AstraZeneca

PROTOCOL SYNOPSIS

A Randomised, Double-blind, Double-dummy, Parallel Group, International (Asian), Multicenter, Phase 3 Study to Assess Safety and Efficacy of AZD6140 on top of low dose Acetyl Salicylic Acid (ASA) versus Clopidogrel on top of low dose ASA in Asian/Japanese Patients with Non-ST or ST Elevation Acute Coronary Syndromes (ACS) for whom PCI is planned

International Co-ordinating Investigator

Study centres and number of subjects planned

This study will be conducted in approximately 110 investigational centres in Japan, South Korea, and Taiwan. It is expected that 800 subjects will be randomised to study treatment.

It is expected that the majority of sites will recruit 10 or more subjects.

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

Objectives

Primary objective

- To assess short and long term safety and tolerability (especially bleeding) of AZD6140 90 mg bid compared with clopidogrel 75 mg qd in Asian/Japanese patients with non-ST or ST elevation Acute Coronary Syndrome (ACS) for whom percutaneous coronary intervention (PCI) is planned

- To evaluate effect of AZD6140 90 mg bid in the prevention of vascular events compared with clopidogrel 75 mg qd in Asian/Japanese patients with non-ST or ST elevation ACS for whom PCI is planned

Secondary objectives

1. To investigate the population pharmacokinetic (PK) of AZD6140 in this patients population and

   - To assess the effect of demographics, concomitant therapies and disease state on PK of AZD6140

   - To assess relationship between steady-state exposure of AZD6140 and AR-C124910XX (active metabolite) and various safety and efficacy outcomes

2. To investigate efficacy of AZD6140 in this patients population in comparison with efficacy in total patients and Asian cohort from study D5130C05262 (PLATO)

3. To investigate safety of AZD6140 in this patients population in comparison with safety in total patients and Asian cohort from study D5130C05262 (PLATO)

4. To investigate population PK of AZD6140 in this patients population in comparison with the results in total patients and Asian cohort from study D5130C05262 (PLATO)

5. To compare Inhibition of platelet aggregation (IPA) of AZD6140 treated patients with IPA in clopidogrel treated patients, and establish PK/Pharmacodynamics (PD) relationship for AZD6140, in a subpopulation of patients.

Optional: Exploratory objectives

To collect and store DNA for potential future exploratory research into genes/genetic variation that may influence response to AZD6140 and/or co-medications and/or clopidogrel (ie, distribution, safety, tolerability and efficacy) and susceptibility to and prognosis of cardiovascular disease.

Study design

This is a randomised, double-blind, double-dummy, parallel group, international, multicenter, Phase III study to assess efficacy and safety of AZD6140 on top of low dose acetyl salicylic acid (ASA) versus clopidogrel on top of low dose ASA in Asian/Japanese patients with non-ST or ST elevation ACS for whom PCI is planned.

Target subject population

Male and female patients aged 20 years and over, with documented evidence of non-ST or ST segment elevation ACS in the 24 hours before randomisation, and for whom PCI is planned, are eligible for enrolment.

Investigational product, dosage and mode of administration

AZD6140 90 mg (tablet) taken twice daily, orally, with an initial 180 mg loading dose will be given.

Comparator, dosage and mode of administration

Clopidogrel 75 mg (over-encapsulated) taken once daily, orally, with an initial 300 mg loading dose for clopidogrel naïve patients (See Section 5.5.2).

Concomitant Acetyl Salicylic Acid

In addition to randomised study medication all patients should receive concomitant Acetylic Salicylic Acid (ASA) 75 to 100 mg daily during the treatment period according to local practice. A loading dose of 162 to 330 mg ASA is allowed according to local practice. Following stenting, up to 330 mg of ASA daily is allowed for up to 6 months following placement of bare metal or drug eluting stents according to local practice, at the investigators' discretion.

Duration of treatment

Patients will be randomised to treatment no later than 24 hours after the most recent symptoms of the onset of their index event; there is no run-in period. The duration of treatment for an individual patient is estimated to be at least 6 months up to a maximum of 12 months (depending on the time of entry to the study). In addition, the study may be terminated early if a clear harmful effect of the study treatment is detected during the Data Safety Monitoring Board (DSMB) review.

Outcome variables:

Primary Safety variables

- The time to first occurrence of any total major bleeding event (to be adjudicated using PLATO criteria).

Secondary Safety variables

- Bleeding events (to be adjudicated using PLATO criteria)
  - Total, non-procedure-related, coronary procedure-related[1] and non-coronary procedure-related major bleeding events.
  - Total, non-procedure-related, coronary procedure-related and non-coronary procedure-related minor bleeding events.
  - Combined major and minor bleeding events for each of the categories.
  - Total minimal bleeding events.
- Adverse events (AEs), laboratory values, physical examination, electrocardiography (12-lead ECG), Holter ECG and vital signs.

[1] Coronary procedure-related includes coronary artery bypass graft (CABG), PCI and coronary angiography only.

Primary Efficacy variables

- The time to first occurrence of any event from the composite of death from vascular causes, myocardial infarction (MI) or stroke.

Secondary Efficacy variables

- The time to first occurrence of any event from the composite of all-cause mortality, MI or stroke
- The time to first occurrence of any event from the composite of death from vascular causes, MI (including silent MI by ECG), stroke, recurrent cardiac ischaemia, transient ischaemic attack (TIA) or other arterial thrombotic events
- The time to first occurrence of each component of the primary composite efficacy endpoint individually in the order of MI, death from vascular causes and then stroke
- The time to occurrence of all-cause mortality

PK and PD variables

- Maximum plasma drug concentration at steady state ($C_{ss,max}$), minimum plasma drug concentration at steady state ($C_{ss,min}$), average plasma concentration at steady state ($C_{ss,av}$), time to reach peak or maximum concentration or maximum response following drug administration at steady state ($T_{ss,max}$), half-life ($t_{1/2}$) and area under plasma concentration-time curve at steady state (AUC_{ss}) for AZD6140 and AR-C124910XX
- The relationship between predicted individual $C_{ss,max}$ or AUC_{ss} and outcome events
- IPA: Final extent at each assessment points

Statistical methods

All safety and efficacy variables will be summarised descriptively by treatment group.

For safety, an analysis of the time from first dose of study medication to each of the following endpoints will be performed:

- Total, non-procedure-related, coronary procedure-related and non-coronary procedure-related major bleeding events
- Total, non-procedure-related, coronary procedure-related and non-coronary procedure-related minor bleeding events
- Combined major and minor bleeding events for each of the categories.

The treatment groups will be compared using the Cox proportional hazards model with a factor for treatment group. Kaplan-Meier estimates of the cumulative risk of each event will

be calculated and plotted and 2-sided 95% confidence intervals for the hazard ratios presented. The proportion of patients experiencing above events will also be presented for each treatment group, along with the difference between treatment groups and 2-sided 95% confidence interval.

For efficacy, the time to first occurrence of any event from the composite of death from vascular causes, MI or stroke will be analysed based on a Cox proportional hazards model including treatment group. The hazard ratio and 2-sided 95% confidence interval will be reported. Kaplan Meier estimates of the cumulative risk 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. Other relevant efficacy variables will be analysed in similar manner.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACC	American College of Cardiology
ACS	Acute coronary syndromes
ADP	Adenosine diphosphate
AE	Adverse event (see definition in Section 6.4.1)
ALT	Alanine aminotransferase
ASA	Acetyl salicylic acid (aspirin)
AST	Aspartate aminotransferase
AUC_{ss}	Area under plasma concentration-time curve at steady state
bid	Twice a day dosing
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
Cardiac ischaemic symptoms	Chest pain or discomfort or equivalent (eg, neck or jaw symptoms, dyspnoea believed to represent an angina pectoris equivalent) believed due to impaired coronary flow secondary to atherosclerotic disease
CEC	Clinical Endpoint Committee
CK-MB	Creatine kinase myocardial band
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
$C_{ss,av}$	Average plasma concentration at steady state
$C_{ss,max}$	Maximum plasma (peak) drug concentration at steady state
$C_{ss,min}$	Minimum plasma drug concentration at steady state
CT	Computed tomography
CURE, COMMIT, CLARITY- TIMI28	Acronyms for clinical studies in patients with ACS/MI that were part of the clinical development programme of clopidogrel
CV	Coefficient of variation

Abbreviation or special term	Explanation
CYP3A	Cytochrome P450 3A – the most abundant of the P450 enzymes, responsible for initial drug metabolism in the liver
DAE	Discontinuation of Investigational Product due to Adverse Event
DDAVP	Desmopressin
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
Endpoint	Symptomatic or asymptomatic events that are centrally adjudicated and specifically defined in the protocol as efficacy or safety outcome variables
EoT	End of Treatment (refers to study visit at which patient is discontinued from study medication)
Enrolled patient	A patient who has signed informed consent form and subsequently been allocated an Enrolment code
ESC	European Society of Cardiology
FAS	Full analysis set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPIIb/IIIa	Glycoprotein IIb/IIIa receptor
GRand	AstraZeneca Global Randomisation system
Hb	Haemoglobin
HDL	High density lipoprotein
HDPE	High density polyethylene
H-FABP	Human heart fatty acid binding protein
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ID	Identification
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
Index event	The event of ST or Non-ST elevation ACS which was used to fulfil the primary inclusion criterion for the study
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
IRB	Institutional Review Board

Abbreviation or special term	Explanation
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
Killip class	Hemodynamic classification of patients with acute MI
LBBB	Left bundle branch block
LDL	Low density lipoprotein
LIMS	Laboratory Information Management System
LMWH	Low molecular weight heparin
Measurement	An observation made on a variable using a measurement device
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NSAID	Non-steroidal anti-inflammatory drug
NSTEMI	Non-ST segment elevation myocardial infarction
NT-proBNP	N-terminal pro-brain natriuretic peptide - a cardiac neuro-hormone that is elevated in patients with congestive heart failure
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
Outcome variable	A variable (usually a derived variable) specifically defined to be used in the analysis of a study objective
Parameter	A quantity (usually unknown) that characterises the distribution of a variable in a population of patients
PCI	Percutaneous coronary intervention
PD	Pharmacodynamics
PK	Pharmacokinetic
PLATO	Study acronym – A study of PLATelet inhibition and patient Outcomes
PRBCs	Packed red blood cells
Principal investigator	A person responsible for the conduct of a clinical study at an investigational study site. Every investigational study site has a principal investigator
P2 (purinergic) receptor	A widespread class of cell surface receptors for purines
$P2Y_{12}$	A sub-type of P2 receptor found on platelets
qd	Once daily dosing
Randomised patient	A patient who has received a Randomisation code
RAVE	Proprietary name for Medidata Solutions, Inc. web based data capture software

Abbreviation or special term	Explanation
SAE	Serious adverse event (see definition in Section 6.4.2).
SDV	Source Data Verification
SOP	Standard Operating Procedure
STEMI	ST segment elevation myocardial infarction
$t_{1/2}$	Half-life
TIA	Transient ischaemic attack
TIMI	Thrombolysis in Myocardial Infarction
TIMI risk score	Assessment of risk for non-ST elevation with predefined variables
$T_{ss,max}$	Time to reach peak or maximum concentration or maximum response following drug administration at steady state
UFH	Unfractionated heparin
Variable	A characteristic or property of a patient that may vary eg, from time to time or between patients
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background

AZD6140 is a reversible, oral adenosine diphosphate (ADP) receptor antagonist acting via the $P2Y_{12}$ receptor which can effectively block ADP-mediated platelet activation and aggregation. AZD6140 is not a pro-drug and does not require metabolic activation, unlike the pro-drugs clopidogrel sulphate and ticlopidine, which block the $P2Y_{12}$ receptor response in humans to variable degrees (receptors remaining unoccupied during maintenance therapy with clopidogrel sulphate can be blocked by the addition of AZD6140 in vitro). AZD6140 completely protects against thrombosis in the canine femoral artery cyclic flow model at doses that do not cause significant bleeding time extension. This is not true of platelet membrane glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, which cause much more bleeding time extension at the antithrombotic dose (AZ internal report SC-103289). Additionally, $P2Y_{12}$ receptor antagonists can block platelet activation, secretory granule release, and adhesive epitope expression at anti-aggregatory concentrations (Storey RF et al 2000). These potentially beneficial properties are not shared by acetyl salicylic acid (ASA) and the GPIIb/IIIa antagonists, and are likely to be suboptimal with clopidogrel sulphate and ticlopidine since they provide modest and variable receptor blockade.

In recent years, there have been many improvements in the approach to and management of the incidence and complications of acute coronary syndrome (ACS). Angioplasty, stenting, beta-blockers, lipid lowering therapies, ASA, clopidogrel sulphate, low molecular weight heparins (LMWH) and thrombin inhibitors have all contributed to a substantial improvement in outcome. Despite this, a substantial morbidity and mortality persists due to inadequate control of thromboembolism and atherosclerotic events. The importance of platelets in the acute development of thrombotic occlusion at the site of plaque rupture is well established, and ADP is one of the primary mediators of platelet activation and aggregation. Inhibition of ADP-mediated platelet activation and aggregation by ticlopidine and clopidogrel sulphate has been shown to provide improved efficacy over ASA therapy alone, with a favourable bleeding profile (Jneid H et al 2003). However the action of ticlopidine and clopidogrel sulphate at the ADP receptor has a slow onset, is irreversible and incomplete and between 15% and 30 % of patients seem to be non-responders to clopidogrel sulphate treatment (Gurbel PA et al 2003). It has also been reported that 14% of Japanese patients are resistant to clopidogrel sulphate that is defined based on inhibition of platelet aggregation (IPA), and there is a wide variability of IPA among Japanese patients on clopidogrel sulphate (Hoshino K et al 2009). Furthermore non-responders have a higher rate of ischaemic events during clopidogrel sulphate treatment (Matetzky S et al 2004). In addition, antiplatelet effects of clopidogrel are dependent on CYP2C19 metabolizer status. In percutaneous coronary intervention (PCI) eligible patients a higher rate of cardiovascular events has been reported in poor or intermediate metabolizers compared to extensive metabolizers. Thus the development of new ADP receptor antagonists with improved efficacy and/or safety profiles is desirable.

The Global Phase III study (PLATO/D5130C05262) is an international, multicenter, double-blind, randomised, two-arm parallel group, comparative trial. In this study, we compared

AZD6140 (180 mg loading dose, 90 mg bid thereafter) and clopidogrel (30 to 600 mg loading dose, 75 mg qd thereafter) for the prevention of cardiovascular events in 18,624 patients admitted to the hospital with an ACS (with or without ST-segment elevation).

Cardiovascular events in patients with ACS still often result in significant morbidity and mortality despite the increasing rates of PCI. The results from PLATO showed that AZD6140 prevented cardiovascular events, compared to clopidogrel with statistical significance. This may be relevant to the situation in Japan, where the incidence of ACS is rising.

1.2 Research hypothesis

There is similar or superior efficacy, and similar safety and tolerability, for AZD6140 vs clopidogrel when given on top of low dose ASA. No formal statistical hypothesis test will be made.

1.3 Rationale for conducting this study

Data from Global Phase I studies in human volunteers demonstrate acceptable tolerability of AZD6140 over an orally administered dose range of up to 900 mg and have confirmed a positive relationship between plasma concentration of AZD6140 and the degree of IPA, with substantial (over 80%) IPA achievable in all volunteers studied to date.

The Global Phase IIA study (DISPERSE/D5130C00008) investigated the pharmacodynamics (PDs), pharmacokinetics (PKs), safety and tolerability of AZD6140 in the total daily dose range 100 to 400 mg during 28 days of treatment in 200 patients with stable atherosclerotic vascular disease. The 50 mg twice daily dose of AZD6140 conferred a similar degree of IPA as clopidogrel 75 mg once daily during maintenance treatment but with a much faster onset with a maximal effect reached with AZD6140 already within the initial 2 hours after the first dose. The AZD6140 100 mg and 200 mg twice daily as well as 400 mg once daily resulted in a clearly higher percentage of IPA (over 20% absolute difference with all doses) and still with the maximal effect reached with AZD6140 already within the initial 2 hours after the first dose. After the initial dose there was a 10 to 15% higher degree of platelet inhibition with the 400 mg dose compared to the 100 and 200 mg doses. However, during maintenance treatment there was no significant difference in platelet inhibition between the 100 mg, 200 mg twice daily or 400 mg once daily. The pattern of IPA was the same using either final or maximal extent for ADP-induced platelet aggregation.

Based on this data doses of 100 mg and 200 mg twice daily were considered promising for further evaluation. A new tablet formulation of AZD6140 was subsequently made available in tablet strengths of 90 and 180 mg (equivalent to 100 and 200 mg of the original formulation due to improved relative bioavailability of the new formulation).

The Global Phase IIB study (DISPERSE 2/D5130C00002) examined the longer-term (up to 12 weeks) safety and PDs of AZD6140 in patients with non-ST elevation ACS. In total, 990 patients were randomised into three groups: AZD6140 90 mg or 180 mg twice daily or clopidogrel 75 mg once daily. Half of the AZD6140 patients received a loading dose of 270 mg and all clopidogrel-naive patients in the clopidogrel group received a 300 mg loading

dose. Major plus minor bleeding rates at 4 weeks (primary objective) were comparable in the three groups with no dose response relationship. Most bleedings occurred early and were associated with coronary interventions (ie, either PCI or coronary artery bypass graft [CABG]). Both doses of AZD6140 were well tolerated with no differences in premature discontinuations for adverse events (AEs) observed across the treatment groups. As in DISPERSE, dose related dyspnoea was reported up to 30 days of treatment more frequently with AZD6140 than with clopidogrel, but it was in most cases mild and with few discontinuations. There were very few cases with new onset of dyspnoea after 30 days. Furthermore, the finding of an approximately 10% increase in blood uric acid levels compared with clopidogrel from the previous study was confirmed. Small increases in AEs of nausea, vomiting, diarrhoea; hypotension, pyrexia, insomnia, arrhythmias, and renal impairment with AZD6140 compared with clopidogrel were reported. For all of these events, it is difficult to draw any conclusions of relationship to AZD6140 since the number of cases was small and a dose response was not obvious. Other AEs that were commonly reported but that did not appear to be increased in frequency with AZD6140 were dizziness, headache, abdominal pain, dyspepsia, constipation, and anxiety.

