be interpreted descriptively. Hazard ratios and 95% confidence intervals will be reported for each subgroup. Relevant subgroups for the following factors will be examined: age, sex, race, weight/BMI, geographic region, prior antiplatelet therapy, medical history characteristics (eg, risk factors for developing atherothrombosis and risk factors for bleeding), composite cardiovascular risk score (eg, REACH risk score, [Wilson et al 2007]), revascularization history, history of coronary stent implantation, time from qualifying MI to initiation of study therapy, moderate CYP3A inhibitor usage at randomization, ASA dose at randomization, and degree of compliance. Tests for the interaction with treatment for each of these factors will also be performed.

12.2.2. Secondary efficacy variables

The statistical analysis of the primary composite efficacy endpoint will be repeated for the secondary efficacy variables listed here:

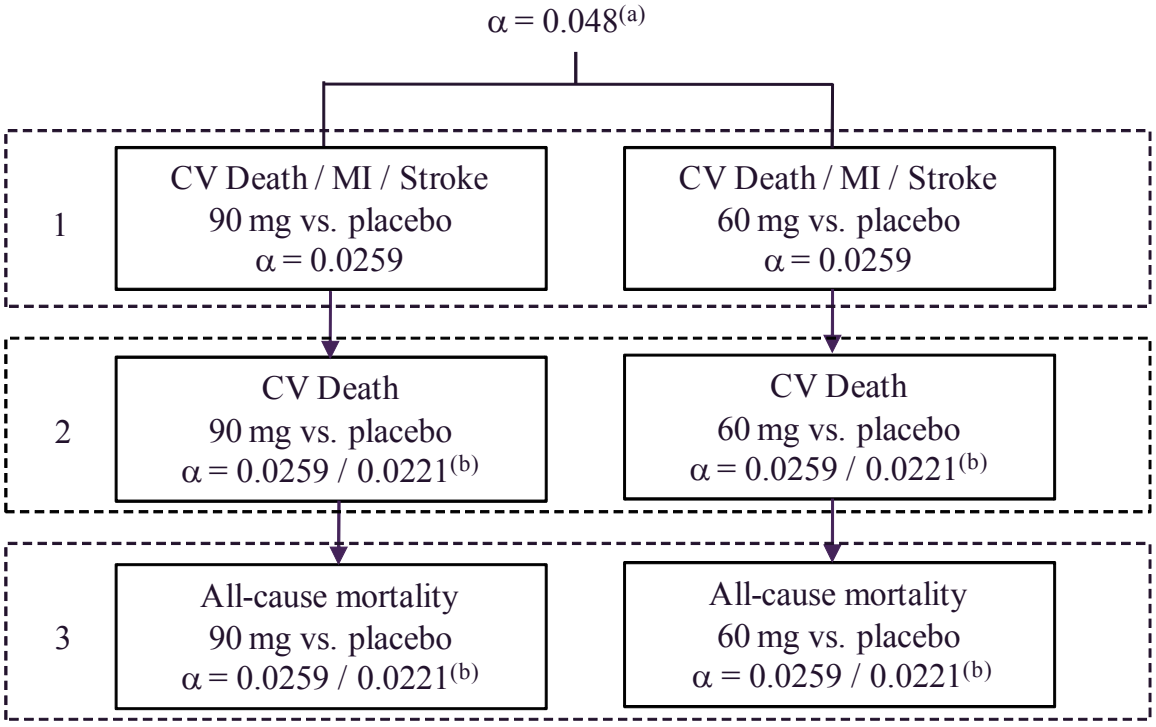
- Time to occurrence of cardiovascular death after randomization
- Time to occurrence of all-cause mortality after randomization

The analysis of the primary and secondary efficacy variables will comprise the confirmatory analysis.