In PLATO, the incidence of cardiovascular events, the primary endpoint (a composite of death from vascular causes, myocardial infarction [MI], or stroke) was compared. At 12 months, the primary end point had occurred in 9.8% of patients receiving AZD6140 as compared with 11.7% of those receiving clopidogrel (hazard ratio, 0.84; 95% confidence interval [CI], 0.77 to 0.92; P<0.001). Predefined hierarchical testing of secondary end points showed significant differences in the rates of MI alone (5.8% in the AZD6140 group vs. 6.9% in the clopidogrel group, P=0.005) and death from vascular causes (4.0% vs. 5.1%, P=0.001) but not stroke alone (1.5% vs. 1.3%, P=0.22). The rate of death from any cause was also reduced with AZD6140 (4.5%, vs. 5.9% with clopidogrel; P<0.001).

No significant difference in the rates of major bleeding was found between the AZD6140 and clopidogrel groups (11.6% and 11.2%, respectively; P=0.43), but AZD6140 was associated with a higher rate of major bleeding not related to CABG (4.5% vs. 3.8%, P=0.03). There was no difference observed in total fatal bleeding events between AZD6140 and clopidogrel (21 and 24, respectively). There are 13 fatal non-procedural bleeding events in the AZD6140 group (11 intracranial and 2 in other locations and 13 in the clopidogrel group (one intracranial and 12 in other locations). AZD6140 was associated with a higher rate of major + minor bleeding (16.1% vs. 14.6%, p=0.0084).

Dyspnoea was investigated in detail in PLATO and Holter monitoring was performed in a subset of PLATO patients to detect bradyarrhythmias, since results from Phase I and II studies had raised concerns that they might be AZD6140 specific AEs.

In the PLATO safety analysis set, the number of patients with bradycardiac events was similar between treatment groups (4.7% vs. 4.4%). Similar rate of permanent pacemaker placement was also found (0.4% vs. 0.4%).

Holter monitoring was conducted in 2,908 patients. The number of patients with ventricular pause (≥3 sec) was numerically greater in the AZD6140 group compared to clopidogrel (6.0%

and 3.5%). Ventricular pause did not correlate well with clinically important events (such as syncope, atrioventricular block, or pacemaker insertion).

Percentage of patients who complained of any type of dyspnoea during the study period was significantly higher in the AZD6140 group (13.8%) than in the clopidogrel group (7.8%), respectively. Percentage of patients who developed dyspnoea, leading to discontinuation was 0.9% and 0.1% in the AZD6140 group and the clopidogrel group, respectively. However, most cases of dyspnoea associated with AZD6140 were of mild to moderate intensity, and dyspnoea resolved during continued treatment with AZD6140 in the majority of patients with this AE.

Other AEs observed in PLATO were consistent with what has been reported from the previous studies, and there are no reports of unexpected AEs.

China, South Korea, Taiwan, Hong Kong, Indonesia, Malaysia, Philippines, Singapore, and Thailand are regarded as Asian counties and Asian cohort analysis was done to investigate the efficacy and safety of AZD6140 in Asians. There are 1,056 patients in this cohort out of 18,624 patients in overall PLATO.

Average body weight in Asian cohort was 66.0 kg while that in PLATO was 80.4 kg. Proportion of ST segment elevation myocardial infarction (STEMI) in the Asian cohort was high (46.4%) while that in PLATO overall was 37.7%. Other than these profiles, background of these two populations was similar.

The treatment effect for AZD6140 vs. clopidogrel observed for the entire PLATO population was similar (in all primary and secondary composite endpoints) in the Asian cohort of patients. In the Asian cohort, at 12 months, cardiovascular events, the primary end point (a composite of death from vascular causes, non-fatal myocardial infarction, or non-fatal stroke) had occurred in 13.0% of patients receiving AZD6140 as compared with 16.2% of those receiving clopidogrel (hazard ratio, 0.82; 95% confidence interval [CI], 0.59 to 1.14; P=0.233) and there was a similar treatment effect for the individual components death from vascular causes (7.1% vs. 10.2%) and all cause mortality (7.9% vs. 10.9%). The rates of MI (7.2% vs. 7.7%) and stroke (2.3% vs. 1.8%) were similar for AZD6140 and clopidogrel in the Asian cohort. Overall, the treatment effect for AZD6140 compared to clopidogrel observed in the entire PLATO population is consistent with the effect in the Asian cohort of patients.

Total major bleeding in Asian patients was 10.9% on AZD 6140 vs. 10.8% on clopidogrel compared to 11.6% vs. 11.2% in the rest of PLATO. AZD 6140 was associated with a numerically higher rate of major + minor bleeding in Asian patients with no statistically differences (17.1% vs. 14.0%, p=0.0984) which was similar to the entire PLATO population. Other bleeding events occurred with similar frequency compared with the whole PLATO safety population. The bleeding pattern in the Asian cohort was consistent with that observed in the whole PLATO patient population.

The clinical benefit of AZD6140 compared to clopidogrel for a composite efficacy and safety endpoint (death from vascular causes, MI, stroke, or PLATO-defined major bleeding) is conserved in the Asian cohort.

Two Phase I studies in Japanese healthy volunteers were completed. In single ascending dose (SAD) Study (D5130C05266), 19 Japanese-Hawaiian and 19 Caucasian-Hawaiian were split into 2 cohorts, which received ascending single doses of AZD6140 50 mg, 200 mg and 400 mg or 100 mg, 300 mg and 600 mg, with PK and PD assessments, respectively. Although C_{max} and AUC in Japanese volunteers were higher by 50% and 30%, respectively, compared with Caucasian volunteers at the highest dose of 600 mg, there were no significant differences between Japanese and Caucasian healthy volunteers at all other doses. There were no clinically relevant differences between Japanese and Caucasian volunteers in ADP-induced final or maximum extent IPA. Single ascending doses of 50 to 600 mg of AZD6140 were well tolerated in healthy Japanese and Caucasian volunteers. In multiple ascending dose (MAD) study (D5130C05267), 36 Japanese and 36 Caucasian healthy volunteers were divided into 2 cohorts who received either 100 mg or 300 mg doses of AZD6140 as an oral single dose to assess PK and PD. Following a 3-day washout, all subjects received AZD6140 100 mg or 300 mg twice daily for 7 days as oral repeated doses to assess PK and PD at steady state. Single dose and steady state C_{max} and AUC values of AZD6140 and the metabolite following AZD6140 100 mg and 300 mg were statistically significantly higher in Japanese volunteers, compared to Caucasian volunteers (about 40% higher, about 20% higher after weight-adjustment). Single and multiple 100 mg and 300 mg doses of AZD6140 produced near complete IPA rapidly in both ethnic groups. Single and multiple doses of 100 mg and 300 mg bid AZD6140 were well tolerated in both healthy Japanese Caucasian volunteers.

Overall, clinical study data indicate that AZD6140 overall has a large evidence showing improved efficacy and risk/benefit balance when compared to clopidogrel. The AZD6140 90 mg twice daily dose, starting with a loading dose of 180 mg, has been selected as the maintenance dose for this study in Phase III since it is used in PLATO and therefore will offer the best balance of safety with anticipated improved efficacy over clopidogrel.

1.4 Benefit/risk and ethical assessment

The Investigator's Brochure (IB) for AZD6140 contains the information supporting the overall risk/benefit assessment of the investigational agent and is available as a reference for investigators. It contains a summary of all the relevant pharmaceutical, nonclinical and clinical findings with AZD6140.

AZD6140 is intended for use to prevent the thrombotic complications (death from vascular causes, MI, and stroke) associated with ACS and its sequelae. Aspirin, and clopidogrel in combination with aspirin, have been shown to reduce the risk of these complications with acceptable benefit/risk profiles. Despite the established incremental efficacy of clopidogrel over aspirin alone, its requirement for metabolic activation (slow onset of action), irreversibility (slow offset of action with prolonged period of partial blockade) and high degree on inter-patient variability in the IPA (with an inadequate IPA response in up to 31% of patients undergoing PCI) (Gurbel PA et al 2003) underscore the need for a better agent.

The more modest effects on platelet aggregation, and the larger inter-patient variability of effect, of clopidogrel compared to newer agents like AZD6140 suggests that the risk for such events can be further substantially reduced.

Previous studies show that administration of AZD6140 results in substantially higher levels (more than 20% mean absolute increase) of *ex vivo* IPA with less variability compared to clopidogrel (with or without ASA background therapy).

The results from PLATO showed that AZD6140 statistically significantly decreased the incidence of thromboembolic events (death from vascular causes, non-fatal myocardial infarction and non-fatal stroke) in ACS patients, compared to clopidogrel, demonstrating the greater preventive effect of AZD6140 on thromboembolic events without increased overall risk of Major bleeding risk.

Since AZD6140 offers the potential for superior efficacy to clopidogrel based on PLATO data and the trial will be analysed by intention-to-treat principles, it is important to keep patients on their assigned treatment regimen for as long as possible. Many patients after ACS will have a compelling reason for continued $P2Y_{12}$ blockade (eg, presence of a drug-eluting stent) even in the setting of possible clinical intolerance. Patients who have clinical intolerance and do not have a compelling reason for continued $P2Y_{12}$ therapy should generally be discontinued from study medication and treated according to currently recommended medical practice.

2. STUDY OBJECTIVES

2.1 Primary objective

- To assess short and long term safety and tolerability (especially bleeding) of AZD6140 90 mg bid compared with clopidogrel 75 mg qd in Asian/Japanese patients with non-ST or ST elevation ACS for whom PCI is planned

- To evaluate effect of AZD6140 90 mg bid in the prevention of vascular events compared with clopidogrel 75 mg qd in Asian/Japanese patients with non-ST or ST elevation ACS for whom PCI is planned

2.2 Secondary objectives

1. To investigate the population PK of AZD6140 in this patients population and

   – To assess the effect of demographics, concomitant therapies and disease state on PK of AZD6140 and

   – To assess relationship between steady-state exposure of AZD6140 and AR-C124910XX (active metabolite) and various safety and efficacy outcomes

2. To investigate efficacy of AZD6140 in this patients population in comparison with efficacy in total patients and Asian cohort from study D5130C05262 (PLATO)

3. To investigate safety of AZD6140 in this patients population in comparison with safety total patients and Asian cohort from study D5130C05262 (PLATO)

4. To investigate population PK of AZD6140 in this patients population in comparison with the results in total patients and Asian cohort from study D5130C05262 (PLATO)

5. To compare IPA of AZD6140 treated patients with IPA in clopidogrel treated patients, and establish PK/PD relationship for AZD6140, in a subpopulation of patients.

2.3 Exploratory objectives (Optional)

To collect and store DNA for potential future exploratory research into genes/genetic variation that may influence response to AZD6140 and/or co-medications and/or clopidogrel (ie, distribution, safety, tolerability and efficacy) and susceptibility to and prognosis of cardiovascular disease. See Appendix D for details.

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

Study design

This is a randomised, double-blind, double-dummy, parallel group, international, multicenter, Phase III study to assess efficacy and safety of AZD6140 on top of low dose ASA versus clopidogrel on top of low dose ASA in Asian/Japanese patients with non-ST or ST elevation ACS for whom PCI is planned.

Since this study is based on intent-to-treat analysis of clinical outcomes it is critical that study treatment be maintained according to randomised treatment group, if at all possible and that all patients be followed to the end of the study. This necessitates using all reasonable efforts to maintain contact with study patients for the total duration of the study and continuing study medication treatment even if an endpoint event or investigator unblinding has occurred.

Study committees and organisation

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

Pre-specified suspected endpoint events will be reported to and centrally adjudicated by Clinical Endpoint Committee (CEC) (See Section 12.5).

An independent, external Data Safety Monitoring Board (DSMB) will monitor data on an ongoing basis to ensure that patient safety is not compromised and will make recommendations for early safety termination (See Section 12.4).

In addition, Executive Committee comprising a co-ordinating investigator from each country and non-voting representatives from AstraZeneca will be appointed to oversee the running of the study in his or her country with scientific oversight of the study.

Patient population and recruitment

Male and female patients aged 20 years and over, with documented evidence of non-ST or ST segment elevation ACS in the 24 hours before randomisation, and for whom PCI is planned, are eligible for enrolment. Initiation of study medication should take place as soon as possible after randomisation in order to maximise potential clinical benefits.

It is expected that 800 patients will be randomised to study treatment.

It is expected that approximately 110 investigational centres may participate in depending on local approval. The approximate distribution of patients by country or region is as follows:

- Japan (730)
- Asia: South Korea (30), Taiwan (40)

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

Study treatment

Two treatment groups will be studied, AZD6140 90 mg twice daily and clopidogrel 75 mg once daily, both taken orally using matching placebos to maintain study blinding. Two treatment groups dosing and the use of loading doses is described in Section 5.5.2 and 5.5.3.2.

The duration of treatment for an individual patient is variable and estimated at 6 to a maximum of 12 months depending on their time of entry to the study. The average study duration is expected to be approximately 10 months per patient. The study may be terminated early if a clear harmful effect of the study treatment is detected during the DSMB review. Should the study be terminated early due to a clear harmful effect of study treatment the duration of treatment may be shortened to less than 6 months for some patients or other changes in study plan.

Patients will be randomised to treatment group in the ratio 1:1 by using a central Interactive Web Response System (IWRS) or Interactive Voice Response System (IVRS).

The first dose of study medication should be taken directly after randomisation at Visit 1. Subsequent doses should be taken in the morning and evening preferably with a 12-hour interval between dosing.

In addition to randomised study medication (AZD6140 or clopidogrel) all patients should be treated with concomitant ASA 75 to 100 mg daily during the treatment period according to local practice. ASA dosing and the use of loading doses is described in Section 5.5.3.1.

PK and PD Sub-Study

Japanese patients who provide a signed informed consent for this sub-study will be invited to participate in a PK and PD Sub-Study. Participation is voluntary in the selected sites which are provided the equipment and training for PD measurement. The target is to recruit 20 patients each arm. Full details of the PK and PD Sub-Study are given in Section 6.7 and Appendix E.

Holter ECG Sub-Study

Japanese patients who provide a signed informed consent for this sub-study will be invited to participate in a Holter ECG Sub-Study. Participation is voluntary and in the selected sites which are provided the equipment and training for ECG measurement. The target is to recruit 55 patients each arm. Full details of the Holter ECG Sub-Study are given in Section 6.4.8.1.

Pharmacogenetics

Patients who provide a separate signed informed consent will be invited to participate in an additional pharmacogenetic research component. Participation is voluntary and requires provision of additional signed informed consent independent of consent to participation in the main study. The target is to recruit 400 patients. Full details of the pharmacogenetic research component to the study are given in Appendix D.

Visit plan

The study will consist of an in-patient period of hospitalisation (Visit 1) during which patients will be enrolled and randomised, followed by a treatment period of variable duration. Following discharge, patients will attend the clinic every month until 6 months after the index event. Visits will then occur at intervals of approximately 3 months from the index event to ensure compliance with the study protocol, record information on any adverse events (AEs)/clinical endpoint events and to re-supply the patient with study medication.

The total number of visits and duration of treatment for an individual patient may be dependent on the following:

(a) when the patient was recruited into the study

(b) any decision to terminate the study early for a clear harmful effect

(c) plans to phase the closure of the study

If a patient has the planned maximum of 12 months treatment, the visit schedule will be as follows:

Visit 1 at Day 1 until discharge (Index hospitalisation)

Visit 2 at 1 month after the index event

Visit 3 at 2 months after the index event

Visit 4 at 3 months after the index event

Visit 5 at 4 months after the index event

Visit 6 at 5 months after the index event

Visit 7 at 6 months after the index event

Visit 8 at 9 months after the index event

Visit 9 (End of Treatment Visit) at 12 months after the index event

Follow-up Visit at 1 month after the End of Treatment Visit

Visits of Visit 2 to 7should preferably take place ±5 days of the target date for the visit and visits after Visit 7 should preferably take place ±10 days of the target date for the visit.

For the study plan see Table 1.

Visit 1: Enrolment (Index Hospitalisation)

Patients will already be hospitalised due to their acute condition. After signing the informed consent form, eligibility tests will be performed in line with the inclusion/exclusion criteria. Each patient will be allocated a strictly sequential enrolment code (E code) within each centre. Patients must be enrolled and randomised within 24 hours of the onset of their most recent cardiac ischaemic symptoms of their non-ST or ST segment elevation ACS event that meets entry criteria and prior to any urgent PCI. Randomisation should take place as soon as possible after presentation. If there is an indication for clopidogrel therapy the aim should be to immediately randomise the patient to study medication and not to start with open clopidogrel before randomisation. Initial dosing of study medication should start as soon as possible after randomisation.

The following enrolment assessments will be performed: demographics (date of birth, gender, race and ethnic group), relevant medical/surgical history, smoking history, family history of coronary heart disease, Thrombolysis in Myocardial Infarction (TIMI) risk score for non-ST elevation ACS, targeted physical examination, weight, height, medications, vital signs (heart rate and blood pressure [BP]) and Killip class (Killip T et al 1967). The weight and height may be performed during hospitalization.

Local laboratory analysis for safety tests (clinical chemistry and haematology) and cardiac biomarkers (troponin I, troponin T, creatine kinase myocardial band [CK-MB] or human heart fatty acid binding protein [H-FABP]), ECG, physical examinations, vital signs, pregnancy test, weight and height carried out on admission for the index event (ie, prior to signing

informed consent) may be used to assess patient eligibility if part of the normal routine with the patient's agreement.

All concomitant medications will be recorded including use of antiplatelet and anticoagulant medications for the 7 days prior to enrolment.

AEs and endpoint events will be recorded from enrolment.

Visit 1: Randomisation until hospital discharge (Index Hospitalisation)

If the patient is eligible to be randomised, the baseline laboratory blood sample for safety tests and myocardial necrosis biomarker (troponin I and CK-MB) will be collected prior to randomisation and sent to the central laboratory for all patients. The results from the central laboratory are not required prior to randomisation.

Patients will be randomised to study medication using IVRS/IWRS. The enrolment and randomisation assignments can both be done with one interaction with the IVRS/IWRS.

Initiation of study medication should take place as soon as possible after randomisation and should not be delayed to allow procedures to take place. Time and date of first dose will be recorded. Patients may be randomised at any point prior to PCI including post-angiography if all inclusion/exclusion criteria are fulfilled. Compliance and drug accountability will be assessed from randomisation.

A blood sample for pharmacogenetic research will be collected from the patients who have provided signed informed consent for this research (see Appendix D). This sample should be collected as close to randomisation as possible.

Myocardial necrosis biomarker (troponin I and CK-MB) will be collected at 8-12 hours and 12-24 hours after PCI and sent to the central laboratory for all patients. For patients whom elective PCI is performed, ie, PCI is not performed immediately after randomisation, will be required to collect an additional blood sample for myocardial necrosis biomarker (troponin I and CK-MB) as pre-PCI. This will not be required for patients whom emergency PCI is performed immediately after randomisation since a blood sample for myocardial necrosis biomarker (troponin I and CK-MB) collected prior to randomisation will serve as pre-PCI.