With, for example, 2 interim analyses at 50% and 75% of events the significance level applicable to each dose at the final analysis would be 0.0259 (2-sided). With correlation 0.5 between the two dose test statistics, this corresponds to an overall significance level of 0.048 for the final analysis. The family-wise error rate in the confirmatory analysis of primary and secondary endpoints will be controlled in a Dunnett/Bonferroni parallel gatekeeping procedure (Dmitrienko et al 2006, Xu et al 2009), in this example at 4.8%, Figure 3. In this example, only if the treatment effect of the primary composite efficacy variable is found to be significant for a given dose of ticagrelor at significance level 2.59% will cardiovascular death be tested for that dose in a confirmatory sense. If tests of both doses are significant for the primary variable then cardiovascular death for a given dose will be tested at 2.59%. If the

primary variable is significant for only one of the doses, then cardiovascular death will be tested for that dose at 2.21%. Similarly, only if cardiovascular death is confirmatory significant for a given dose will all-cause mortality be tested for that dose in a confirmatory sense. If tests of both doses are significant for cardiovascular death then all-cause mortality will be tested at 2.59%. If cardiovascular death is significant for only one of the doses, then all-cause mortality will be tested for that dose at 2.21% significance level.

Figure 3 Multiple testing procedure



(a) This is an example based on 2 interim analyses at 50% and 75% of events. The α, overall and for each dose, depends on the number and timing of interim analyses, and will be determined by the Haybittle-Peto spending function.

(b) If tests of both doses are significant for the endpoint at the previous level in the hierarchy, then both doses will be tested at alpha=0.0259. If one of the tests is significant for the previous endpoint, then this dose will be tested at alpha=0.0221.

In general, the Haybittle-Peto spending function will determine the residual significance level applicable to each dose-placebo comparison at the final analysis given the number and timing of the preceding interim analysis(es). If this significance level is denoted α_f and the overall significance level at final analysis is α_T then the schema in Figure 3 remains the same with 0.048 replaced by α_T, 0.0259 replaced throughout by α_f and 0.0221 replaced by $\alpha_T - \alpha_f$.

Explorative analyses of each endpoint with the 2 doses combined vs. placebo will also be performed.

Hazard ratios and 95% confidence intervals will be reported for each endpoint. No multiplicity adjustment will be made to the confidence intervals as they will be interpreted descriptively and used as measures of precision.

Kaplan-Meier estimates of the cumulative risk of each composite endpoint and its components will be calculated and plotted.

12.2.3. Safety variables

Specific focus will be on:

- Time to first TIMI major bleeding event, as well as time to first TIMI major or minor bleeding event and time to first PLATO major bleeding event
- Time to discontinuation of study medication due to any bleeding event
- Evaluation of AEs

In the analysis of time to bleeding endpoints, each treatment group will be compared to placebo using the Cox proportional hazards model with a factor for treatment group. Kaplan-Meier estimates of the cumulative incidence of each event will be calculated and plotted and 95% confidence intervals for the hazard ratios presented. The safety assessment will also include analysis of total major bleeding events, fatal bleeding events, fatal or life threatening bleeding events, combined major and minor bleeding events across different categories as well as different categories of major and minor bleeding events separately. Exploration of potential risk factors for bleeding events, including subgroups and use of concomitant antithrombotic therapy, will be performed.

Bleeding events will be analyzed according to TIMI, PLATO, GUSTO and ISTH bleeding definitions as interpreted by the CEC. Bleeding definitions are described in references (Morrow et al 2009, James et al 2009, GUSTO Investigators 1993 and Schulman et al 2005).

MedDRA will be used for the coding and classification of AEs and SAEs in the database. AEs will be summarized by system organ class and preferred term using MedDRA. Summaries will be presented by treatment group using descriptive statistics. All AEs relating to bleeding will be summarized separately and the total number of bleeding events will be assessed. Exploration of potential risk factors for AEs that are increased with ticagrelor dosing may be done.

To identify factors that may predict treatment persistence, additional explorative analysis of time to permanent premature discontinuation of study drug will be performed, assessing patient characteristics such as demographics, medical history and concomitant medication.

Clinical laboratory and vital sign measurements will be summarized using descriptive statistics by treatment and protocol scheduled time.

12.2.4. Health Economics variables

EQ-5D data and hospitalization data for all admissions during the course of the study will be summarized using descriptive statistics.

12.2.5. Demographics

Demographic variables will be summarized by randomized treatment using descriptive statistics.

12.2.6. Interim analyses

The IDMC will perform interim analyses of unblinded data. At least one interim analysis of efficacy is planned after 50% of the total planned number of events for the primary endpoint have occurred, with the possibility of further interims as considered necessary by the IDMC. Each of the 60mg and 90mg doses will be compared separately vs. placebo. A 1-sided significance level of 0.001 will be applied to each ticagrelor dose-placebo comparison at each interim efficacy analysis. As noted above, the Haybittle-Peto alpha spending function will govern interim and final statistical testing to ensure an overall Type I error of 5% (East 5.2). The following procedure will be used to assess the beneficial effect at the interim analysis:

1. All-cause mortality will be tested for each of the ticagrelor doses (60 mg and 90 mg) separately vs. placebo at a one-sided significance level 0.001.

2. If the test of all-cause mortality is significant for both ticagrelor dose-placebo comparisons or if significant for one of the ticagrelor dose-placebo comparisons with the other having a HR $\geq$0.92 (which corresponds to approximately less than a 10% probability of achieving statistical significance if the study were to run to completion), then the primary endpoint will be tested for the doses that achieved significance for all-cause mortality.

3. For the individual ticagrelor dose-placebo comparisons that meet significance for all-cause mortality, a similarly robust result will be required on the primary endpoint to support stopping the trial. To ensure the overall Type I error for the trial does not exceed 0.05, a p value <0.001 is required. If the test of the primary endpoint is significant for the individual dose-placebo comparisons that meet significance for all-cause mortality and there is no concern for excess non-fatal intracranial haemorrhage, then the trial may be stopped for overwhelming benefit.

The IDMC charter contains more information about the IDMC procedures.

A copy of the treatment codes will be made available to the statistician on the IDMC. The Executive Committee and AstraZeneca will not be made aware of the treatment codes until after clean file and database lock are declared. Similarly, all summary output reviewed at each IDMC meeting will be held in confidence by the IDMC members until the end of the study when clean file and database lock are declared. Further details are given in the IDMC charter.

12.3. Determination of sample size

The expected primary composite efficacy event rate is 3.5%/12 months. The following information contributes to this estimate. An analysis conducted in patient with prior MI in the CHARISMA (Bhatt et al 2007) study observed a 3.64%/12 months event rate in their MI, vascular death, or stroke composite. Because of advances in current medical practice including the use of new drugs, the observed event rates of the composite of MI, stroke and cardiovascular death mentioned here are viewed as an overestimate of the current event rates on ASA. A constant event rate is also assumed.

The target relative risk reduction (RRR) for ticagrelor is 20% (equivalent to a hazard ratio of 0.7971). In patients in CHARISMA with a prior MI (Bhatt et al 2007), a RRR of 22.6% was observed with clopidogrel vs. placebo on a background of ASA. This trial will include patients who are more ill and at higher risk than the population studies in the paper mentioned above. Using IPA data from the DISPERSE study and assuming that the log hazard ratio is proportional to the ratio of mean IPA for the 60 mg dose relative to the 90 mg dose, an estimated hazard ratio for ticagreleor 60 mg of 0.814 was obtained.

Under the above assumptions, with 24 months accrual period and a 14-month follow-up period, randomization of 21000 patients is expected to yield 1360 primary events (518, 425 and 417 in the placebo, 60 mg and 90 mg group respectively). This provides 89.2% power (935 events) for 90 mg vs. placebo and 82.5% power (943 events) for 60 mg vs. placebo at 2.59% significance level (assuming 2 interim efficacy analyses by the IDMC). The sample size is based on 14 months minimum follow-up, but the study may be stopped after 12 months of minimum follow-up if the targeted number of events have been reached

For all-cause mortality a yearly event rate of 2.1% has been used. This is based on what was seen in a relevant subset of patients from the CHARISMA trial (Bhatt et al 2007), with the estimate conservatively (downward) adjusted with similar reasoning as for primary endpoint rate. With hypothesized mortality hazard ratios of 0.85 and 0.87 for the 90mg and 60mg doses (conservative estimates extrapolated from the PLATO data), for all three dose arms 856 deaths are anticipated in total, or approximately 571 per dose-placebo comparison at the final analysis and 285 deaths per dose-placebo comparison at the interim analysis.