A blood sample for population PK will be collected from all patients (except for patients participating in PK/PD sub-study described below) on Day 4 post-enrolment or at discharge from hospital, whichever is sooner. The blood sample will be collected at pre-dose and 1-4 hours post-dose. The date and time of sample collection will be recorded in the medical records and the eCRF as well as the date and time of the dose of study medication.

A blood sample for PK/PD sub-study will be collected from the patients who have provided signed informed consent for the sub study on Day 4 post-enrolment or at discharge (or the day before discharge) from hospital, whichever is sooner. The blood sample will be collected at pre-dose and 1,2, 4, 8, 12 hours post-dose. The date and time of sample collection will be

recorded in the medical records and the eCRF as well as the date and time of the dose of study medication.

At discharge from hospital or Day 4 post-enrolment, whichever is sooner a 12-lead ECG will be taken for the assessment of heart rate and Q waves.

All medications will be recorded from randomisation until hospital discharge. Endpoint events and AEs will continue to be recorded during hospitalisation.

Holter ECG will be recorded in patients who have provided signed informed consent for the sub study. Recordings will start as soon as possible but within 24 hours at the latest after randomisation and intake of study drug. Holter ECG will continue for 24 hours.

Visit 1: Hospital Discharge (Index Hospitalisation)

Suspected endpoint events, AEs and all medications will continue to be recorded during hospitalisation, and a further check will be carried out at the time of hospital discharge.

Visit 2 (1 month)

All patients will have this visit unless they discontinue from the study prematurely and withdraw consent from the study participation.

Vital signs, suspected endpoint events, AEs and current medications (see Section 5.6) will be recorded.

Study medication will be returned and drug accountability will be performed by pill-count. Sufficient study medication will be dispensed to last until the next visit.

A 12-lead ECG will be performed to enable the investigator to make an assessment of heart rate and the occurrence of silent MI since the Visit 1.

A blood sample for population PK will be obtained from all patients (except for patients participating in PK/PD sub-study described below). The blood sample will be collected at pre-dose and 1-4 hours post-dose. The date and time of sample collection will be recorded in the medical records and the eCRF as well as the date and time of the dose of study medication.

A blood sample for PK/PD sub-study will be collected from the patients who have provided signed informed consent for this sub study at pre-dose and during 1-4 hours post-dose for PK, and at 1 time point of either at pre-dose or during 1-4 hours post-dose (same time point as that for PK) for PD. The date and time of sample collection will be recorded in the medical records and the eCRF as well as the date and time of the dose of study medication.

A blood sample for safety tests (clinical chemistry and haematology will be collected and sent to the central laboratory.

Holter ECG will be recorded for 24 hours in patients who have provided signed informed consent for the sub study.

Visit 3 (2 months)

All patients will have this visit unless they discontinue from the study prematurely and withdraw consent from the study participation.

Vital signs, suspected endpoint events, AEs and current medications (see Section 5.6) will be recorded.

Visit 4 (3 months)

All patients will have this visit unless they discontinue from the study prematurely and withdraw consent from the study participation.

Vital signs, suspected endpoint events, AEs and current medications (see Section 5.6) will be recorded.

Study medication will be returned and drug accountability will be performed by pill-count. Sufficient study medication will be dispensed to last until the next visit.

A blood sample for safety tests (clinical chemistry and haematology will be collected and sent to the central laboratory.

Visit 5 (4 months) or Visit 6 (5 months)

All patients will have this visit unless they discontinue from the study prematurely and withdraw consent from the study participation.

Vital signs, suspected endpoint events, AEs and current medications (see Section 5.6) will be recorded.

Visit 7 (6 months)

All patients will have this visit unless they discontinue from the study prematurely and withdraw consent from the study participation.

Vital signs, suspected endpoint events, AEs and current medications (see Section 5.6) will be recorded.

Study medication will be returned and drug accountability will be performed by pill-count. Sufficient study medication will be dispensed to last until the next visit.

A blood sample for safety tests (clinical chemistry and haematology) will be collected and sent to the central laboratory.

Urine pregnancy test should be taken for females of child bearing potential.

Visit 8 (9 months)

Vital signs, suspected endpoint events, AEs and current medications (see Section 5.6) will be recorded.

Study medication will be returned and drug accountability will be performed by pill-count. Sufficient study medication will be dispensed to last until the next visit.

Visit 9 - End of Treatment Visit: EoT (planned or premature discontinuation)

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

Suspected endpoint events, AEs and current medications (see Section 5.6) will be recorded.

All remaining study medication will be returned and drug accountability will be performed by pill-count.

A 12-lead ECG will be performed to enable the investigator to make an assessment of heart rate and the occurrence of silent MI during the study.

A blood sample for safety tests (clinical chemistry and haematology) will be collected and sent to the central laboratory.

Urine pregnancy test should be taken for females of child bearing potential.

A targeted physical examination, weight and vital signs assessment will be performed.

In addition the investigator will decide which antiplatelet medication the patient should receive as part of his/her ongoing clinical care. This medication(s) will be open label, obtained locally, and will also be recorded in the electronic Case Report Form (eCRF) by the investigational site.

Follow-up Visit (1 month after EoT Visit)

The patient will return to the clinic 1 month after the End of Treatment visit. Any new suspected endpoints, AEs and current medications (see Section 5.6) will be recorded.

A blood sample for safety tests (clinical chemistry and haematology) will be collected and sent to the central laboratory.

Prematurely discontinued patients

Patients who discontinued study treatment prematurely and have not withdrawn consent, will do the End of Treatment Visit and one month later a Follow-up Visit (including clinical chemistry & haematology blood samples). The patients will subsequently continue the scheduled visit plan according to protocol until 12 month after randomization is passed or the study is closed. Protocolled data collection and procedures should continue according to the study protocol with the exception of clinical chemistry and haematology blood draws. Patients who discontinued study treatment prematurely and refused to come for the Follow-up visit and have not withdrawn consent should be contacted via a telephone call and the contact should be recorded in the eCRF.

Final Visit

All randomised patients who are attending study visits when all patients have been treated for a minimum of 6 months should return for the final visit(s) as soon as possible, no later than 2 months beyond the date when all patients have been treated for a minimum of 6 months.

- Patients who are under treatment will return to the clinic as soon as possible for an End of Treatment visit, and do the Follow up visit 1 month after.

- Patients who have prematurely discontinued study treatment and are attending study visits will return for the final visit. If the patient had not already returned for a Follow-up Visit, the Follow-up Visit will be the final visit. If the patient had already done the Follow-Up Visit, the final visit will be to confirm endpoint events or SAEs.

Patients who are not attending study visits when all patients have been treated for a minimum of 6 months but have not withdrawn consent will be contacted for assessment of health status or vital status as per agreement, ie, by telephone, by checking medical record or by collecting information from publicly available sources.

Unscheduled Visits

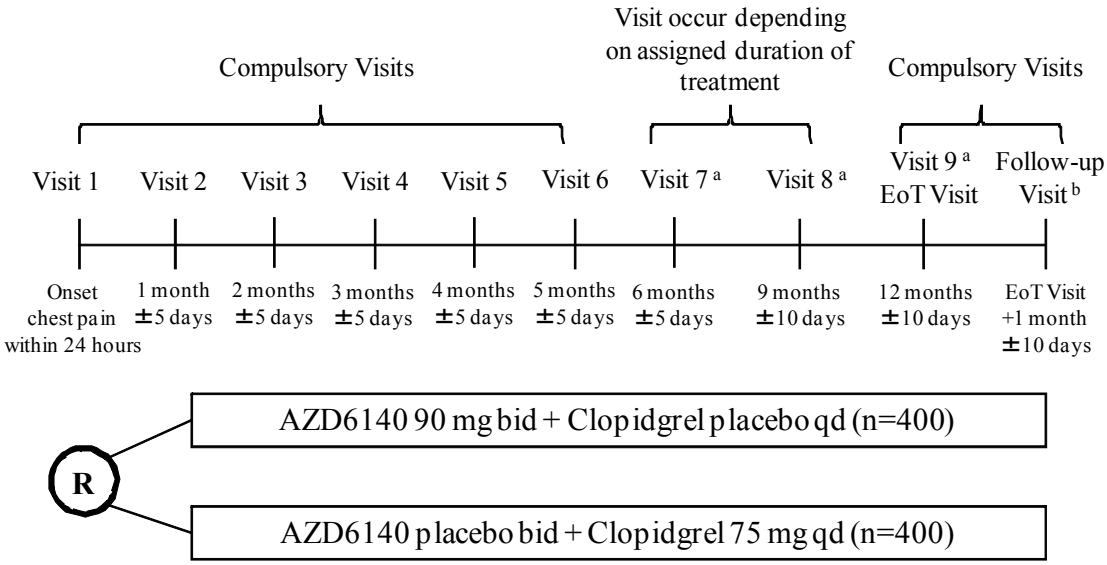
Extra visits may be necessary for safety reasons. These visits will be recorded in the eCRF as unscheduled visits, necessary safety blood samples sent to the central laboratory and AE/SAE section completed as deemed appropriate by the Investigator.

If needed, study medication will be returned and drug accountability performed by pill-count and the new bottles will be dispensed to last until the next visit and the reason recorded in the eCRF.

Lost to follow-up

Repeated attempts will be made to locate and determine the vital status and occurrence of any MI or stroke for those patients who are considered initially lost to follow up and have not withdrawn consent. A patient will be classified as lost to follow up only if, he/she has failed to return for the required study visits and his/her vital status remains unknown despite multiple attempts to contact him/her via telephone, fax, email, certified letter or through patient locator agencies (if allowed per national regulation).

Figure 1 Study flow chart



R: Randomisation

a For subjects who continue the study, Visit 7, Visit 8 or Visit 9 may be the end of Treatment (EoT) Visit, when all measurements should be performed.

b Patients who discontinue treatment prematurely will have a Follow-up Visit one month after the EoT Visit and then should be followed according to the visit schedule.

Table 1 Study plan

Assessment	Visit 1			Visit 2	Visit 3	Visit 4	Visit 5, 6	Visit 7	Visit 8	Visit 9	End of Treatment Visit (EoT)	Follow-up Visit
	Enrol-ment	Random-isation	Dis-charge	1 m ±5d	2 m ±5d	3 m ±5d	4/5 m ±5d	6 m ±5d	9 m ±10d	12 m ±10d		EoT Visit +1 m ±10d
Signed informed consent	X											
Signed informed consent for pharmacogenetic research (optional)	X											
Inclusion and exclusion	X											
Relevant medical & surgical history, smoking history, family history of cardiac disease	X											
Demography	X											
Vital signs	X			X	X	X	X	X	X	X	X	
Physical examination and weight (Visit 1, 9/EoT only), Killip class and height (Visit 1 only)	X[a]									X	X	
Access IVRS/IWRS	X			X		X		X	X	X	X	X
12-lead ECG	X[b]		X[c]	X						X	X	
Clinical chemistry & haematology		X		X		X		X		X	X	X
Urine and/or blood pregnancy test	X	X						X[d]		X[d]	X[d]	
Myocardial necrosis biomarkers (Central lab)		X[e]										
PK blood sample [f]			X[c]	X								
PK/PD sample (n=40) [g]			X[c]	X								
Holter ECG (n=110) [h]		X		X								
Pharmacogenetic research sample [i]	< ---	---------	----- >									
Dispense investigational product		X		X		X		X	X			
Return investigational product				X		X		X	X	X	X	
Compliance/ drug accountability			X	X	X	X	X	X	X	X	X	

Table 1 Study plan

Assessment	Visit 1			Visit 2	Visit 3	Visit 4	Visit 5, 6	Visit 7	Visit 8	Visit 9	End of Treatment Visit (EoT)	Follow-up Visit
	Enrol-ment	Random-isation	Dis-charge	1 m ±5d	2 m ±5d	3 m ±5d	4/5 m ±5d	6 m ±5d	9 m ±10d	12 m ±10d		EoT Visit +1 m ±10d
Medications	X	X	X	X	X	X	X	X	X	X	X	X
AEs, SAEs & endpoints	X	X	X	X	X	X	X	X	X	X	X	X
Post-study antiplatelet therapy										X	X	X

a Weight and height may be assessed during Visit 1.
b For eligibility, for silent MI. (See Section 6.4.8)
c Discharge or 4 days post-enrolment, whichever is sooner.
d For females of child bearing potential a urine pregnancy test should be repeated every 6 months.
e Samples for troponin I and CK-MB will be taken prior to randomisation, 8-12 hours and 12-24 hours after PCI for all patients. For patients whom PCI is not performed will be required to collect only prior to randomisation. For patients whom elective PCI is performed, ie, PCI is not performed immediately after randomisation, will be required to collect an additional blood sample for myocardial necrosis biomarker (troponin I and CK-MB) as pre-PCI.
f PK samples will be collected at pre dose and 1-4 hours after dose both Visit 1 (Discharge or Day 4 post-enrolment) and Visit 2 from all patients (except for patients participating in PK/PD sub-study).
g PK/PD samples will be collected as Table 2 from the 40 Japanese patients.
h Holter ECG will be performed during Hospitalization but within 24 hours at the latest after randomisation and at Visit 2 in 110 Japanese patients only.
i A blood sample for pharmacogenetic research will be collected after patients who have provided signed informed consent for this research. This sample should be collected as close to randomisation as possible.

Table 2 PK or PD blood sampling schedule

Assessment	Visit 1						Visit 2	
	Discharge or Day 4 post-enrolment, whichever is sooner [a]						1 month	
Hours (relative to dose)	Pre	1	2	4	8	12	Pre	1-4
PK blood sample (All subjects except for patients participating in PK/PD sub-study)	X	< ----------X [b] ---------- >					X	X [b]

Table 2 PK or PD blood sampling schedule

Assessment	Visit 1						Visit 2	
	Discharge or Day 4 post-enrolment, whichever is sooner [a]						1 month	
PK blood sample (PK/PD sub group)	X	X	X	X	X	X	X	X [b]
PD blood sample (PK/PD sub group)	X	X	X	X	X	X	< ----------X [c] --------- >	

a Blood sampling in PK/PD sub group is allowed to start and end on the day before discharge.
b One time point during 1-4 hours post-dose
c Same time point as that for PK either at pre-dose or during 1-4 hours post-dose

3.2 Rationale for study design, doses and control groups

This study is designed to investigate the efficacy and safety of AZD6140 compared with clopidogrel when given on top of low dose ASA for the study population.

Primary endpoint

The PLATO result shows AZD6140 has a favourable risk benefit profile delivering a relative risk reduction of thrombotic events (MI, stroke, death from vascular causes) of 16% (1.9% absolute decrease) in patients with ACS, no clinically meaningful difference in either fatal bleeds or PLATO-defined major bleeds compared to clopidogrel.

To be consistent with PLATO, the primary endpoints, the major bleeding and the composite event of death from vascular causes, MI, and stroke, will be assessed in this study to investigate efficacy and safety in Asian patients.

AZD6140 dosing regimen

Based on the analysis of the Asian subgroup of patients enrolled in PLATO demonstrated a consistent benefit and risk ratio of AZD6140 versus clopidogrel sulphate, compared with the overall population, while no new safety concerns were observed in Asian patients. It was considered appropriate that the recommended dose of AZD6140 for Japanese would also be 90 mg bid, the dose of PLATO.

Currently, Phase II study (D5130C00065) is being conducted in Japanese and Asian patients with Stable Coronary Artery Disease to investigate effect of two doses of AZD6140 45 mg and 90 mg, twice daily on Inhibition of Platelet Aggregation. Interim review of Japanese patients was performed. IPA in AZD6140 90 mg twice daily was greater than AZD6140 45 mg twice daily by more than 5%, and no obvious safety issues were observed among the 2 doses. It was considered that AZD 6140 90 mg twice daily was also appropriate in Japanese patients.

AZD6140 is a substrate for CYP3A and the concomitant use of strong CYP3A inhibitors like azole antifungal agents are excluded from this study. A Clinical Pharmacology study has established that steady-state administration of diltiazem (a representative moderate CYP3A inhibitor) increases plasma exposure to AZD6140 (but not its active metabolite) approximately twofold. However, PK sampling in patients receiving such moderate inhibitors in DISPERSE 2 did not distinguish them from patients not receiving such concomitant medications based on similar PK sampling. While these data are not considered definitive, they may reflect variability in “real life” concomitant use of such moderate CYP3A inhibitors or may simply reflect the intrinsic variability in plasma exposure to AZD6140 both in the presence and absence of a variety of moderate CYP3A inhibitors. Data on the safety of AZD6140 has not documented a relationship between the degree of plasma exposure and the occurrence of adverse events. It is also important to note that the exposure to 180 mg AZD6140 twice daily, a level of exposure to parent molecule that may be achieved during concomitant use of moderate CYP3A inhibitors, has been studied in patients for up to 12 weeks in DISPERSE 2, with an acceptable safety profile. Given these considerations it is not

expected that important differences in the safety profile of the drug in patients treated with moderate CYP3A inhibitors and those not so treated will be observed in this study.

Control group and background therapy

The control group in this study will receive a standard therapeutic dosing regimen of clopidogrel. Long-term treatment with clopidogrel has been shown to significantly reduce the incidence of death from vascular causes, MI and stroke in non-ST elevation ACS (Yusuf S et al 2001) and is among a range of standard therapies recommended for the management of patients with non-ST elevation ACS in current guidelines (Braunwald E et al 2002). Similar efficacy of clopidogrel treatment has recently been observed in the CLARITY- TIMI28 (Sabatine MS et al 2005) and COMMIT studies (Chen ZM 2005) for patients with ST elevation ACS. Furthermore both in the non-ST-elevation and ST-elevation populations clopidogrel is a standard treatment both during and after PCI procedures, which today is a widely practiced approach to both in ST-elevation and non-ST-elevation ACS (Bertrand ME et al 2002, Braunwald E et al 2002, Silber S et al 2005). The standard regimen of a 300 mg clopidogrel study medication (active or placebo) loading dose followed by 75 mg once daily clopidogrel will be administered to patients not pre-treated with clopidogrel. Pre-treated patients will receive the 75 mg maintenance dose (active or placebo) as their first dose. An additional 300 mg clopidogrel dose will be allowed for PCI at the discretion of the investigator according to local practice. A loading dose of AZD6140 180 mg study medication (active or placebo) will be given, both initially and in the event of interruption of study therapy for more than 5 days, if the patient is treated in hospital for an ACS. An additional dose of 90 mg AZD6140 study medication will be administered to all patients prior to PCI, if the intervention takes place >24 hours after randomisation.