The final sample size will depend on multiple factors including the rate of accrual of the primary endpoint events. Therefore, the sample size may be increased if planning assumptions are modified based on blinded data review.

The sample size was based on a test using the logrank statistic and was calculated using East v5.2.

Any decision to increase or decrease patient numbers or extend or shorten treatment duration will be based on blinded event rate data. The Executive Committee of the trial will monitor the aggregate (blinded) event rate and may increase the sample size or duration of follow-up to achieve the planned target number of events and the minimum treatment duration of 12 months, in consultation with the sponsor.

The planned formal interim analysis for efficacy at 50% events, and possibly further interim analyses as considered necessary by the IDMC, will be reviewed by the IDMC as well as safety data at a frequency described in the IDMC charter. The IDMC will have the authority to recommend early study termination to the Executive Committee if either a clear beneficial or harmful effect of the study treatment is detected. Should the study be terminated early, either due to a clear beneficial or harmful effect of study treatment or because the number of primary efficacy endpoint events has been reached, the duration of treatment may be shortened for some patients.

12.4. Data monitoring committee

An IDMC will monitor the progress of the study and will ensure that the study meets the highest standards of ethics and patient safety.

The IDMC will bear the primary responsibility for monitoring of study data for trends in mortality, morbidity, and drug safety. The IDMC will review all AEs/SAEs on an ongoing basis. These events include events rated to bleeding, renal function and renal failure, dyspnea, bradycardia, syncope, and gout. A recommendation by the IDMC to stop the study for adverse effects observed in the ticagrelor treatment arm may be made to the Executive Committee at any time. Specific statistical guidelines for monitoring safety throughout the study will be detailed in the IDMC Charter.

Early efficacy recommendations will occur only at the planned formal interim analysis/analyses. The members of the IDMC will have no other stake in the study. The IDMC will review the results of the interim analysis in strict confidence and will have the authority to recommend early study termination to the Executive Committee if either a clear beneficial or harmful effect of the study intervention is detected. Only members of the IDMC will be aware of the interim analysis results.

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 TIMI hotline. Contact details for personnel at AstraZeneca involved in the study are presented below.

Name	Role in the study	Address & telephone number
	Study Delivery Team Leader	

Name	Role in the study	Address & telephone number
	Study Delivery Team Physician	
	24-hour Emergency Cover at central R&D site	
Local contact persons can be added in wet-ink.		

13.2. Overdose

An overdose is defined as any intake of study medication greater than 360 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 the IB.

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 1**

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 Section 6.4.4. For other overdoses, reporting should be done within 5 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 1 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 CRF 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 1 day** as described in the maternal exposure section 13.3.1.

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AstraZeneca

Clinical Study Protocol Appendix B

Drug Substance	Ticagrelor
Study Code	D5132C00001
Edition Number	FINAL
Date	

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Study Protocol Appendix C

Drug Substance	Ticagrelor
Study Code	D5132C00001
Edition Number	FINAL
Date	

Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D
Cardiovascular Biomarker Substudy

TABLE OF CONTENTS PAGE

1. BACKGROUND

Over 16 million individuals are estimated to have stable CAD in the United States alone and this number is likely to continue to grow (Rosamond et al 2007). The term "stable," however, is a misnomer. Data from invasive studies have shown that 40% of individuals with stable CAD have lipid-rich "vulnerable" plaques (Maehara et al 2002). Registry data in this population demonstrate the rate of cardiovascular death, MI, stroke or hospitalization for atherothrombosis exceeds 15% per year (Steg et al 2007). Thus, a major challenge for clinicians is to identify which patients with apparently stable CAD are, in fact, vulnerable to major adverse outcomes in the ensuing years.

To that end, circulating cardiovascular biomarkers can provide insight into a patient's underlying pathobiology and thus enhance risk assessment and direct therapeutic decision-making (Morrow et al 2007). Moreover, reflecting the complexity of atherothrombosis, there is proof-of-principle that the combined use of multiple biomarkers that reflect distinct pathobiologic contributors to atherothrombotic risk enhances assessment of prognosis (Sabatine et al 2002).

Biomarkers that identify patients at higher risk for thrombotic events can be used to tailor therapy. Patients at higher risk for adverse events will, by definition, enjoy a greater *absolute* risk reduction for a given relative risk reduction from a therapy and hence require a smaller number needed to treat to prevent an adverse event. Moreover, pathobiologically relevant biomarkers may identify a specific subset of patients who enjoy a larger *relative* risk reduction with a given pharmacotherapeutic intervention, and thus an even greater absolute risk reduction.

In terms of specific biomarkers, cardiac troponin is commonly used for diagnosis of acute myocardial infarction. More recently, however, the advent of high-sensitivity assays has now permitted quantification of troponin in stable individuals and the demonstration that higher levels of troponin are associated with an increased risk of cardiovascular mortality (Omland et al 2009). Similarly, the natriuretic peptides (eg, BNP and NT-proBNP) have been used to risk stratify patients with ACS, and now have also been shown to act as robust predictors of the short and long-term risk of cardiovascular death in patients with stable ischemic heart disease (Kragelund et al 2005 and Omland et al 2007).

Inflammation is central to atherothrombosis and thus biomarkers that provide insight into the inflammatory processes that precede and lead up to atherothrombosis such as oxidative stress, leukocyte recruitment and activation, and fibrous cap degradation offer predictive value. For example, high-sensitivity measurement of C-reactive protein (hs-CRP), an acute phase reactant and global barometer of inflammation, has been shown to predict risk of first MI in healthy cohorts (Ridker et al 2000 and Danesh et al 2004) and future coronary events in patients with stable CHD(Haverkate et al 1997 and Sabatine et al 2007). Enzymes such as lipoprotein-associated and secretory type II phospholipase A_2 (Lp-PLA_2 and sPLA_2) that hydrolyze phospholipids to generate pro-atherogenic compounds are independent predictors of recurrent coronary events in stable patients (Koenig et al 2006, Sabatine et al 2007, Kugiyama et al 1999 and Mallat et al 2007). Chemokines for and products released by leukocytes (such as monocyte chemoattractant protein-1, CXCL16, myeloperoxidase, and neopterin) have been associated with the risk of coronary events (Herder et al 2006, de Lemos et al 2003, de Lemos

et al 2007, Meuwese et al 2007, Baldus et al 2003, Morrow et al 2008 and Jansson et al 2009). In addition, elevated levels of circulating metalloproteinases, (enzymes that disrupt the integrity of the atheroma's protective cap) and growth factors have been linked to an increased risk of coronary events (Elesber et al 2006, Heeschen et al 2004 and Wollert et al 2007).

Elevated circulating levels of several biomarkers of platelet activation, thrombosis, and endothelial dysfunction not only predict events, but may offer insight into which patients benefit the most from antithrombotic therapy. For example, soluble CD40 ligand, (a marker of platelet activation and potential direct participant in plaque destabilization), has been shown to identify patients who derive the greatest benefit from potent anti-platelet therapy in the acute setting (Heeschen et al 2003). Myeloid-related protein (MRP)-8/14 was discovered using transciptomics to be upregulated during ACS. Plasma levels of MRP-8/14 are an independent predictor of coronary events (Healy et al 2006 and Morrow et al 2008). von Willebrand factor (vWF) is a ligand for platelet glycoproteins that is released from injured and dysfunctional endothelial cells. In patients with angina, those who subsequently suffered an acute coronary event had significantly higher baseline levels of vWF than did those who did not (Thomspon et al 1995), and in a small study of 123 MI survivors, higher vWF levels were associated with an increased risk of death or reinfarction (Jansson et al 1991).

Serum thromboxane B_2 (TXB_2), which reflects the capacity of activated platelets to synthesize TX via the COX-1 pathway, is a sensitive measure of aspirin response (Maree et al 2005), and has been endorsed as the most reliable biomarker of aspirin resistance (Kuliczkowski et al 2009).

In terms of platelet function, several studies have found that patients with greater degrees of platelet aggregation have an increased risk of ischemic outcomes, and those with lesser degrees of platelet aggregation may have an increased risk of bleeding outcomes. However, a large-scale study defining and validating the optimal degree of platelet inhibition to minimize ischemic events as well as bleeding complications is needed.