Both AZD6140 and clopidogrel will be administered against a background of ASA therapy since ASA is standard therapy for prevention of thrombotic events and new therapies will be adjunctive (Chen ZM 2005, Sabatine MS et al 2005, Yusuf S et al 2001). A once daily ASA dose of 75 to 100 mg has been recommended since previous clinical studies (Peters RJG et al 2003, Patrono C et al 2004) have indicated this as a suitable daily dose range for ASA in combination therapy to protect against thrombotic events. For patients not previously on ASA, a loading dose of 162 to 330 mg ASA is permitted according to local practice. For maintenance, a once daily dose of 75 to 100 mg is allowed according to local practice. Following stenting, up to 330 mg of ASA daily is allowed for up to 6 months following placement of bare metal or drug eluting stents according to local practice, at the investigators' discretion.

Study design

This study is mirror study of PLATO. However, this is not a confirmative study of PLATO. A variable, long-term treatment duration of approximately 6 months to 12 months, has been selected based on PLATO. The average study duration is expected to be approximately 10 months per patient. The risk of recurrent events following ACS is highest early but persists chronically so that long term antiplatelet therapy is required. In this study monthly visits have been scheduled until 6 months after randomization, which is more frequent than specified in

the PLATO protocol, in order to safeguard the safety of subjects. After the initial 6 months period post-ACS patients are expected to be in a stable phase on maintenance antiplatelet therapy. Consequently the intervals between study visits are prolonged beyond 6 months. If judged needed, the visit frequency may be reconsidered based on results of an ongoing Phase II study, after its completion.

Study patient population

In order to compare with PLATO data , the study patient population need to keep consistency with PLATO.

The sites selected in this study will represent a range of treatment practices, however a particular emphasis will be placed on selecting sites with access to catheterisation facilities with a view to ensuring a study population that is treated in accordance with international guidelines recommending an early invasive approach for high risk patients.

4. SUBJECT SELECTION CRITERIA

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

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

4.1 Inclusion criteria

For inclusion in the study subjects should fulfil the following criteria:

1. Provision of signed informed consent prior to any study specific procedures

   Due to the nature of the target disease, its treatment and the study design (randomisation within 24 hours of onset of index event), it is highly likely that the local laboratory tests and ECG will be performed as normal procedure prior to obtaining signed informed consent form. These data could be used for eligibility evaluation for this study after obtaining signed consent from the subjects or their guardian/legal representative.

2. Male or female aged at least 20 years

3. Index event of non-ST or ST segment elevation ACS and correspond **all to below**

   - The patient hospitalised for chest pain, potential ACS, and primary PCI planned

   - The onset of the most recent cardiac ischaemic symptoms of the index event must occur within the 24 hours before randomisation

- Be documented by cardiac ischaemic symptoms of ≥10 minutes duration at rest

And correspond one of the followings

- Persistent ST segment elevation ≥1mm (0.1 mV) in 2 or more contiguous leads
- New or presumed new left bundle branch block (LBBB)
- Cardiac ischaemic symptoms of ≥10 minutes duration at rest **and at least 2 of the following 3 criteria:**

(i) ST segment changes on ECG indicative of ischaemia:

Either

- ST segment depression ≥1mm (0.1mV) in 2 or more contiguous leads

or

- Transient ST segment elevation ≥1 mm (0.1 mV) in 2 or more contiguous leads

(ii) Positive biomarker evidence of myocardial necrosis:

Either

- Troponin T, troponin I, CK-MB or H-FABP is greater than the laboratory upper normal limit on at least one occasion in association with the index clinical event (ie, any elevated troponin level)

or

- Troponin T, troponin I, CK-MB or H-FABP is positive by qualitative test at least one occasion in association with the index clinical event

(iii) Having at least one of the following risk factors:

- Aged 60 or over
- Previous MI or CABG
- Known multi-vessel coronary artery disease (CAD) (50% or more stenosis in 2 or more vessels)
- Previous ischaemic stroke, transient ischaemic attack (TIA) (hospital based diagnosis), carotid stenosis (50% or more) or cerebral revascularisation

- Diabetes mellitus
- Peripheral arterial disease (intermittent claudication with prior objective confirmation, previous revascularisation or ankle-brachial index less than 0.9)
- Chronic renal dysfunction (creatinine clearance calculated by Cockcroft Gault equation is less than 60 mL/min).

4. Females of child-bearing potential (ie, females who are not chemically or surgically sterilised or females who are not post-menopause) must have a negative urine or blood pregnancy test at enrolment and be willing to use 2 methods of reliable contraception, one of which must be a barrier method.

For inclusion in the pharmacogenetic research, patients must fulfil the following criterion:

5. Provision of signed informed consent for pharmacogenetic research.

If a patient declines to participate in the pharmacogenetic research, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study described in this Clinical Study Protocol, so long as they consent.

The patient should be excluded from this pharmacogenetic research if a previous bone marrow transplant has been performed or non-leukocyte depleted whole blood transfusion in 120 days of the genetic sample collection has been performed..

4.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Contraindication or other reason that clopidogrel, AZD6140 or ASA should not be administered (eg, hypersensitivity, active bleeding, moderate or severe liver disease, history of previous intracranial bleed, GI bleed within the past 6 months, major surgery within 30 days or ischemic stroke within the previous 14 days)

2. Index event is an acute complication of PCI

3. Patient has undergone PCI after the index event and before the first dose of study treatment

4. Oral anticoagulation therapy that cannot be stopped (ie, patient requires chronic therapy)

5. Fibrinolytic therapy in the 24 hours prior to randomisation, or planned fibrinolytic treatment following randomisation (eg, for STEMI or PE)

6. The conditions associated with increased risk of bradycardic events (eg, no pacemaker with known sick sinus syndrome, second degree A-V block, third degree A-V block or previous documented syncope suspected to be due to bradycardia excluding the transient conditions associated with index event)

7. Patient requires dialysis

8. Known, clinically important thrombocytopenia

9. Known, clinically important anaemia

10. Any other condition which in the opinion of the investigator, may either put the patient at risk or influence the result of the study (eg, cardiogenic shock or severe haemodynamic instability, active cancer, risk for non-compliance, risk for being lost to follow up)

11. Pregnancy or lactation

12. Concomitant oral or intravenous therapy (see examples below) with strong CYP3A inhibitors or CYP3A substrates which cannot be stopped for the course of the study

    – CYP3A strong inhibitors, such as ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir

    – CYP3A substrates: simvastatin at dose >40 mg or lovastatin at dose >40 mg.

13. Participation in another investigational drug or device study in the last 30 days

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

15. Previous enrolment or randomisation of treatment in the present study.

Procedures for withdrawal of incorrectly enrolled subjects see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

There are no specific dietary or activity restrictions other than those typical for a patient with this disease and grapefruit juice over 1L per day.

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

Restrictions regarding concomitant medications are described in Section 4.2 and Section 5.6.

5.2 Subject enrolment and randomisation

The Principal Investigator will:

1. Obtain signed informed consent from the potential subject and/or their legal representative before any study specific procedures are performed.

   The acute version of informed consent form can be used in acute cases where the subject is having symptoms due to ACS and impossible to take enough time to provide consent by the full version of informed consent form. The subject must sign the acute version of informed consent form him/herself. If the subject is impossible to sign by him/herself, then their legal representative can provide signed consent. If either the acute version of informed consent form is used, or informed consent was signed by the legal representative, then the subject must provide signed informed consent by the full version of informed consent form after PCI/CABG has been performed and the subject's condition is stable.

2. Assign potential subject a unique enrolment number, beginning with 'E'.

3. Determine subject eligibility. See Sections 4.1 and 4.2.

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

5.2.1 Procedures for randomisation

Patient eligibility will be established before treatment randomisation. Patients will be enrolled/randomised strictly sequentially, as patients become eligible for enrolment/randomisation. If a patient discontinues from the study, the patient number will not be reused, and the patient will not be allowed to re-enter the study.

At Visit 1, for patients who fulfil all the eligibility requirements, the investigators will access the IVRS/IWRS. The IVRS/IWRS will allocate a randomisation code and provide the investigator with unique treatment pack ID numbers for that patient for the Visit 1 supply of medication.

Following randomisation, the first dose of study medication will be administered.

Pack ID numbers for supplies in case of PCI, treatment interruptions, and for subsequent visits will also be provided by accessing the IVRS/IWRS.

The randomisation codes will be computer-generated by AstarZeneca R&D using Grand (AZ Global Randomisation system) and loaded into the IVRS/IWRS database. A blocked randomisation schedule by site will be produced for the main study.

Patient discontinuation information (study treatment and/or study participation) will be recorded into the IVRS/IWRS.

5.3 Procedures for handling subjects incorrectly enrolled or randomised

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

Where subjects that do not meet the selection criteria are randomised in error or incorrectly started on treatment, or where subjects subsequently fail to meet the study criteria post initiation, a discussion should occur between the AstraZeneca Study Delivery Team Physician and the Investigator regarding whether to continue or discontinue the subject from treatment. In situations where an agreement cannot be reached, the subject should have their study therapy stopped.

The AstraZeneca Study Delivery Team Physician is to ensure all such decisions are appropriately documented.

5.3.1 Procedure for handling subjects randomised but PCI is not done or CABG is done instead of PCI

When subjects are randomised but PCI is not done or CABG is done instead of PCI, the investigators will decide whether to continue or discontinue the subject from study treatment based on needs of dual anti platelet therapy. In situation where the investigators decide that continued dual anti platelet therapy is indicated, study treatment may continue and the scheduled visits on treatment is followed. In a situation where the investigators decide that continued dual anti platelet therapy is not indicated the subject will discontinue study treatment, and the procedure for prematurely discontinuation should be followed.

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 and double-dummy. To ensure blinding of the treatments, matching AZD6140 placebo tablets will be provided. The active clopidogrel capsule (over-encapsulated clopidogrel tablet) and the placebo capsule to match will also be provided. Each treatment group will consist of the same combination of matching active and placebo tablets and matching active and placebo capsules, so medication provided for each treatment groups are identical in appearance (that is, the same number, size and packaging of the tablets and capsules). Each pack will be labelled with a unique pack ID number that will be used to assign the treatment to the patient but will not indicate the treatment allocation to the investigator or patient.

The DSMB will have access to unblinded data during the study.

5.4.2 Methods for unblinding the study

In addition to the IVRS/IWRS, within AstraZeneca the treatment codes will be available by accessing the GRand system. Access to GRand and unblinding procedures are strictly

controlled and an audit trail will be maintained according to AstraZeneca Standard Operating Procedures (SOPs).

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

For Japan, replace the above paragraph with the paragraph below

Individual treatment codes, indicating the treatment randomisation for each randomised subject, will be available to the investigator(s) or pharmacists, and the personnel who are independent to the study evaluation at the Patient Safety Department, AstraZeneca from the IVRS/IWRS.

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

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

5.5 Treatments

5.5.1 Identity of investigational product(s)

AZD6140 90 mg tablets and their matching placebo tablets will be used in the study together with clopidogrel 75 mg tablets that have been over-encapsulated and their matching placebo capsules (see Table 3 and Table 4 for further details).

Table 3 Identity of investigational product

Investigational product	Dosage form and strength	Manufacturer
AZD6140 90 mg	Plain, round, yellow, film-coated tablet, 90 mg	AstraZeneca
AZD6140 90 mg placebo	Plain, round, yellow, film-coated tablet, placebo to match 90 mg	AstraZeneca

Table 4 Identity of comparator

Investigational product	Dosage form and strength	Manufacturer
Clopidogrel, over encapsulated	Orange brown capsule, containing one 75 mg Clopidogrel tablet (cut into 2 halves)	AstraZeneca
Clopidogrel placebo	Orange brown capsule containing zero active therapy (identical in appearance to active)	AstraZeneca

A Global Phase I study (D5130C00020) indicates that the process of halving and over-encapsulating clopidogrel tablets into capsule form does not affect its pharmacodynamic or PK characteristics.

5.5.1.1 Packaging of investigational products

AZD6140 90 mg tablets and matching placebo tablets will be packed in HDPE bottles with an induction seal and child-resistant cap containing 60 tablets each.

Over-encapsulated clopidogrel tablets and matching placebo capsules will be packed in HDPE bottles with a tamper evident seal and child-resistant cap containing 30 capsules each. Sufficient bottles of each will be issued at each dispensing visit to cover the period to the next scheduled visit. Bottles will be labeled with a unique identification (ID) number. The IVRS/IWRS will provide pack ID numbers to be dispensed to the patient according to the randomised treatment at each dispensing visit.

5.5.2 Doses and treatment regimens

At Visit 1 (randomisation) eligible patients will be randomly assigned to one of two treatment groups, AZD6140 90 mg twice daily or clopidogrel 75 mg once daily, taken orally.

Randomisation and treatment pack assignment will be managed via the IVRS/IWRS and the first dose of study medication should be taken directly after randomisation at Visit 1. 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 should not be altered (eg, crushed, put in another vehicle) and should not be given by nasogastric tube or other routes.

All patients should receive a loading dose of AZD6140 study medication (two tablets of either 90 mg or matching placebo).

Provision will be made for patients to receive a standard loading dose of clopidogrel whilst ensuring blinding of the treatment allocation. There are two scenarios:

- **Clopidogrel treated:** a patient who has already received a loading dose of 300 mg clopidogrel as part of their initial clinical care prior to randomisation, or who has

already been taking maintenance doses of clopidogrel or ticlopidine for at least 5 days immediately prior to randomisation, will receive a maintenance dose (75 mg) of clopidogrel study medication (active or placebo) as their first dose and continue on this maintenance dose of study medication thereafter.

- **Clopidogrel-naïve patient:** a patient who has not already received a loading dose of clopidogrel as part of their initial clinical care prior to randomisation or who has not been receiving maintenance doses of clopidogrel or ticlopidine for ≥5 days immediately prior to randomisation, will receive a 300 mg loading dose of clopidogrel study medication (active or placebo) as their first dose followed by a maintenance dose of study medication thereafter.

5.5.3 Additional study drug

5.5.3.1 Concomitant ASA

In addition to randomised study medication all patients should be treated with concomitant ASA 75 to 100 mg daily during the treatment period according to local practice.

For patients not previously on ASA, a first loading dose of 162 to 330 mg ASA is allowed according to local practice. Following stenting, up to 330 mg of ASA is allowed for up to 6 months following bare metal or drug eluting stents according to local practice at the Investigator's discretion.

5.5.3.2 Additional study medication for patients undergoing PCI

Patients undergoing PCI during the treatment period should receive an additional loading dose of 90 mg AZD6140 blinded study medication (active or placebo) if the intervention takes place >24 h after randomisation. Such patients may also be administrated an additional loading dose up to 300 mg clopidogrel blinded study medication (active or placebo) at the discretion of the investigator, irrespective of the timing in relation to randomisation according to local practice.

Any additional doses should be recorded in the eCRF. If necessary additional supplies will be allocated by the IVRS/IWRS.

5.5.4 Interruptions to study medication

In case of treatment interruption for more than 5 days and if the patient is treated in hospital for an ACS, patients should be administered a loading dose of 180 mg AZD6140 (2x90 mg tablets) blinded study medication. Patients may be administered a corresponding loading dose of 300 mg clopidogrel (4 capsules) blinded study medication at the discretion of the investigators.

Four clopidogrel 75 mg capsules of blinded study medication and two AZD6140 90 mg tablets of blinded study medication will be taken as a loading dose. If necessary additional supplies will be allocated by IVRS/IWRS.

Missed doses of AZD6140 or clopidogrel 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). If a patient cannot take oral medication then study treatment should be interrupted until oral therapy can be resumed.

Any temporary interruption of investigational products ≥ 48 hours should be recorded in the eCRF.

5.5.5 End of the study

At the end of the planned treatment period or if the patient discontinues prematurely from the study treatment, the investigator will decide which antiplatelet medication the patient should receive as part of his/her ongoing clinical care. This medication(s) will be open label, obtained locally, and will also be recorded in the eCRF by the investigational site.

5.5.6 Labelling

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

The label will include the following information: (Multi Language label will be used)

- Name of sponsor (AstraZeneca) and address
- Product name, dosage form and quantity
- Study code
- Pack ID number
- Directions for use
- Storage conditions
- Expiry date (where required by local regulations - excludes US).
- Lot number
- Keep out of reach of children
- For clinical trial use only

5.5.7 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle specifies the appropriate storage.

For Japan, replace this section with the paragraph below

A description of the appropriate storage conditions is specified in the document 'Procedure of storage conditions for investigational product'.

5.6 Concomitant and post-study treatment(s)

All medications will be recorded from 7 days prior to enrolment until completion of the last scheduled study visit.

5.6.1 Parenteral anticoagulants

Treatment with approved parenteral anticoagulants (eg, unfractionated heparin [UFH], LMWH, bivalirudin, fondaparinux) is allowed pre-study and/or during the study. However, long-term treatment with LMWH in outpatients (post-discharge) in combination with study medication is not allowed. Particular care should be taken in dosing LMWH in elderly patients (over 65 years of age) or those with renal or hepatic impairment. Heparins should be dosed carefully when used in conjunction with GPIIb/IIIa antagonists and with PCI.

5.6.2 Oral anticoagulants

Concomitant treatment with oral anticoagulant drugs is not allowed 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 can be stopped.

5.6.3 GPIIb/IIIa receptor antagonists

Treatment with GPIIb/IIIa receptor antagonists is allowed pre-study and/or during the study.

5.6.4 Oral antiplatelet therapies and NSAIDs

ASA: All patients should take open label ASA at a dose of 75 to 100 mg once daily throughout the study according to local practice. ASA dosing and the use of loading doses is described in Section 5.5.3.1. ASA for pain relief should where possible be discouraged and paracetamol (acetaminophen) given.

Clopidogrel: Patients who have received a loading dose and/or are currently taking clopidogrel are eligible to enter the study. Clopidogrel dosing and the use of loading doses is described in Section 5.5.2 and 5.5.3.2. Further dosing with clopidogrel in addition to study medication is not allowed. Investigators should note that patients will be randomised in the study to receive either clopidogrel or AZD6140.

Ticlopidine, dipyridamole and cilostazol: Patients who are currently taking any of these drugs are eligible to enter the study but treatment must be discontinued on randomisation. Further dosing of any of these drugs in addition to study medication is not allowed.

Other oral antiplatelets: Clinical experience with other drugs with antiplatelet effect (eg, non-steroidal anti-inflammatory drugs (NSAIDs)) in combination with AZD6140 is limited at this time. Treatment with these types of drug (including NSAIDs) is allowed pre-study and/or during the study, at the investigator's discretion. However, chronic daily dosing with non-selective NSAIDs (eg, patient with rheumatoid arthritis) may increase the potential for GI bleeding so either alternative therapy or concomitant acid suppression is recommended. Treatment with selective cycloxygenase-2 inhibitors is permitted, although use is cautioned.