2. OBJECTIVES

1. To evaluate the value of biomarkers for predicting ischemic/thrombotic and bleeding events.

2. To evaluate whether patients indentified at higher risk on the basis of biomarkers experience a greater absolute and/or relative risk reduction in ischemic/thrombotic events with long-term treatment with ticagrelor vs. placebo.

3. To evaluate the correlation between platelet inhibition and ischemic/thrombotic and bleeding outcomes.

4. To evaluate whether treatment with ticagrelor reduces levels of biomarkers of inflammation, platelet activation, thrombosis, and endothelial dysfunction.

3. METHODS

1. At baseline, blood samples will be collected (~10 ml EDTA-anticoagulated plasma, ~10 ml serum) in approximately 10,000 patients in selected countries.

2. At 4 months, blood samples will be collected (~6 ml EDTA-anticoagulated plasma, ~6 ml serum) in approximately 750 patients in selected countries.

3. At 4 months, ~2.7 ml of citrate-anticoagulated whole blood will also be collected in approximately 5000 patients enrolled in the United States.

Detailed procedures are described in the Central Lab Manual. In brief, careful separation of plasma and serum will be performed on site and stored at -20°C or colder until shipped to the central laboratory on dry ice, where samples will be stored at -70°C or colder until thawed for analysis. The citrate-anticoagulated whole blood sample will be shipped at ambient temperature to a central laboratory via overnight carrier.

Categories of biomarkers of interest and specific examples are listed below; specific biomarkers to be explored will depend on the totality of published data at the time of analysis

Biomarkers of myocardial injury: high-sensitivity cardiac troponin

Biomarkers of hemodynamic stress: BNP/NTproBNP, copeptin, MR-adrenomedullin, ST-2, galectin-3

Biomarkers of inflammation: hs-CRP, Lp-PLA_2, $sPLA_2$, myeloperoxidase, cytokines (eg, IL-1β, IL-1Ra, IL-6, IL-18, TNF), chemoattractants (eg, MCP-1, CCR1 and CCR2, CXCL16), neopterin, metalloproteinases (eg, PAPP-A, MMP-1, MMP-3, MMP-8, MMP-9, MMP-11), cathepsins, ADMA, growth factors (eg, placental growth factor, soluble Flt-1, GDF-15)

Biomarkers of thrombosis and endothelial function: MRP-8/14, sCD40L, vWF, d-dimer, soluble thrombomodulin, e-selectin, VCAM, ICAM-1

Biomarkers of aspirin resistance: TXB_2

Biomarkers of metabolism, lipids, and renal function: LP(a), oxidized lipoproteins, adiponectin, cystatin-c, NGAL

As the field of biomarkers is rapidly evolving, future data may suggest a role of additional biomarkers in the risk for cardiovascular outcomes and the response to treatment, which may lead to additional exploratory research.

In addition to analysis of existing biomarkers, proteomics and metabolomic analyses may be performed on samples to develop and test novel protein markers of cardiovascular outcomes.

Platelet inhibition will be measured using platelet vasodilator-associated phosphoprotein (VASP) phosphorylation, using the platelet reactivity index (PRI).

Blood samples may be analyzed by AstraZeneca, the and may be shared with each of their respective collaborators and/or vendors. Samples will be stored for up to 20 years (or sooner as required by local regulations) and then destroyed.

4. BIOSTATISTICAL ANALYSES

Biomarker data from the will be merged with the clinical database for statistical analysis. Analyses will be for exploratory purposes. Correlation between serum/plasma markers and outcomes will be analyzed with the marker data both as continuous and categorical variables. Clinical outcomes examined will include the primary efficacy endpoint, major secondary endpoints, other efficacy endpoints, and safety endpoints. Hazard ratios for the benefit of ticagrelor vs. placebo will be calculated in patients stratified by biomarker levels. The change in biomarkers from baseline to 4 months will be calculated in each treatment arm and compared.

Platelet function data will be merged with the clinical database for statistical analysis. Analyses will be for exploratory purposes and stratified by treatment arm. PRI will be correlated with ischemic outcomes (the primary composite endpoint of CV death, MI, stroke, and other ischemic outcomes specified in the protocol) and bleeding outcomes

A sample size of 10,000 patients will provide at least 80% power to detect an odds ratio of ≥1.42 for the primary endpoint for patients above vs. those below the median level and an odds ratio of ≥1.17 per 1 standard deviation of the biomarker. This sample size will also provide 80% power to detect interaction hazard ratios (the ratio of HRs for the benefit of ticagrelor on the primary endpoint in those above and below the median of a biomarker) of ≤0.50 (assuming a treatment effect of 0.79 and a risk of 1.42 for the biomarker). These values are in keeping with risk estimates and interactions seen with other biomarkers and represent the thresholds of clinical importance. These calculations assume an event rate of 6% over 2 years and that 5% of samples will be non-evaluable for a given biomarker, and uses a two-sided alpha threshold of 0.05 (no correction for multiple hypotheses testing as all analyses are exploratory). We will also have 90% power to detect a normalized difference, δ (the difference in means divided by the standard deviation), of 10%.

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Drug Substance	Ticagrelor
Study Code	D5132C00001
Appendix Edition Number	FINAL
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Appendix E
Pharmacogenetics Research Substudy

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
CAD	Coronary artery disease
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
GWAS	Genome wide association studies
HR	Hazard Ratio
LDL-C	Low density lipoprotein-cholesterol
MI	Myocardial Infarction
SNP	Single Nucleotide Polymorphism

1. BACKGROUND AND RATIONALE

Over 16 million individuals are estimated to have stable CAD (in the United States alone and this number is likely to continue to grow (Kathiresan et al 2009). The term "stable," however, is a misnomer. Data from invasive studies have shown that 40% of individuals with stable CAD have lipid-rich "vulnerable" plaques (Rossi et al 2006). Registry data in this population demonstrate the rate of cardiovascular death, myocardial infarction (MI), stroke or hospitalization for atherothrombosis exceeds 15% per year (Wheeler et al 2004). Thus, a major challenge for clinicians is to identify which patients with apparently stable CAD are, in fact, vulnerable to major adverse outcomes in the ensuing years.

Genetic variation can contribute to an individual's risk of adverse clinical outcomes as well as to their response to pharmacotherapy. Specifically, genetic polymorphisms can identify individuals at increased risk of adverse clinical outcomes, through known and as yet to be discovered pathobiological pathways. Genetic variants that identify patients at higher risk for thrombotic events might be used to tailor therapy. Patients at higher risk for adverse events will, by definition, enjoy a greater *absolute* risk reduction for a given relative risk reduction from a therapy and hence require a smaller number needed to treat to prevent an adverse event. Moreover, pathobiologically relevant genetic variants may identify a specific subset of patients who enjoy a larger *relative* risk reduction with a given pharmacotherapeutic intervention, and thus an even greater absolute risk reduction.

At least nine loci have been identified and validated from genome-wide association studies (GWAS) that have common DNA sequence variants related to risk for MI: 9p21, 1p13, 10q11, 1q41, 19p13, and 1p32, 21q22, 6p24, and 2q33 (Kathiresan et al 2009). When individuals were categorized on the basis of an MI genotype score, individuals in the top quintile had greater than two-fold increased risk for MI compared with bottom quintile (Kathiresan et al 2009). Of note, the MI genotype score confers risk of a magnitude comparable to other established risk factors such as plasma LDL-C (HR 1.62 for top versus bottom quintile of LDL-C). In addition to loci from GWAS, variants from multiple candidate genes involved in vascular biology, oxidative stress, adrenergic transmission, platelet function, hemostasis, and thrombosis have been tentatively linked to the risk of MI (Rossi et al 2006, Wheeler et al 2004, Lanfear et al 2005, Cambria-Kiely et al 2002, Kathiresan et al 2006 and Ye et al 2006).

In terms of genetic variants related to drug metabolism, we have demonstrated the impact of CYP450 SNPs on the pharmacologic and clinical response to clopidogrel, a prodrug that requires CYP450-mediated oxidative biotransformation. We found that, compared with noncarriers, carriers of at least 1 *CYP2C19* reduced-function allele (~30% of the population) had significantly lower exposure to clopidogrel active metabolite, less platelet inhibition, and higher rates of death and ischemic complications, including stent thrombosis (Mega et al 2009). There are also some data that variants in *MDR1* (which encodes P-gp, a xenobiotic efflux pump) can alter clinical response to clopidogrel and other drugs that are P-gp substrates (Simon et al 2009). Variants in the genes encoding a variety of other drug-metabolized enzymes have also been shown to alter the response to medications including warfarin and statins (Klein et al 2009 and The Search Collaborative Group 2008).