5.6.5 Fibrinolytic therapy

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

Clinical experience of fibrinolytics in combination with AZD6140 is not available at this time and caution should be used. If treatment with fibrinolytic therapy is required during the study, please refer to Section 13.1.3.

5.6.6 P-glycoprotein interactions

AZD6140 and AR-C124910XX (active metabolite) are substrates and inhibitors of the p-glycoprotein transporter (also known as MDR1). In healthy volunteers mean trough digoxin (a p-glycoprotein substrate) levels were increased about 30% with AZD6140 co-administration with maximum increases of about 3-fold. Levels of digoxin should be monitored closely following initiation of study medication and with any change in study medication. Other p-glycoprotein substrates may be expected to have similar changes in PK.

5.6.7 CYP3A interactions

Strong CYP3A Inhibitors (eg, ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir): Co-administration of ketoconazole with AZD6140 increased AZD6140 C_{max} and AUC equal to 2.4-fold and 7.3-fold, respectively. The C_{max} and AUC of the active metabolite were reduced by 89% and 56% respectively. These drugs are not allowed during the study. If treatment with such therapies is necessary study medication dosing should be interrupted and then resumed if possible when administration of the inhibitor is no longer required.

CYP3A substrates: In healthy volunteer studies AZD6140 was found to increase simvastatin levels an average of about 50% with maximum individual increases of about 2- to 3 fold and increase atorvastatin levels an average of about 35%. As simvastatin has recommended restrictions for concomitant therapy with inhibitors of CYP3A due to increased reporting of myopathy, treatment with simvastatin or lovastatin (which is very similar pharmacokinetically to simvastatin) at doses higher than 40 mg is not allowed during the study. There are no restrictions to other statin therapies as either they are not metabolised by CYP3A (pravastatin, rosuvastatin, fluvastatin) or have no restrictions for concomitant use with mild or moderate inhibitors of CYP3A (atorvastatin).

5.6.8 CYP2C19 inhibitors

CYP2C19 inhibitors including some Proton Pump Inhibitors may reduce the formation of active metabolites of clopidogrel. The use of such drugs should be decided at the discretion of the investigator based on a clinical assessment of benefit and risk.

5.6.9 Other medications

Other medication, which is considered necessary for the subject's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

5.6.10 Treatment after the end of the study

After the patient has completed or discontinued the study they will be treated according to local medical practice. At the End of Treatment Visit, the investigator will be free to decide what antiplatelet medication the patient should receive as part of his/her ongoing clinical care following the end of study treatment. This medication will be open label and obtained locally.

If continued $P2Y_{12}$ inhibition is required, it is recommended that dosing with 75 mg open label clopidogrel once daily should commence 12 to 24 hours after the last dose of study medication. At the investigator's discretion, a first loading dose of 300 mg clopidogrel may be given.

The treatment given should be recorded in the eCRF.

5.7 Treatment compliance

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

Patients will be asked to bring all unused investigational products and empty packages to the clinic at each visit. The patient's compliance will be assessed by the pill count and recorded in the eCRF. If the patient has taken study medication for more than 80% of the days between each visit the patient will be regarded as compliant.

If the patient is continuing in the study, new additional medication will be dispensed to last until the next visit.

5.7.1 Accountability

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

The study personnel will account for all study drugs dispensed to and returned from the subject.

Study site personnel will account for all received study drugs and return all unused study drugs to the sponsor. Certificates of delivery and return should be signed.

For Japan, replace the above 3 paragraphs with the paragraph below

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The Investigational Product Storage Manager is responsible for managing the study drug from receipt by the institution until the return of all unused study drug to AstraZeneca. AstraZeneca will provide the study documents 'Procedures for drug accountability' and 'Procedures for drug storage' which describes the specific requirements. The investigator(s) is responsible for ensuring that the subject has returned all unused study drug.

The investigational product provided for this study is for use only as directed in the protocol. The investigator or delegate must maintain accurate records accounting for receipt of investigational product. This record keeping consists of a dispensing record including the identification of the person to whom the drug is dispensed, the quantity and the date of dispensing.

Patients will be asked to return all unused investigational products and empty bottle to the investigational centre at each visit to check compliance by pill count and further bottles will be dispensed to last until the next visit. The investigator will make an assessment in the eCRF regarding patient treatment compliance.

Any investigational product deliberately or accidentally destroyed must be accounted for. Any discrepancy between dispensed and returned investigational products should be explained.

The investigator or delegate will retain the returned medication until the AstraZeneca 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.

5.8 Discontinuation of investigational product

Subjects may be discontinued from investigational product (IP) in the following situations:

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment
- Safety reasons as judged by the investigator and/or AstraZeneca (eg, clinically significant ventricular pauses, syncope related to bradycardia, persistent increase in serum creatinine level of clinical relevance, persistent, unexplained anaemia (eg, Haemoglobin [Hb] <100g/L) or thrombocytopenia (eg, platelet count <100 $x10^9$/L)
- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca

- Incorrect enrolment (ie, the patient does not meet the required inclusion/exclusion criteria)
- Pregnancy

Once randomised into the study all patients will be assessed until the 12 month after randomisation is passed or the study is closed unless informed consent is withdrawn for study participation.

Temporary and permanent treatment discontinuations should be kept to a minimum, as this will reduce the ability to detect differences between the treatments. If possible, therapy should be continued after endpoint events and investigator unblinding.

For specific reasons for discontinuing a patient from the pharmacogenetic research see Appendix D.

5.8.1 Procedures for discontinuation of a subject from investigational product

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

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

For Japan, replace the above 2 paragraphs with the paragraph below

A subject that discontinues will always be asked about the reason(s) for discontinuation and the presence of any adverse events. The Principal Investigator/sub-investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the subject. They will also immediately inform AstraZeneca of the withdrawal. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4), and study drug should be returned by the subject.

The Investigator should always ask the patient to allow contact at the end of the study for a final follow-up even if participation in other visits is not agreed. This agreement should be noted and signed by both the Investigator and the patient on the Informed consent form, as well as entered in the medical records. The reason for discontinuation and the date of discontinuation from the study must be documented in the eCRF.

If the patient is permanently discontinued from study medication, the patient should do the End of Treatment visit as soon as possible after discontinuation, and then attend a Follow-up Visit off treatment (1 month after the End of Treatment visit). The patient subsequently continues the scheduled visits according to the protocol until 12 months after randomization is passed or the study is closed. 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 treatment at visits following the 1-month Follow-up Visit.

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. The approach taken should be registered in the eCRF, medical records and ICF.

5.9 Withdrawal from study

Subjects are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects 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. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4) and study drug should be returned by the subject.

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.

Repeated attempts will be made to locate and determine the vital status and occurrence of any MI or stroke for those patients who are considered initially lost to follow up. A patient will be classified as lost to follow up only if, he/she has failed to return for the required study visits and his/her vital status remains unknown despite multiple attempts to contact him/her via telephone, fax, email, certified letter and through patient locator agencies (if allowed per national regulation).

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRF as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.

For Japan, add the below paragraph

The Principal Investigator/sub-investigator will record data on the observations, tests and assessments specified in the protocol on the eCRF provided by AstraZeneca. The eCRF will be accompanied with 'Instructions for the Investigator', which should be followed. These instructions provide guidance for the recording of study data in the eCRF including how to change data incorrectly recorded.

6.2 Data collection and enrolment

6.2.1 Primary variable

The primary endpoint in this study will for safety be the time to first occurrence of any major bleeding even and for efficacy the time to first occurrence of any event from the composite of death from vascular causes, MI and stroke. This outcome measures are used as the basis for the sample size calculation (see Section 12.3). Once randomised, all patients will be assessed for the primary outcome until study closure unless informed consent is withdrawn for study participation.

6.2.2 Screening and demographic measurements

Each patient will undergo enrolment procedures during Visit 1, prior to randomisation. The following data will be collected in the eCRF:

- Demographics (including sex, date of birth, race, ethnic group)
- Smoking history, family history of coronary heart disease
- Safety laboratory blood analyses (clinical chemistry and haematology)
- Pregnancy test (for females of child bearing potential)
- Relevant medical and surgical history
- TIMI risk score for non-ST elevation ACS components
- Current concomitant medications
- Targeted physical examination including vital signs (supine heart rate and BP), Killip class, weight and height (weight and height may be assessed during the hospitalization)
- 12-lead ECG
- Myocardial necrosis biomarker (troponin I and CK-MB)

6.3 Efficacy

6.3.1 Collection and reporting of clinical endpoints

6.3.1.1 Methods of assessment

Clinical efficacy endpoints (death from vascular causes, all-cause mortality, MI, stroke, TIA, severe recurrent cardiac ischaemia, recurrent cardiac ischaemia and arterial thrombotic events) 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 (major and minor bleeding 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 and Bleeding Manual for Investigators. The package will be sent to the 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.

For suspected cardiac ischaemic events, the investigator must determine if the event is an acute cardiac ischaemic event (including the clinical terms for ACS, MI, unstable angina, etc). Such acute cardiac ischaemic events, which an investigator considers could be classified as MI or recurrent cardiac ischaemia, will be recorded and reported to the CEC for central adjudication. MIs will be classified as STEMI or Non-ST segment elevation myocardial infarction (NSTEMI) based on initial presentation and also Q wave or non Q wave based on subsequent evaluations. Milder intensity occurrences of cardiac ischaemia, not meeting endpoint definitions, will be recorded in the eCRF but will not be required to be sent to the CEC.

The CEC will adjudicate and evaluate all endpoints as described in the CEC Charter.

6.3.1.2 Definition of myocardial infarction

- Recurrent MI within 18 hours of onset of a previous MI

  New ST elevation of ≥1 mm (0.1 mV) in at least 2 contiguous leads and recurrent cardiac ischaemic symptoms[a] ≥20 minutes at rest (those that started with exercise or spontaneously and continued with rest).

- Recurrent MI after 18 hours of onset of a previous MI but before myocardial necrosis biomarkers have returned to normal

  Myocardial necrosis biomarker re-elevation (troponin or CK-MB) defined as an increase of at least 50% over a previous value that was decreasing and at least one of the following:

– Recurrent cardiac ischaemic symptoms[a] ≥20 minutes at rest (those that started with exercise or spontaneously and continued with rest).

or

– One of the following ECG changes

(i) New ST elevation of ≥1 mm (0.1 mV) in at least 2 contiguous leads

(ii) Development of new pathological Q waves[b] on the ECG

(iii) New LBBB.

- MI in patients without an index MI, or patients with recurrent MI after myocardial necrosis biomarkers have returned to normal (excluding MI in patients undergoing PCI or CABG in the previous 24 hours)

  Elevation of myocardial necrosis biomarkers typical of acute MI[c] with **at least 1 of the following:**

  – Recurrent cardiac ischaemic symptoms[a] ≥20 minutes at rest (those that started with exercise or spontaneously and continued with rest).

  – Development of new pathological Q waves[b] on the ECG

  – ECG changes indicative of ischaemia[d]

  or

  – Pathological findings of an acute MI.

- MI within 24 hours after PCI:

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

  or

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

- MI within 24 hours after CABG:

  – CK-MB ≥5x local or central laboratory upper normal limit[e], and, if the pre-CABG CK-MB was >ULN, both an increase by at least 50% over the previous

value and documentation that CK-MB was decreasing prior to the suspected recurrent MI and development of new pathological Q waves[b] on the ECG (no symptoms are required)

or

– CK-MB ≥10x local or central laboratory upper normal limit[e] and, if the pre-CABG CK-MB was >ULN, both an increase by at least 50% over the previous value and documentation that CK-MB was decreasing prior to the suspected recurrent MI (with or without Q waves) (no symptoms are required).

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

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

  or

  – Pathological evidence of an acute MI.

- Silent MI:

  – Development of new or presumed new pathological Q waves[b], in the absence of cardiac ischaemic symptoms[a].

Definition of terms

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

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

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

Maximal value of CK-MB (preferably CKMB mass) exceeding the 99th percentile of the values for a reference control group on 2 consecutive samples (mass), or maximal activity

exceeding twice the upper limit of normal (CK-MB activity) for the specific institution on one occasion during the first hours after the index clinical event. Values for CKMB should rise and fall.

[d] **ECG changes indicative of ischaemia - any of the following:** ST-segment elevation: New or presumed new ST-segment elevation ≥1.0 mm (0.1 mV) in 2 or more contiguous leads. New or presumed new ST-segment depression of ≥0.5 mm (≥0.05 mV) in 2 or more contiguous leads. New or presumed new T-wave abnormalities - inversion of ≥1 mm (0.1 mV) in 2 or more contiguous leads.

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

6.3.1.3 Definition of recurrent cardiac ischaemia

Recurrent cardiac ischaemia

Cardiac ischaemic symptoms[a] ≥10 minutes at rest[b], resulting in hospitalisation if an outpatient or prolongation of hospitalisation if an inpatient but not fulfilling criteria for MI.

Severe recurrent cardiac ischaemia

Recurrent cardiac ischaemia and at least one of the following, but not fulfilling the criteria for MI:

- New or presumed new ischaemic ECG changes (ST elevation ≥1 mm (0.1 mV) or ST depression ≥0.5 mm (0.05 mV), or T wave inversion ≥1 mm (0.1 mV) in at least 2 adjacent leads)

- Leading to urgent revascularisation (PCI or CABG) unless not advised on reasoned grounds.

Urgent revascularisation (PCI or CABG) must occur during the same hospitalisation as an in-patient episode of recurrent ischaemia or be performed during the rehospitalisation resulting from an out-patient episode of recurrent myocardial ischaemia. In countries where waiting lists for revascularisation procedures exist, revascularisation within 30 days of an episode of recurrent ischaemia will qualify as urgent. For patients with a previous PCI it will be recorded if revascularisation is necessary for previously treated vessels (ie, urgent target vessel revascularisation) and any occurrences of stent thrombosis will be documented. PCI is defined as any attempt at revascularization even if not successful (eg, angioplasty, atherectomy, or stenting).

6.3.1.4 Definition of stroke/TIA

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

Stroke will be further sub-classified as:

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

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

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

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

6.3.1.5 Definition of Stent Thrombosis

All suspected cases of stent thrombosis will be reported and adjudicated by CEC. The definition proposed by the Academic Research Consortium (ARC) will be used by CEC for classification of definite, probable and possible ST (Cutlip DE et al 2007) (see Table 5 and Table 6).

Table 5 Stent Thrombosis: Timing

Acute stent thrombosis	0 to 24 hours after stent implantation
Subacute stent thrombosis	>24 hours to 30 days after stent implantation
Late stent thrombosis [a]	>30 days to 1 year after stent implantation
Very late stent thrombosis [a]	>1 year after stent implantation

Stent thrombosis should be reported as a cumulative value over time and at the various individual time points specified above. Time 0 is defined as the time point after the guiding catheter has been removed and the patient has left the catheter laboratory.

a Includes primary as well as secondary late stent thrombosis; secondary late stent thrombosis is a stent thrombosis after a target lesion revascularization.

Table 6 Definite [a], Probable, and Possible Stent Thrombosis

Definite stent thrombosis

Angiographic confirmation of stent thrombosis [b]

The presence of a thrombus [c] that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:

- Acute onset of ischemic symptoms at rest
- New ischemic ECG changes that suggest acute ischemia
- Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)
- Nonocclusive thrombus:
  Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.
- Occlusive thrombus
  TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).

Pathological confirmation of stent thrombosis

Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

Probable stent thrombosis

Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within the first 30 days
- Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

Possible stent thrombosis

Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

a Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation.

b The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).
c Intracoronary thrombus.

6.3.1.6 Definition of other arterial thrombotic events

Other arterial thrombotic events include events such as renal infarction, retinal infarction, bowel infarction or foot amputation or gangrene due to peripheral ischemia. For inclusion in the third secondary composite efficacy endpoint the event must either require hospitalisation if an outpatient or prolong hospitalisation if an inpatient. Definitions for events in this category will be included in the CEC charter.

6.3.1.7 Classification of death

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

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

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

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

Deaths with unknown/uncertain cause will be categorised as vascular death and included in the composite endpoint. Any death with unknown/uncertain cause within 30 days of a stroke, MI or procedure/surgery will be considered a death due to the stroke, MI or procedure/surgery respectively. [Note: for Drug Safety reporting purposes any death with unknown/uncertain cause should be reported as death, if the cause of death becomes known, then the cause is reported as the SAE.]

6.3.2 Biomarkers

Troponin I and CK-MB will be analysed at baseline as a biomarker for myocardial necrosis (Visit 1 randomisation)

Samples will be batched and shipped from each participating centre on a regular basis to the central laboratory.

6.3.2.1 Methods of assessment

Blood samples for determination of troponin I and CK-MB will be analysed by the central laboratory. The central laboratory will provide the materials for blood sampling. Instructions

for the labelling, storage and shipment of the samples will be found in the Laboratory Manual. The date and time of all blood collections will be recorded. Samples will be processed and then frozen upright and stored at -20°C or lower until transfer for analysis.

The volumes of blood to be drawn are given in Section 7.1.

All blood sample tubes will be labelled and the appropriate laboratory requisition form completed before being adequately packaged for transportation. The samples will be couriered to the central laboratory at -20°C or lower and analysed according to standard methods.

6.4 Safety

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

6.4.1 Definition of adverse events

An adverse event 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.

For Japan, add the below paragraph

For cases where it could be suspected that a tissue-derived medicine has been contaminated by a pathogen, information about any of the above conditions (including infection) should be collected.

6.4.2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation

For Japan, replace the 3rd bullet with the paragraph below

Requires in-patient hospitalisation or prolongation of existing hospitalisation (including hospitalisation for tests related to adverse events), except hospitalisation that has been planned before enrolment (eg. Hospitalisation for follow-up coronary angiography).

- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

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

6.4.3 Recording of adverse events

Time period for collection of adverse events

AEs will be recorded from Visit 1 (enrolment) following signed informed consent form, until completion of the last scheduled study visit.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the follow-up 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 subject 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
- investigator causality rating against the investigational product (yes or no)
- action taken with regard to investigational product
- outcome

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

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

The intensity will be rated according to the following definition:

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

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

Causality collection

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

For SAEs causal relationship will also be assessed for other medication and study procedures and additional study drug. 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 subject 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 summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, ECG, Holter ECG should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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

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

Since AZD6140 is an anti-platelet agent, surveillance for possible bleeding events will be undertaken as follows:

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

Bleeding AEs will be further classified as described in Section 6.4.6.

6.4.4 Reporting of serious adverse events

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

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

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

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

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

If the WBDC system is not available, then the Investigators or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone or FAX.

The AstraZeneca representative will advise the Investigators/study site personnel how to proceed.

6.4.5 Reporting of Stent Thrombosis

In addition to being reported as AEs/SAEs, all suspected cases of stent thrombosis will be sent to CEC for adjudication. CEC will classify each case as either definite, probable, possible or no stent thrombosis (see Section 6.3.1.5).

6.4.6 Bleeding assessments

For all bleeding events the investigator(s) will complete information on the eCRF specific to that bleeding event, including classification of the event as described in Section 6.4.6.1 below and a determination of whether it is an adverse event. For all bleeding events (excluding minimal) relevant additional source information will be compiled into a 'Endpoint Package', as described in the Endpoint and Bleeding Manual for Investigators. The package will be sent to the CEC for central adjudication.

The CEC will adjudicate and evaluate point and bleeding events (excluding minimal) as described in the CEC Charter.

6.4.6.1 Definitions of bleeding events

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

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

Major bleed – fatal/life-threatening

Any one of the following:

- Fatal
- Intracranial
- Intrapericardial bleed with cardiac tamponade
- Hypovolaemic shock or severe hypotension due to bleeding and requiring pressors or surgery
- Clinically overt or apparent bleeding associated with a decrease in Hb of more than 50 g/L[a]
- Transfusion[b] of 4 or more units (whole blood or packed red blood cells [PRBCs]) for bleeding.

Major bleed – other

Any one of the following:

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

Minor bleed

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

Minimal bleed

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

Definitions of Terms

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

[b] To account for transfusions, Hb measurements will be adjusted for any PRBCs or whole blood given between 2 blood measurements. A transfusion of one unit of blood will be assumed to result in an increase of 10 g/L in Hb. Therefore, to calculate the true change in Hb if there has been an intervening transfusion between 2 blood measurements, the following calculations should be performed:

Δ Hb = [baseline Hb – post transfusion Hb] + [number of transfused units x conversion factor in Hb [c]]

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

All blood product transfusions given during the study will be recorded in the eCRF both as volume (mL) and number of transfusion units. In addition all haemoglobin values obtained in the 7 days preceding, during and for 7 days after a bleeding event or CABG will be recorded in the eCRF. Bleeding event data will be collected in sufficient detail so that categorisation according to other previously published scales (eg, TIMI) will be possible. Further guidance concerning definitions and examples for significantly disabling events and medical interventions to stop or treat bleeding will be contained in the CEC charter and the Endpoint and Bleeding Manual for Investigators will be provided separately to investigators.

6.4.6.2 Bleeding associated with procedures

Information regarding the relationship of any bleed (excluding minimal) to coronary (CABG, PCI or coronary angiography) or non-coronary procedures will be recorded on the eCRF. For CABG, additional information about type of procedure, chest tube drainage, blood product transfusions, haemostatic agent use and any reoperations for bleeding will be collected. All CABG surgeries will be submitted for central adjudication of bleeding according to the classification in Section 6.4.6.1.

Bleeding associated with procedures should only be reported as an AE if it exceeds what can normally be expected for the procedure.

6.4.7 Laboratory safety assessment

The following laboratory variables will be analysed at the central laboratory for all patients at Visit 1 (randomisation) and at Visit 2 (1 month), Visit 4 (3 months), Visit 7 (6 months), Visit 9 (End of Treatment) and the Follow-up Visit:

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

Clinical chemistry (S denotes serum)	Haematology (B denotes whole blood)
S-Alanine aminotransferase (ALT)	B-White blood cells
S-Total Bilirubin	B- Haemoglobin A1c
	B-White blood cells (differential)
S-Uric acid	
S-N-terminal pro-brain natriuretic peptide (S-NT-proBNP)	
S-Total, Low density lipoprotein (LDL), High density lipoprotein (HDL) cholesterol	
S-glucose	
S-pregnancy test (Only Visit1 [randomisation] for females of child bearing potential)	

Follow-up testing for abnormal laboratory results should be performed according to local practice using the central laboratory (eg, for ALT elevations).

Further U-pregnancy testing (U denotes urine) using dipstick should be carried out during the study at Visit 1 and every 6 months (Visit 7 and Visit 9) and at the investigator's discretion for women of child-bearing potential.

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

For the local laboratory sample used to assess patient eligibility at Visit 1, a minimum of all variables required by the inclusion/exclusion criteria (Section 4) must be analysed as indicated below:

Locally analysed Haematology (B denotes whole blood):

- B-Haemoglobin
- B-Platelets
- U-pregnancy test using dipstick (females of child bearing potential)

6.4.7.1 Methods of assessment

Blood samples for determination of haematology and clinical chemistry parameters will be taken at the times given in the study plan. Blood samples will be analysed by the central laboratory. The central laboratory will also provide the materials for blood sampling. Instructions for the labelling, storage and shipment of the samples will be found in the Laboratory Manual.

For blood volume see Section 7.1

All blood sample tubes will be labelled and the appropriate laboratory requisition form completed before being adequately packaged for transportation. The samples will be

couriered to the central laboratory at room temperature and analysed according to standard methods. The laboratory will provide up-to-date reference ranges throughout the study.

Due to the nature of the target disease, its treatment and the study design (randomisation within 24 hours of onset of index event), it is highly likely that the local laboratory tests will be performed as normal procedure prior to obtaining signed informed consent form. These data will be used for eligibility evaluation for this study after obtaining signed consent from the subjects or their guardian/legal representative.

For females of child bearing potential, a U-pregnancy test using dipstick for eligibility assessment and a S-pregnancy test will be taken at enrolment. A U-pregnancy test using dipstick should then be taken every 6 months (Visit 7 and Visit 9) and at the Investigators discretion.

6.4.8 Vital signs, ECG, and physical examination

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

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.

All original ECGs must be stored in the patient's medical record as source documentation. Copies of ECG traces will be included in any relevant 'Endpoint Package' sent to the CEC for central adjudication.

ECG evidence of ACS: ECGs should be obtained on hospital admission for the index event, and according to local practice during the hospitalisation. Due to the study design (randomisation within 24 hours of onset of index event) it is highly likely that the ECG assessment for inclusion into the study will have been performed prior to signing informed consent form. Prior to signing informed consent form, current guidelines and local clinical practice should be followed. These data could be recorded in the eCRF and utilised for the purposes of the study, this will be clearly stated in the informed consent form.

Enrolment ECG: A baseline ECG is required and this should be the same ECG as that obtained to document evidence of the index ACS.

Visit 1(discharge/Day 4 post-enrolment), Visit 2 (1 month), and Visit 9 (End of Treatment) ECG: Visit 1, Visit 2 and End of Treatment ECGs will be recorded in order for the investigator to assess heart rate and any occurrences of silent MI. If the investigator concludes that new Q waves are present according to the silent MI definition, an 'Endpoint Package' will be compiled and sent to the CEC for adjudication.

Other ECG recordings: ECG should be performed according to local clinical practice to document any occurrences of MI or recurrent cardiac ischaemia during the study. A pre

discharge ECG should be obtained following any occurrence of MI to aid in the assessment of future silent MI.

Physical examinations should be performed by medically qualified individuals. The targeted examination should include skin, cardiovascular, lung, abdomen, and neurological evaluations. Results will be recorded as an overall normal or abnormal with a listing of abnormalities.

Killip classification will be assessed as:

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

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

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

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

Abnormal findings from the ECG recording will be analysed and reported separately from AEs in the Clinical Study Report (CSR). They should only be recorded as AEs if they constitute SAEs, lead to discontinuation of treatment with the investigational product, or the investigator considers them to be of such clinical importance as to merit recording as an AE. Clinical symptoms associated with such ECG abnormalities should, however, be reported as AEs.

6.4.8.1 Holter ECG

For 110 patients who attend the sub study at selected sites, the holter recordings are analysed centrally using an automated arrhythmia detection program followed by cardiologist review. During Visit 1(start within 24 hours at the latest after randomisation and intake of study drug) and at Visit 2, 24-hour Holter ECG will be recorded. Variables included the following:

- Heart rate (mean, minimum, maximum)
- Ventricular pauses (including duration and mechanism): defined as an ECG finding showing the absence of ventricular electrical activity (QRS complex) for ≥3 seconds as a result of sinus node dysfunction (SA node pause), atrial fibrillation with slow ventricular response, or sinus or other supraventricular rhythm with high degree A-V block (AV node pause) or other mechanism (other pause).
- Bradycardia: defined as an ECG finding characterised by at least 4 consecutive beats at a rate of ≤45 beats per minute
- Atrial fibrillation: defined as an ECG finding of supraventricular tachyarrhythmia characterised by irregular A-V conduction and absence of regular p waves

- Atrial flutter: defined as an ECG finding of supraventricular tachyarrhythmia characterised by a rapid atrial rhythm (220-350 bpm), slower ventricular response, and the presence of atrial flutter waves

- Other supraventricular tachycardias: defined as an ECG finding that includes all other supraventricular tachycardias not classified as atrial fibrillation or atrial flutter

- Ventricular premature contraction: defined as an ECG finding of wide QRS complex that is premature relative to normal RR interval and not preceded by a P wave. Whether the origin is monofocal or multifocal should be evaluated.

- Nonsustained ventricular tachycardia: defined as an ECG finding of ventricular tachycardia lasting <30 seconds

- Sustained ventricular tachycardia (monomorphic and polymorphic): defined as an ECG finding of a ventricular tachycardia (HR >100 bpm) that lasts >30 seconds and has 1 dominant morphology ("monomorphic") or has more than one dominant morphology ("polymorphic").

- Ventricular fibrillation: defined as an ECG finding showing irregular and changing (ventricular) wave patterns of varying contours and amplitude without discernible QRS complexes (duration not specified).

- ST-T change: defined as an ECG finding showing horizontal or downsloping ST-segment depression ≥1mm or ST-segment elevation ≥2mm.

6.4.9 Myocardial Necrosis biomarkers

Myocardial necrosis biomarkers are required at Visit 1 to document the index event and should be obtained to evaluate any recurrences of cardiac ischaemia. Details specified in this section are in accordance with the ESC/ACC redefinition of MI (Alpert JS et al 2000). Samples for myocardial necrosis biomarkers will be collected and analysed at the local laboratory according to local procedures and in addition, for those patients undergoing PCI or CABG, samples will be collected for central laboratory analysis of CK-MB and troponin I.

All local laboratory results and relevant reference ranges must be stored in the patient's medical record as source documentation. All local laboratories must indicate the cardiac troponin assay or CK-MB assay used. These assays should be used throughout the study. Only assays from companies that have published their data in peer-reviewed journals and have participated in quality control and evaluative studies done by laboratory groups such as the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) should be used.

Time of sample collection and results will be recorded in the eCRF for all myocardial necrosis biomarkers obtained during the study to evaluate the index event and any recurrences of

cardiac ischaemia and included in any MI 'Endpoint Package' sent to the CEC for central adjudication.

The following myocardial necrosis biomarkers are considered acceptable for this study:

- Troponin I
- Troponin T
- CK-MB

Due to the superior sensitivity and cardiospecificity the Global Task Force on Redefinition of MI strongly recommends the use of cardiac troponins. If cardiac troponin assays are not available, the best alternative is CK-MB, measured by mass assay. CK-MB is less tissue-specific than cardiac troponin but the data documenting its clinical specificity for irreversible injury are more robust. As with cardiac troponin, an increased CK-MB value, ie, above the decision limit for MI, is defined as one that exceeds the 99th percentile in a reference control population. Measurement of total CK is not recommended for the routine diagnosis of acute MI, because of the wide tissue distribution of this enzyme.

6.4.9.1 Myocardial necrosis biomarkers obtained for the index event or in case of recurrent ischaemia during the study

Samples should be obtained locally for myocardial necrosis biomarker testing on hospital admission for the index event/any recurrent cardiac ischaemia and again at 12 to 24 hours if the earlier samples are negative and the clinical index of suspicion is high.

Due to the study design (randomisation within 24 hours of onset of index event) it is highly likely that samples for inclusion into the study will have been taken prior to signing informed consent form. These data could be recorded in the eCRF and utilised for the purposes of the study, this will be clearly stated in the informed consent form. Prior to signing informed consent form, current guidelines and local clinical practice should be followed.

6.4.9.2 Myocardial necrosis biomarkers during the process of PCI or CABG

During process of PCI/CABG at anytime during the study, samples for analysis of CK-MB and troponin I must be collected pre-PCI/CABG and again between 8 to 12 and 12 to 24 hours after the procedure. These samples will be sent to the central lab for analysis. Additional samples of any myocardial necrosis biomarker for local analysis may be performed as necessary. If obtained, the time of sample collection and results will be recorded in the eCRF.

6.5 Patient reported outcomes (PRO) – Not applicable

6.6 Pharmacokinetics-Population PK

Blood sample for determination of AZD6140 and AR-C124910XX concentrations in plasma will be collected at pre-dose and 1-4 hours post-dose of both Visit 1 (discharge or Day 4 post-enrolment) and Visit 2 from all patients (See Table 1). For blood volume see Section 7.1.

Instructions for collection, labelling, storage and shipment of PK samples are given in Section 7.2.1 and further details will be provided in the Laboratory Manual. The specified sampling procedure must be followed to avoid jeopardising the subsequent AZD6140 and AR-C124910XX determination in plasma. At Visits 1 (discharge or Day 4 post-enrolment) and 2, the date and time of sample collection will be correctly recorded as well as the immediately previous dosing date and time of the study medication.

6.7 Pharmacokinetics/Pharmacodynamics-PK/PD Sub Study

Blood sample for determination of PK/PD sub study will be collected at Visit 1 and Visit 2 from the patients who attend the PK/PD sub study at selected sites (See Table 2).

Instructions for collection, labelling, storage and shipment of PK samples are given in Section 7.2.1 and further details will be provided in the Laboratory Manual. Instructions for collection and handling of PD samples and further details will be provided in the Appendix E.

6.8 Pharmacogenetics

The blood sample for pharmacogenetic research will be obtained from the subjects at Visit 1. This sample should be collected as close to randomisation as possible. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an adverse event (AE), such subjects would be important to include in any pharmacogenetic analysis. If for any reason the sample is not drawn at Visit 1, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for pharmacogenetic research during the study. See Appendix D for details. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume see Section 7.1.

6.9 Health economics – Not applicable

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The maximum volume of blood that will be drawn from each patient in this study is shown in Table 7. There may be minor variations in the volume of the blood taken for local laboratory analysis. Additional blood will be drawn should a patient experience a clinical endpoint or require a PCI during the study. The volume of blood drawn will depend on the type of event and intervention.

Normal SOPs for the collection, handling and transportation of biological specimens should be employed. Samples will be shipped in accordance with International Air Transport Authority regulations (See Appendix C).

Table 7 Maximum volume of blood to be drawn from the patients

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Pharmacokinetic		3	4	12
Myocardial necrosis biomarker	Myocardial necrosis biomarker	3.5	4	14
Safety [a]	Clinical chemistry	8	6	48
	Haematology	3	6	18
Pharmacogenetic research (optional)		9	1	9
PK/PD sub study (optional) [b]	Pharmacokinetic	3	4	12
	Pharmacodynamics	10	7	70
Total				101 (183 [b])

a A safety blood sample will be drawn for all patients at Visit 1 (enrolment) and then repeat samples will be drawn at Visit 2 (1 month),Visit 4 (3 months), Visit 7 (6 months), Visit 9 (End of Treatment) and the Follow-up visit. See Section 6.4.7.
b Only subjects who participate the PK/PD sub study

The analyte stability limits defined by the central laboratory will be applied to all analyses performed on behalf of AstraZeneca. The central laboratory will not analyse samples that fall outside these stability limits. Analytical data will not be reported if found to have been derived from a sample that fell outside these stability limits. The standards of procedure followed by the central laboratory may be amended in accordance with its SOPs. The central laboratory will inform AstraZeneca of the stability limits relevant to this study before the first patient gives informed consent to take part in the study.

If the central laboratory chooses to sub-contract the analytical work to another laboratory, the central laboratory must assure itself and provide assurance to AstraZeneca that the other laboratory will apply defined stability limits to all analyses performed on behalf of AstraZeneca. Samples falling outside these limits must not be analysed or data reported. The other laboratory will inform AstraZeneca of the stability limits relevant to this study before the first patient gives informed consent to take part in the study.

7.2 Handling, storage and destruction of biological samples

The long-term stability of the analyte(s) should be documented in method validation produced by the AstraZeneca R&D Drug Metabolism and Pharmacokinetics (DMPK) department. Results from analyses of samples stored longer than the time period for which stability has been demonstrated should not be reported unless complementary analyte(s) stability data is acquired and amended to the relevant method validation report. Documentation of the time period for which stability has been demonstrated should be available at the AstraZeneca R&D DMPK department before the first patient gives informed consent to take part in the study.

7.2.1 Pharmacokinetic samples for population PK

Samples will usually be taken by direct venipuncture. A 3 mL sample of blood will be drawn into a collection tube containing lithium heparin and the heparin and blood will be mixed carefully. The sample will be placed on ice until centrifugation, which will begin within 30 minutes of the sample being obtained. The blood sample will be centrifuged for 10 minutes at a relative centrifugal force of 1500 *g*. The resultant plasma will be transferred to a plain polypropylene tube (screw top) and immediately frozen upright at or below -20°C until transfer for analysis. Here, all blood sampling equipments will be provided from the central laboratory. The frozen samples must be stored at -20°C or lower, before, during and after transport.

The frozen samples must be packed securely to avoid breakage and contain any leaks during transit and should be packed with a sufficient quantity of dry ice to ensure they remain frozen for at least 72 hours to allow for delays in shipment. All applicable shipping regulations will be followed.

Samples for PK determination of AZD6140 and the metabolite AR-C124910XX will be analysed only for the patients receiving AZD6140 by a certified laboratory using validated bioanalytical methods.

7.2.2 Pharmacokinetic and pharmacodynamic samples for PK/PD sub study

Follow same procedure as in Section 7.2.1 for Sample for PK. Individual venipunctures for blood collection at each time point are highly recommended to avoid contamination of saline and heparin by using indwelling venous cannula. However, according to the discretion of investigator, indwelling venous cannula may be used. In that case, saline (heparin must not be used) should be used to keep the cannula patent. On each sampling occasion, the first blood in the cannula should be discarded using plain syringe. And, it should be flushed with saline after each sample is obtained. In case cannula is occluded, venipuncture should be done for further sample collection.

Samples for the measurement of PD will be drawn at each time point in Table 2. At time points where PK and PD (aggregometry) samples coincide, samples may be taken in any order since equal priority is given; however, in the event of a sampling difficulty the PD sample should be prioritised. Full details of the methodology are given in Appendix E.