Collection of DNA samples from this trial population with its well-described clinical characteristics may lead to improvements in the design and interpretation of this and other clinical trials and, possibly, to genetically-guided risk assessment and treatment strategies.

2. GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect and store DNA for exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to ticagrelor and other cardiovascular medications and/or susceptibility to and/or prognosis of cardiovascular, metabolic and related diseases.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic research population

3.1.1 Study selection record

All patients in participating countries will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

3.1.2 Inclusion criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

3.1.3 Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

3.1.4 Discontinuation of patients from this genetic research

Specific reasons for discontinuing a patient from this genetic research are:

Withdrawal of consent for genetic research: Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 7.5 of the main Clinical Study Protocol.

3.2 Collection of samples for genetic research

The blood sample for genetic research will be obtained from enrolled patients. Although genotype is a stable parameter, early sample collection (at enrollment or randomization) is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at enrollment or randomization, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume, see Section 7.1 of the Clinical Study Protocol.

3.3 Coding and storage of DNA samples

Samples will be assigned a coded, unique DNA accession number that does not contain personal identifier information. No personal details identifying the individual will be available to any AstraZeneca employee or contracted third party staff working with the DNA. The link between the patient enrollment/randomization code and the DNA accession number will be maintained and stored in a secure environment, with restricted access. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent. Samples will be stored for a maximum of 20 years from the date of last patient last visit, after which they will be destroyed.

3.4 Genotyping

The genetic research conducted may use a variety of genotyping methodologies as needed. For example, specific sections of DNA may be selected from areas of the genome (e.g., candidate genes) known to encode the drug target, drug metabolizing enzymes, and areas linked to the study disease or related cardiovascular or metabolic diseases as well as associated with mechanisms underlying adverse events. In addition, genome-wide scans involving large numbers of polymorphic markers (e.g., single nucleotide polymorphisms (SNPs)) located throughout the genome may be employed for discovery of novel genetic variants linked to outcomes of interest. Additional methodologies may be used, but only as related the genetic objective stated earlier.

4. ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 8 of the main Clinical Study Protocol.

4.1 Informed consent

The genetic component of this study is optional and the patient may participate in other components of the main study without participating in the genetic component. To participate

in the genetic component of the study the patient must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue from the genetic aspect of the study at any time.

4.2 Patient data protection

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

5. DATA MANAGEMENT

Any genotype data generated in this study will be stored in an appropriate secure system within AstraZeneca, the , an academic research organization at and , and/or third party contracted to work with the aforementioned two groups to analyze the samples.

The results from this genetic research will be reported separately from the CSR for the main study.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

Formal statistical analysis plans will be prepared as appropriate. In brief, the genotypic frequencies of each polymorphism will be evaluated for conformity to those expected under normal conditions by employing Hardy-Weinberg Equilibrium testing. Differences in baseline clinical characteristics and potential contributing covariates may be summarized and compared among genotype (or haplotype) subgroups.

Analyses may be carried out to evaluate the degree of association between patient genotype (or haplotype) and selected phenotypes (e.g., outcomes). In addition to evaluating the main effects of the genotypes (haplotypes or alleles) on the selected phenotypes, the possibility of a treatment group by genotype (haplotype or allele) interaction will also be explored.

A sample size of approximately 18,000 patients would provide 80% power to detect an odds ratio of 1.20 per allele in an additive model for risk alleles with a frequency of ≥0.15. This sample size would also afford us 80% power to detect interaction hazard ratios (HR) (the ratio of HRs for the benefit of ticagrelor on the primary endpoint in carriers vs. non-carriers of an at-risk allele) of ≤0.63 (assuming a treatment effect of 0.79 and a risk ratio of 1.20 for carriers of an at-risk variant with a frequency of 0.15).

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