Pre-dose samples should be obtained shortly (within 30 minutes) before dosing with the investigational product. The date and time of each sample collection will be recorded in the appropriate section of the eCRF.

7.2.3 Pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of the Last Subject's Last Visit, after which they will be destroyed. DNA

is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA).

7.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled 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 subject unless agreed with AstraZeneca and appropriate labelling, 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 subjects 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 during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

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

As collection of the biological samples is an integral part of the study, then the subject is withdrawn from further study participation.

As collection of the biological samples is an optional part of the study, then the subject may continue in the study.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, 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 subject 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.

For Japan, replace the above paragraph with the paragraph below

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. The applicable regulatory requirements in Japan are 'Good Clinical Practice for Trials on Drugs (MHLW Ordinance No.28, 27 March 1997), partially revised by MHLW Ordinance and their related notifications.

8.2 Subject 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.

For Japan, replace the above paragraph with the paragraph below

The Master Informed Consent Form will explain that:

- Study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation.
- Subject data will be maintaining confidentiality in accordance with national data legislation.
- For data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.
- All data computer processed by AstraZeneca will be identified by study code and enrolment code (E-code).

AstraZeneca will not provide individual genotype results to subjects, 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 subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

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 subjects. 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 enrolment of any subject into the study.

The Ethics Committee should approve all advertising used to recruit subjects 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 enrolment of any subject 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.

For Japan, replace this section with below

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 subjects. The investigator/The Head of the study site 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 head of the study site should submit a notification of direction/determination as well as a copy of the IRB written approval to AstraZeneca before enrolment of any subject should into the study.

The Ethics Committee should approve all advertising used to recruit subjects for the study.

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

Study agreement between the study site and the sponsor will be in place before subjects are enrolled. The protocol should be re-approved by the IRB annually. The Principal Investigator should submit progress reports to the IRB via the head of the study site at the time of the protocol re-approval.

Before enrolment of any subject 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, the head of the study site and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

The Head of the study site should submit a written report to the IRB providing the details of

all safety relative information reported by AstraZeneca.

8.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study (See Section 4.1 for Inclusion Criteria 1)
- Ensure the all original, signed Informed Consent Forms by subjects and/or their legal representative are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

For Japan, add the below paragraph

If any new information on the study medication becomes available which may influence the decision of the subject to continue the study, the investigator(s) should inform the subject of such information immediately, record this in a written form, and confirm with the subject if he or she wishes to continue the participation in the study. In addition, if the investigator(s) deem it necessary to revise the Informed Consent Form, they should revise it immediately (Refer to Section 8.5). The investigator(s) should re-explain the subjects using updated Informed Consent Form even if although the subjects have already been informed of the new information verbally. Written informed consent to continue participation in the study should be provided separately.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator, Ethics Committee, Principal 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 centre's Informed Consent Form, AstraZeneca and the centre'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.

For Japan, replace this section with below

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca. If it is necessary for the study protocol to be amended, the amendment should be submitted to the Head of the Study Site and be approved by its IRB. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented. If a protocol amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's IRB should be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used. If an administrative change is required, such a change should be notified to or approved by each IRB according to local requirements.

8.6 Audits and inspections

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

For Japan, add the below paragraph

All study data may undergo a reliability review and onsite-GCP inspection by the regulatory authorities.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

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

- Determine the adequacy of the facilities
- Determine availability of appropriate subjects 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 subject 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) utilised.

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 eCRF, that biological samples are handled in accordance with the Laboratory Manual and that investigational product accountability checks are being performed

- Perform source data verification (a comparison of the data in the eCRF with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)

- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The AstraZeneca representative will be available between visits if the investigator(s) or other staffs 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.

For Japan, add the below paragraph

Source data are any data generated as a result of the subject's inclusion in the study (including run-in and/or follow up related to the study) and includes all related medical examinations and other records. Original data recorded on the eCRF and regarded as source data are stated in Clinical Study Agreement.

For Japan, add the below section

9.3.2 Direct access to source data in Japan

The Head of the institution and the Principal Investigator/sub-investigator will cooperate for monitoring and audit by AstraZeneca, and accept inspection by the IRB or regulatory authorities. All study documents such as raw data will be open for direct access to source data at the request of the monitor and the auditor of AstraZeneca, the IRB, or regulatory authorities.

The monitor(s) will verify data from the eCRF against source data before collecting the eCRF to ensure accuracy and completeness of documentation, and assure that the Principal Investigator/sub-investigator has submitted the eCRF to AstraZeneca. If the investigator wishes to amend the collected eCRF, the monitor will ensure that the Principal Investigator/sub-investigator has documented the amendment in writing (signed and dated) and provided this to AstraZeneca.

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 subjects and in all other respects, not relating to study conduct or treatment of subjects, 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 subjects are enrolled.

9.4.1 Archiving of study documents

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

For Japan, replace the above paragraph with the paragraph below

(i) Study files

AstraZeneca will provide the Principal Investigator with a file in which to organise and retain all study-related documents. All study documents (including letters from AstraZeneca) should be retained in this file by the Principal Investigator. The monitor will regularly check the file to ensure that all relevant documents are retained. The contents of the file may be audited/inspected by AstraZeneca's auditor, regulatory authorities, or IRB.

(ii) Period of record retention

The study site (and the Principal Investigator) will retain the essential documents specified in the ICH GCP (eg, source document such as medical records, contract, signed consent form). Essential documents should be retained at the study site for at least 15 years following completion of the study, or per regulatory obligations if longer, and thereafter destroyed only after agreement with AstraZeneca. However this is not always applied to those that are not preservable such as blood samples. In the event of any inconsistency between the above-mentioned contents and the contract with the study site, the contract shall prevail. These documents should be retained for a longer period however if needed by AstraZeneca, and the specific period and method of retention will be separately discussed between the study site and AstraZeneca. AstraZeneca should notify the head of the study site in writing when the study related records are no longer needed. The records should be managed by a responsible person appointed by the head of the study site.

For Japan, add the below section

9.4.2 Deviation from the clinical study protocol in Japan

The investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the principal investigator and AstraZeneca K.K. or the IRB approval based on its deliberations. However, this shall not apply to cases where the deviation or change is necessary to avoid an immediate hazard to the patients or for other compelling medical reasons, or where the changes involve only logistical or administrative aspects of the clinical trial (eg changes to the organisation/structure of the sponsor, the name/department name of the medical institution, the address or phone number of the medical institution or the sponsor, the job title of the investigator, and monitors).

The investigator(s) should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to the patients or for other medically compelling reason, the investigator should prepare and

submit the records explaining the reasons thereof to the sponsor, and retain a copy of the records.

The investigator(s) may deviate from or make a change to the protocol without documented agreement between the principal investigator and AstraZeneca K.K. or the IRB approval, only in the event of a medical emergency, eg it is only way to avoid an immediate hazard to the patients. In such case, the principal investigator must notify details of the deviation or change, the reason, and a proposed revision in the protocol if required, to AstraZeneca K.K. and the head of the study site and IRB via the head of the study site as soon as possible, in order to obtain their approval. A certificate of approval by the head of the study site as well as AstraZeneca K.K. should be obtained via the head of the study site.

9.5 Study timetable and end of study

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

The study is expected to start in 1st Quarter 2011 and to end by 3rd Quarter 2012.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD6140.

For Japan, add the below section

Planned duration of the study:

Study period: January 2011 - July 2012

Registration period: January 2011 – November 2011

Discontinuation or suspension of the whole study programme

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

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

Completion of the study

Upon terminating the study, the Principal Investigator will report in writing the completion of the study as well as the summary of the results to the head of the study site in accordance with the institution's rules. The head of the study site, who is informed of the termination by the

investigator, will provide a written notification of the results to the IRB and AstraZeneca.

10. DATA MANAGEMENT

Data will be entered in WBDC system at the study site. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the eCRF Instructions. The eCRF Instructions will also guide the study site in performing data entry. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. Site personnel will enter the data in the eCRF. The data will then be Source Data Verified (SDV), reviewed/ queried and updated as needed. The principal investigator will then sign the eCRF electronically. Clean file occurs when all data have been declared clean and signed by the investigator. The data will be frozen and then locked to prevent further editing. A copy of the eCRF will be archived at the study site when the study has been locked.

Medical coding for AEs and medical/surgical history is done using the most current version of medical dictionary of regulatory activities (MedDRA), and Medical coding for medication is done using AstraZeneca Drug Dictionary.

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database (if applicable). Data Management will ensure that the data collection tool (IVRS/IWRS) will be tested / validated as needed. External data reconciliation will be done with the clinical database as applicable.

SAE Reconciliation Reports are produced and reconciled with Patient Safety database and/or the Investigational Site.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

11.1 Calculation or derivation of efficacy variable(s)

The time from randomisation to the following events will be derived:

- First occurrence of any event from the composite of death from vascular causes, MI or stroke.
- First occurrence of any event from the composite of all-cause mortality, MI, or stroke

- First occurrence of any event from the composite of death from vascular causes, MI (including silent MI by ECG), stroke, recurrent cardiac ischaemia, TIA or other arterial thrombotic events

- First occurrence of each component of the primary composite efficacy endpoint individually in the order of MI, death from vascular causes and then stroke

- First occurrence of all-cause mortality

For each endpoint, patients who fail to record any event will be censored at the time of study closure (ie. Date of End of Treatment Visit) or at the time of last available information, if earlier.

11.2 Calculation or derivation of safety variable(s)

Following variables will be calculated:

Bleeding events (to be adjudicated using PLATO criteria)

- Time to first occurrence of any total major bleeding event.

- Time to the first occurrence of non-procedure-related, coronary procedure-related[1] and non-coronary procedure-related major bleeding events

- Time to the first occurrence of total, non-procedure-related, coronary procedure-related and non-coronary procedure-related minor bleeding events.

- Time to the first occurrence of combined major and minor bleeding events for each of the categories.

- Time to the first occurrence of total minimal bleeding events

For each endpoint, patients who fail to record any event will be censored at the time of study closure (ie. Data of End of Treatment Visit) or at the time of last available information, if earlier.

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 judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

[1] Coronary procedure-related includes CABG, PCI and coronary angiography only.

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 – Not applicable

11.4 Calculation or derivation of pharmacokinetic variables

Following PK variables at steady-state will be calculated using population PK analysis (See Section 12.2.3).

Maximum plasma (peak) concentration ($C_{ss,max}$), minimum plasma concentration ($C_{ss,min}$), average plasma concentration ($C_{ss,av}$), time to $C_{ss,max}$ ($T_{ss,max}$), half-life ($t_{1/2}$) and area under plasma concentration-time curve (AUC_{ss}) for AZD6140 and AR-C124910XX.

11.5 Calculation or derivation of pharmacodynamic variable(s)

Maximum and final extent IPA from pre-dose baseline at Visit 1 will be calculated at all subsequent timepoints using the following formula for ADP-induced platelet aggregation:

Percentage Inhibition = 100% x (PAs - PA) / (PAs)

PA is the mean response at the given post dose time point and PAs is the mean response at pre dose baseline. Percentage inhibition will be restricted to the closed interval [0,100]; any data falling outside this range will be truncated to the appropriate limit.

11.6 Calculation or derivation of pharmacogenetic variables

See Appendix D. The result of pharmacogenetic research will be reported separately from CSR.

11.7 Calculation or derivation of health economic variables - Not applicable

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

Statistical analyses will be performed in accordance with the study protocol. The Statistical analysis plan will provide further details of the analyses and presentation of the data. The Statistical analysis plan will be finalised before the database lock.

12.1 Description of analysis sets

Patient inclusion in each of the analysis sets will be determined before database lock.

12.1.1 Efficacy analysis set

Full analysis set (FAS)

All patients who have been randomised to study treatment will be included irrespective of their protocol adherence and continued participation in the study. If a patient prematurely discontinues study medication, every effort will be made to determine the patient's status regarding MI, stroke and mortality at the end of their scheduled study duration. Patients will be analysed according to their randomised study medication. Patients will be followed and their data included using the FAS until either death, study closure or withdrawal of consent. Patients who withdraw consent to participate in the study per se will be included up to the date of their study termination. All efficacy variables will be analysed using the FAS.

12.1.2 Safety analysis set

All patients who take at least one dose of study medication will be included. Patients will be analysed according to the study medication actually received. All safety variables will be analysed using the safety analysis set. The safety analysis set will include data collected during the period starting with first dose of study medication through 7 days after termination of study medication.

12.1.3 Pharmacokinetics analysis set

All patients who have evaluable plasma levels of AZD6140 and/or AR-C124910XX will be included. The definition of evaluable levels will be included in the population PK analysis plan.

12.1.4 Pharmacokinetics/Pharmacodynamics sub study analysis set

The patients who participate in PK/PD sub-study will be included.

12.2 Methods of statistical analyses

12.2.1 Safety data

An analysis of the time from first dose of study medication to each of the following endpoints will be performed:

- Total, non-procedure-related, coronary procedure-related and non-coronary procedure-related major bleeding events
- Total, non-procedure-related, coronary procedure-related and non-coronary procedure-related minor bleeding events
- Combined major and minor bleeding events for each of the categories.

The treatment groups will be compared using the Cox proportional hazards model with a factor for treatment group. Patients who fail to record any corresponding bleeding event will be censored at the time of study closure (ie. date of End of Treatment Visit) or at the time of last available information, if earlier. Kaplan-Meier estimates of the cumulative risk of each

event will be calculated and plotted and 2-sided 95% confidence intervals for the hazard ratios presented. The proportion of patients experiencing above events will also be presented for each treatment group, along with the difference between treatment groups and 2-sided 95% confidence interval. The primary safety endpoint is total major bleeding events. The secondary safety endpoints are the 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.

AEs will be summarised by system organ class and preferred term using MedDRA. Summaries will be presented by treatment group using descriptive statistics. Specific more detailed analyses of dyspnoea and bradycardic events will be performed. All AEs relating to bleeding will be summarised separately. Exploration of potential risk factors for AEs that are increased with AZD6140 dosing may be done.

Transfusions of blood products and safety laboratory parameters will be compared between the 2 treatment groups using descriptive statistics for the actual and change from baseline values, where appropriate. Descriptive analyses of the bleeding events related to CABG and other procedures will be performed including the effect of timing of interruption of study medication.

12.2.2 Efficacy data

The primary efficacy endpoint, the time to first occurrence of any event from the composite of death from vascular causes, MI or stroke, will be analysed based on a Cox proportional hazards model including treatment group. Patients who fail to record any event in the primary composite efficacy endpoint will be censored at the time of study closure (ie. date of End of Treatment Visit) or at the time of last available information, if earlier. The hazard ratio and 2-sided 95% confidence interval will be reported. Kaplan Meier estimates of the cumulative risk 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 contribution of each component of the composite efficacy endpoint to the overall treatment effect will be examined.

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 where there are at least 15 events. Relevant subgroups for the following factors will be examined: age (groups <60, 60-75 and >75 years), sex, weight, BMI, geographic region (Japan and non-Japan), index event characteristics (eg non-ST vs. ST elevation ACS and troponin I level), TIMI risk score, prior antiplatelet therapy, medical history characteristics, revascularisation history, time to initiation of study therapy, concomitant ASA use during the study, PCI during the study, CABG surgery during the study, and moderate CYP3A inhibitor usage at randomisation. The consistency of treatment effects over time will also be assessed

by looking at the time intervals from randomisation to 30 days post randomisation and from randomisation to 90 days post randomisation.

The following variables will similarly be analysed.

(i) The time to first occurrence of any event from the composite of all-cause mortality, MI or stroke

(ii) The time to first occurrence of any event from the composite of death from vascular causes, MI (including silent MI by ECG), stroke, recurrent cardiac ischaemia, TIA or other arterial thrombotic events

(iii) The time to first occurrence of each component of the primary composite efficacy endpoint individually in the order of MI, death from vascular causes and stroke

(iv) The time to occurrence of all-cause mortality

The other components of the secondary composite efficacy endpoints (ie, silent MI, recurrent cardiac ischaemia, severe recurrent cardiac ischaemia, TIA and other arterial thrombotic events) will be presented only descriptively. For silent MI, the time will be calculated from randomisation to the time of detection.

No multiplicity adjustment will be made to the confidence intervals as they will be interpreted descriptively and used as measures of precision.

For the CK-MB and troponin I myocardial necrosis biomarkers obtained before and after PCI and CABG, categorization by different levels of abnormality will be done

12.2.3 Pharmacokinetics data

Using combined data from this study and another study including Japanese ACS patients (D5130C00065), population PK parameters for AZD6140 and its active metabolite AR-C124910XX will be derived based on non-linear mixed effect model using NONMEM. Among age, gender, weight, BMI, ethnic group, and common concomitant medication, factors that may influence the PK of AZD6140 and its active metabolite AR-C124910XX will be explored. The mean and individual Bayes estimate of population PK parameters for AZD6140 and its active metabolite AR-C124910XX will be calculated, and $C_{ss,max}$, $C_{ss,min}$, $C_{ss,av}$, $T_{ss,max}$, $t_{1/2}$ and AUC_{ss} for AZD6140 and AR-C124910XX will be summarised descriptively. The relationship between $C_{ss,max}$ or AUC_{ss} and safety and efficacy will be investigated in exploratory manner.

A separate population PK analysis plan will detail methods for these analyses. The Population PK analysis result will be reported separately from the report of this study.

12.3 Determination of sample size

The sample size (360 Japanese patients per group + 40 non Japanese patients per group) for this study is determined based on feasibility. With the planned number of Japanese patients (360 patients/group) in Phase III study, and assuming, based on PLATO, the annual major bleeding event rate in AZD6140 and clopidogrel sulphate group of 11.58% and 11.20%, respectively, and the annual dropout rate of 6.24%, with 9 months recruitment period, 6 months minimum treatment period and 12 months maximum treatment period, the expected proportion of patients with major bleeding event in this study is approximately 9.5% and 9.2%. In case such result is obtained, then 2-sided 95% confidence interval of the difference between treatment groups in the incidence of major bleeding event is about ±4.3% and we can exclude the difference of approximately 4.6% or greater compared to clopidogrel sulphate group in AZD6140 group.

For efficacy, although it is difficult to estimate the annual event rate for the primary efficacy endpoint for the current Japanese patients, we assume the event rate to be about 6% based on result of JACSS (Ogawa H and Kojima S 2009). Assuming the HR observed in PLATO of 0.84 is observed in Japanese patients, the expected number of primary efficacy events in AZD6140 and clopidogrel groups are 15 and 18, respectively. In this case, the upper 95% CI for the HR AZD6140:clopidogrel will be approximately 1.67. Therefore we will be able to rule out an approximately 67% increase in risk for AZD6140 over clopidogrel.

The number of subjects that will agree to participate in the pharmacogenetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

12.4 Data and safety monitoring board

In this study, a single joint DSMB will be established for this study and the clinical Phase II study (D5130C00065), which are conducted separately.

The DSMB is independent of AstraZeneca and study sites, and will monitor the progress of all aspects of the study (eg, efficacy and safety) and will ensure that the study meets the highest standards of ethics and patient safety.

The DSMB will bear the primary responsibility for monitoring of study data for adverse trends in mortality, morbidity, and drug safety in these two studies.

The DSMB will confirm and evaluate the safety information in an un-blinded manner periodically (at least every 3 months), and make a decision on appropriateness to continue the study. Besides such periodical review, the DSMB will evaluate the safety in the same way as periodical review at time points when the 100th and 400th patients in the overall population are randomised in order to assess appropriateness to continue the study.

In addition to the periodical review during this study, the DSMB will review the data from the Phase II study together with the data from this study, and perform a comprehensive safety

assessment similar to the periodical review to determine the appropriateness of continuing these two studies.

To accurately facilitate this review, clinical events of special interest will be reported by the investigator as soon as possible via the eCRF, and clinical laboratory data and the 24-hour Holter ECG data will be supplied by the central vendors to the investigator and AstraZeneca Data Management. These events include suspected cardiac ischaemic events, symptomatic possible bradycardia events, pacemaker use and major bleeding events.

A recommendation by the DSMB to stop the study for adverse effects observed in the AZD6140 treatment arm may be at any time. Criteria for determination of the appropriateness of continuing studies will be separately detailed in the DSMB Charter.

12.5 Clinical Endpoint Committee

The CEC is independent of AstraZeneca, study sites and DSMB, and the CEC is to independently review and interpret the pre specified events and bleeding events that are reported by the investigator as defined in Section 6.3.1.1 and 6.4.6. This will provide a consistency of interpretation of the events across sites and countries participating in the study. The CEC will implement streamlined, efficient processes of blinded adjudication of reported events.

If the results centrally adjudicated by the CEC are different from those by the investigator, the CEC-adjudicated results will be used for analyses.

Responsibility of the CEC and procedure of central adjudication will be separately detailed in the CEC Charter.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The principal investigator(s) 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 should be reported as such, see Section 6.4.4.**

In the case of a medical emergency the investigator may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician/other physician at the AstraZeneca Research and Development.

Name	Role in the study	Address & telephone number
	Study Delivery Team Leader responsible for the protocol at central R&D site	
	SDT Physician responsible for the protocol at central R&D site	
(JP) Monitor	Study Delivery Team monitor	See Supplement A, "Investigations and Study Administrative Structure"

The treatment code may not be broken unless in an emergency situation where appropriate management of the patient necessitates knowledge of the treatment allocation. If possible, investigators should contact AstraZeneca or designee before breaking the treatment code.

There is no known antidote to reverse the effects of AZD6140. The average half-life of AZD6140 is approximately 12 hours, so blood levels of AZD6140 should be low by 48 to 72 hours (ie, 4 to 6 half-lives) after discontinuation. Platelet transfusions may be given, but new platelets may be inhibited by AZD6140 as long as it is circulating in blood.

13.1.1 Major bleeding events

Major bleeding events should be managed according to need with general support and blood products.

If platelet transfusion is considered, the treatment code should be broken only if deemed necessary by the investigator (see Section 5.4.2 for unblinding procedures) since this approach will likely not reverse the effects of AZD6140. It is understood that new platelets are likely to be inhibited by AZD6140 as long as it is circulating in the blood.

If treatment with Desmopressin (DDAVP), aprotinin, recombinant activated Factor VII or other haemostatic agents is to be used, it should not be necessary to break the treatment code.

If a patient experiences a major bleed as defined in Section 6.4.6.1, study medication should usually be discontinued but may be resumed at the discretion of the investigator provided the cause of bleeding has been identified and controlled.

13.1.2 Minor bleeding events

If a patient experiences a minor bleeding event as defined in Section 6.4.6.1, study medication may be continued, interrupted temporarily or discontinued permanently at the discretion of the investigator.

13.1.3 Need for administration of a fibrinolytic agent

Fibrinolytic treatment within 24 hours of randomisation was an exclusion criterion in PLATO, and concomitant fibrinolytic treatment was specifically restricted while on study. Nevertheless, 66 (0.4%) patients received concomitant fibrinolytic treatments (ATC code B01AD, or as indicated by the exclusion criterion 5) at any time of the study, including patients who received such treatments 1 day prior to the study therapy or while on study therapy. Of the 50 patients who received fibrinolytic treatment during the first 7 days of study drug 8 patients (5 AZD6140 and 3 clopidogrel) had a major bleed.

Large clinical studies have recently demonstrated good tolerability of fibrinolytic agents in combination with clopidogrel (Sabatine MS et al 2005 and Chen ZM 2005). No significant excess risks with regards to major bleedings and intracranial haemorrhage was noted with clopidogrel in those patients given fibrinolytic therapy.

If administration of a fibrinolytic agent is required, treatment with study medication should be temporarily stopped. Study medication may be re-started at least 24 hours after administration of the fibrinolytic agent.

13.1.4 Treatment with PCI

Investigators should maintain an awareness of the increased tendency for bleeding. Details of PCI procedures should be undertaken according to local clinical practice and established methods. Study medication should be continued without interruption (permanent or temporary). An additional dose of 90 mg AZD6140 blinded study medication is required (if >24 h since randomisation) and up to 300 mg clopidogrel blinded study medication is permitted for patients prior to undergoing PCI (at any time in relation to randomisation). This must be given as blinded study medication allocated in the IVRS/IWRS. It should not be necessary to break the treatment code.

13.1.5 Need for major surgery

Since the average half-life of AZD6140 is about 12 hours, platelet function will have returned to near normal in most individuals by 48 to 72 hours after discontinuation. The timing for temporary discontinuation of antiplatelet therapy prior to major surgery must balance the risk of recurrent thrombotic event with that of surgical bleeding. For cardiac surgery, AZD6140 administration with antifibrinolytic medications, including aprotinin, and with desmopressin occurred in PLATO. In general for cardiac surgery, prophylactic administration of antifibrinolytic medications (epsilon aminocaproic acid or tranexamic acid) reduce post-operative blood loss; results with DDAVP are not consistent. If surgery is elective or non-urgent, study medication should be interrupted temporarily according to local practice:

(a) If local practice is to allow antiplatelet effects to dissipate before surgery:

- Capsules (blinded clopidogrel) are withheld 5 days before surgery
- Tablets (blinded AZD6140) are withheld for a minimum of 24 hours and a maximum of 72 hours before surgery

(b) If local practice is to perform surgery without waiting for dissipation of antiplatelet effects:

- Capsules and tablets are withheld 24 hours prior to surgery
- Use of aprotinin or other haemostatic agents is allowed

(c) If local practice is to use IPA monitoring to determine when surgery can be performed both the capsules and tablets are withheld at the same time and the usual monitoring procedures followed

After surgery study medication should be restarted as soon as possible prior to discharge.

See Section 5.5.4 regarding treatment interruptions.

13.1.6 Minor surgery or procedures

Study medication may be continued or interrupted temporarily at the discretion of the investigator. If dissipation of antiplatelet effect is desired before the procedure then the tablets (blinded AZD6140) and capsules (blinded clopidogrel) should be handled independently such that tablets should be withheld for a minimum of 24 hours and a maximum of 72 hours pre-surgery and capsules for at least 5 days pre-surgery/procedure.

13.1.7 Uric acid management

AZD6140 90 mg has been shown to increase levels of uric acid of approximately 15% from baseline in the PLATO. Increases in blood uric acid levels not associated with clinical symptoms do not normally require treatment. However if an increased uric level is observed in association with symptoms in a patient and requires lowering the following options should

be considered before starting specific uric acid lowering pharmacological therapy (eg. allopurinol or uricosurics):

- dietary modification (eg, increased intake of low-fat dairy products and/or decreased intake of red meats, fish or purine rich foods)
- weight loss if overweight
- decreased consumption of beer and liquor

If a patient experiences an acute attack of gout during the study this should be managed symptomatically as necessary. Study medication does not need to be interrupted for treatment of gout.

13.1.8 ECG pauses, pacemakers and bradycardic events

In the PLATO safety analysis set, the number of patients with bradycardiac events was similar between treatment groups (4.7% vs 4.4%). Similar rate of permanent pacemaker placement was also found (0.4% vs 0.4%). Holter monitoring was conducted in 2907 patients. The number of patients with ventricular pause (>3 sec) was numerically greater in the AZD6140 group compared to the clopidogrel (5.8% and 3.6%). Ventricular pause did not correlate well with clinically important events (such as syncope, atrioventricular block, or pacemaker insertion).

In this study all symptomatic events that may possibly be bradycardic in nature (eg, A-V block, sinus pauses, sick sinus syndrome, syncope, unexplained accidents and sudden death) should be reported as soon as possible as AEs of special interest. All pacemaker use (permanent and temporary) will also be recorded and reported as soon as possible. Cardiac telemetry monitoring should be performed in patients as clinically indicated based on investigator judgement and local practice with vigilance for any bradycardic events. Study treatment should be discontinued in case of evidence or suspicion of clinically significant ventricular pauses.

13.1.9 Dyspnoea management

A dose dependent increase in dyspnoea was observed in patients exposed to AZD6140 in the Global Phase II studies, DISPERSE and DISPERSE 2 and PLATO. Dyspnoea infrequently was serious or necessitated discontinuation of AZD6140. The event was characterised by a sensation of shortness of breath that was mostly mild to moderate in intensity and usually short-lasting. In a few cases where detailed examination was done the dyspnoea was not associated with any significant physical finding, eg, bronchospasm or heart failure. No risk factors in terms of age, gender, BMI, smoking status, medical history or concomitant medications have been identified. It is postulated that dyspnoea may be related to alterations in adenosine pharmacology since AZD6140 has been shown to inhibit adenosine uptake into red blood cells *in vitro* and has some structural similarities to adenosine.

If patients experience dyspnoea they should be evaluated with regards to underlying cause (eg, cardiac, pulmonary) using clinical and laboratory examinations as found appropriate. The results of any diagnostic investigations will be recorded in the eCRF as will details concerning the nature of the event. Treatment according to clinical practice should be instituted when required and clinical follow up should be performed.

The suspected aetiology of all dyspnoea events will be classified by the investigator according to the following categories that will be recorded in the eCRF:

- Pulmonary Oedema (cardiac, noncardiac)
- Other Cardiac Etiology (eg chronic heart failure)
- Asthma
- Chronic Obstructive Pulmonary Disease
- Pulmonary Vascular Disease (pulmonary hypertension, pulmonary embolism)
- Parenchymal Lung Disease
- Infection (eg, pneumonia or bronchitis)
- Metabolic Disorder
- Anxiety Disorder
- Other known cause
- Unexplained

13.2 Overdose

An overdose is defined as any intake of study medication beyond 360 mg/day of AZD6140.

In the event of an overdose with AZD6140 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. Bleeding is the most likely pharmacological effect of excessive AZD6140 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. In the event of overdose with clopidogrel, medical management of patients should be in accordance with the products' local prescribing information.

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

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

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

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

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

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca. The PREGREP module in the eCRF is used to report the pregnancy. A paper form of the PREGOUT module is kept at the study site to report the outcome of the pregnancy.

13.3.1 Maternal exposure

If a subject becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product 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 subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day** 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 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.

13.3.2 Paternal exposure

There are no restrictions against fathering a child when treated with AZD6140. If paternal exposure pregnancy occurs in the course of the study, then investigators or other site personnel should inform appropriate AstraZeneca representatives within one day as described in the maternal exposure Section 13.3.1. 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 subject was discontinued from the study.

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Clinical Study Protocol Appendix B

Drug Substance	AZD6140
Study Code	D5130C00027
Edition Number	1
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.

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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.

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Appendix D
Pharmacogenetics Research

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
ACS	Acute Coronary Syndrome
ADP	Adenosine diphosphate
CYP2C19	Specific gene encoding a member of the cytochrome P450 (CYP) superfamily of enzymes, which are involved in drug metabolism.
DNA	Deoxyribonucleic acid
LIMS	Laboratory information management system
MDR1 (ABCB1)	Multidrug resistance protein 1 gene encoding P-glycoprotein transporter protein
$P2Y_{12}$	A sub-type P2 receptor found on platelets

1. BACKGROUND AND RATIONALE

AstraZeneca intends to perform genetic research in the AZD6140 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD6140 and its use. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to optimised treatment strategies for the disease under study.

To achieve this goal a systematic collection of deoxyribonucleic acid (DNA) for genetic analysis (derived from blood samples taken from consenting study subjects) will be implemented across a broad range of relevant clinical studies. The ability to acquire appropriate consent to collect blood samples to establish an archive and allow future meta-analysis of data derived from a number of studies for AZD6140 is of the utmost importance. This genetic research forms part of this strategy and the results of this study may be pooled with genetic data from other studies on AZD6140 to generate hypotheses to be tested in future studies.

The benefits of being able to explore associations between genes and clinical outcomes within the AZD6140 programme are potentially many and include:

- Identifying markers of any observed pharmacokinetic variability
- Identifying markers of response to AZD6140 and/or co-medication and/or clopidogrel, where the term response is used broadly to include efficacy, safety and tolerability
- Aiding in the understanding mechanisms of action of any safety signals that may become apparent during the study
- Aiding in the understanding of susceptibility to the cardiovascular disease under study within the protocol

2. GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect and store DNA for potential future exploratory research into genes/genetic variation that may influence response to AZD6140 and/or co-medications and/or clopidogrel (ie, distribution, safety, tolerability and efficacy) and susceptibility to and prognosis of cardiovascular disease.

Genes that may be investigated include:

- Genes postulated to be involved in the disposition (absorption, distribution, metabolism and excretion) of AZD6140 and clopidogrel such as genes coding for the drug metabolising enzyme CYP2C19 and the drug transporter MDR1 (ABCB1)

- Genes that may influence response to AZD6140 and clopidogrel, such as the gene coding for the drug target, the $P2Y_{12}$ ADP receptor

In addition to the above named genes which we believe may influence therapeutic response to AZD6140 and clopidogrel it is likely that additional information on other genes important for these drugs and for susceptibility to and prognosis of cardiovascular disease (encompassing acute coronary syndrome [ACS] and platelet aggregation) for which the drug is being developed will become available in the future. It is, therefore important to retain the possibility of investigating additional genes in the context of this AZD6140 clinical study.

It is emphasised that AstraZeneca will only look for markers within genes relevant to the mode of action of, and response to AZD6140 and co-medication and clopidogrel and cardiovascular disease.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic research population

3.1.1 Study selection record

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

3.1.2 Inclusion criteria

For inclusion in this genetic research, subjects 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 the genetic sample collection.

3.1.4 Discontinuation of subjects from this genetic research

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

Withdrawal of consent for genetic research: Subjects 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 the subjects at Visit 1 at or after randomisation. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event, such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 1 it may be taken at any visit until the last study visit. Only one sample should be collected per subject 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

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality.

Samples will be stored for a maximum of 15 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the subject enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. 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.

All DNA samples will be stored under secure conditions with restricted access. The blood, DNA samples or data derived from the samples may be made available to groups or organisations working with AstraZeneca on this study or as part of the development drug project. However, the samples and any results will remain the property of AstraZeneca at all times. AstraZeneca will not give blood, DNA samples or data derived from the samples to any other parties, except as required by law.

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 subject 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 subject 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 subject and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue from the genetic aspect of the study at any time.

4.2 Subject data protection

AstraZeneca will not provide individual genotype results to subjects, 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 subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject'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 the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze the samples.

The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

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

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

7. LIST OF REFERENCES – NOT APPLICABLE

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Appendix E
Method sheets

ADP-INDUCED PLATELET ADDREGOMETRY-OPTICAL AGGREGEOMETRY

A standard methodology will be used across all centres in which this assessment is applicable. Depending on the equipments for analysis, there might be variations with regard to the amount of sample, reagents and procedure. However, according to the following standard procedure, technicians who are trained appropriately can perform this experiment.

1. Prepare a 10 mL graduated polystyrene tubes, each containing 1 mL 3.13% w/v trisodium citrate dehydrate, for each subject at the protocol timepoints specified in the study plan.

2. Take 10 mL of venous blood into a plain syringe and dispense 9 mL down the inside of tubes containing 1 mL 3.13% citrate. Immediately cap the tube and gently invert 3 times to ensure adequate mixing, place in a rack at room temperature to await collection or delivery to the laboratory.

3. Ensure the sample is correctly labelled with details of the subject ID and the exact time of sample collection.

4. Ensure that the sample is delivered to the laboratory as quickly as possible following collection. Avoid agitating the blood sample during transfer. The preparation of platelet rich plasma (PRP) needs to start within 15 minutes of the sample collection.

5. Centrifuge the sample at room temperature for 10 minutes at 80 g to obtain PRP.

6. After centrifugation of the citrated blood sample, remove the upper turbid layer of PRP from the tube using a polypropylene pipette (Pastette) taking care not to disturb the red cell layer and place into a clean polystyrene tube.

7. Centrifuge the residual blood for 10 minutes at 2000 g to obtain platelet poor plasma (PPP) and remove the upper clear layer and place in a clean polystyrene tube. If the PPP appears to be turbid, re-centrifuge or filter to obtain a clear sample.

8. Measure the platelet count of the PRP and using the PPP adjust the platelet count of the PRP to 250,000 platelets/μL. If the platelet count is below 250,000 record the value and use undiluted. Begin the aggregation analysis of the sample (ie, setting 100% baseline with PPP) at one hour (±10 minutes) after collection.

9. Pipette 200 μL of PPP into an aggregometer test tube and set the 100% baseline for the rest wells, autologous PPP should be used for the PRP sample under investigation.

10. Pipette 200 µL of PRP into 4 cuvettes containing stir bars and place in the incubation wells (set at 37°C). Leave each to incubate for one minute and then transfer to the test wells and depress the channel operation switches to begin the 0% baseline tracings (this may be different for other aggregometers).

11. After one minute stirring in the test well add the platelet aggregating agent, ADP set for target concentration, to the first 2 cuvettes and no reagent is added to other 2 cuvettes and used as blank. Ensure that the agonist is added quickly and carefully to the bottom of the tube.

12. Follow the aggregation in each channel for exactly 6 minutes following agonist addition and record this final aggregation extent (%) in the case report form (CRF).

13. Examine the aggregation traces once they are completed and record the maximum extent of aggregation (%) for each trace in the CRF.