Clinical Study Protocol

Drug Substance	AZD6140
Study Code	D5130C00065
Edition Number	1
Date	

A Randomised, Double-Blind, Parallel Group, International (Asian), Multicenter Study, to Assess Pharmacokinetic and Pharmacodynamic Profile of 2 Doses of AZD6140 on Low Dose Acetyl Salicylic Acid Therapy on Platelet Aggregation in Japanese and Asian Patients with Stable Coronary Artery Disease

Sponsor:

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The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

AstraZeneca

PROTOCOL SYNOPSIS

A Randomised, Double-Blind, Parallel Group, International (Asian), Multicenter Study, to Assess Pharmacokinetic and Pharmacodynamic Profile of 2 Doses of AZD6140 on Low Dose Acetyl Salicylic Acid Therapy on Platelet Aggregation in Japanese and Asian Patients with Stable Coronary Artery Disease

Principal Investigator

The name of the investigators in Japan are described in Supplement A, "Investigations and Study Administrative Structure".

Study centre(s) and number of subjects planned

Study Centres: Approximately 18 centres are planned for participation

Number of Subjects: Totally 135 randomised subjects (45 patients per group (At least 34 Japanese patients and 7 Non-Japanese Asian patients per group))

Study period		Phase of development
Estimated date of first subject enrolled	April 2010	PhII
Estimated date of last subject completed	April 2011	

Objectives

Primary Objective

To investigate effect of two doses of AZD6140 (45 mg and 90 mg bid) on Inhibition of Platelet Aggregation in Japanese patients with Stable Coronary Artery Disease

Secondary Objectives

1. To evaluate overall safety and tolerability (especially in Bleeding) of two doses of AZD6140 (45 mg and 90 mg bid) in Japanese and Non-Japanese Asian patients.

2. To evaluate overall safety and tolerability (especially in Bleeding) of two doses of AZD6140 (45 mg and 90 mg bid) in Japanese patients.

3. To investigate pharmacokinetic profile of AZD6140 in Japanese patients in comparison with Non-Japanese Asian patients.

4. To compare relationship of AZD6140 and AR-C124910XX plasma concentrations and on Inhibition of Platelet Aggregation between Japanese and Non-Japanese Asian patients.

5. To compare the safety and tolerability of two doses of AZD6140 (45 mg and 90 mg bid) plus Acetyl Salicylic Acid with clopidogrel 75 mg qd plus Acetyl Salicylic Acid in Japanese and Non-Japanese Asian patients.

6. To investigate Inhibition of Platelet Aggregation of AZD 6140 in Japanese patients by visual comparison with Inhibition of Platelet Aggregation from study D5130C00008 (DISPERSE)

7. To investigate pharmacokinetic profile in Japanese patients in comparison with profile from study D5130C00008 (DISPERSE)

8. To compare relationship of AZD6140 and AR-C124910XX plasma concentrations and Inhibition of Platelet Aggregation in Japanese patients with study D5130C00008 (DISPERSE)

9. To assess the pharmacodynamic effects of two doses of AZD6140 (45 mg and 90 mg bid) in the presence of Acetyl Salicylic Acid compared to clopidogrel 75 mg qd plus Acetyl Salicylic Acid, in Japanese patients

Study design

This is a randomised, double-blind, parallel group, Asian, multicenter trial, to assess efficacy of 2 doses of AZD6140 on top of low dose Acetyl Salicylic Acid therapy on platelet aggregation in Japanese and Non-Japanese Asian patients with stable coronary artery disease.

Target subject population

Male and female patients ≥20 years and ≤80 years of age with stable coronary artery disease (having documented evidence of past percutaneous coronary intervention and/or Post acute coronary syndrome more than 3 months prior to randomisation).

Investigational product, dosage and mode of administration

AZD6140 45mg or 90mg (tablet) taken twice daily will be given, orally.

Comparator, dosage and mode of administration

Clopidogrel 75mg (over-encapsulated) taken once daily will be given, orally as a reference drug.

Duration of treatment

4 weeks

Outcome variable(s):

Primary Outcome variable

- Inhibition of Platelet Aggregation final extent at each assessment points

Secondary Outcome variable(s)

- Adverse events, laboratory values , physical examination, 12-lead ECG, Holter ECG, and vital signs.
- Major, minor and minimal bleeding events (to be adjudicated using DISPERSE and PLATO definitions)
- Pharmacokinetics of AZD6140 and AR-C124910XX (C_{max}, $C_{ss,max}$, t_{max}, $t_{ss,max}$, C_{min}, $C_{ss,min}$, C_{av}, $C_{ss,av}$, AUC_{0-tau}, $t_{1/2,}$ R_{ac}, CL/F accumulation ratios)
- Relationship of mean exposure of AZD6140/AR-C124910XX and Inhibition of Platelet Aggregation final extent at each assessment points
- Inhibition of Platelet Aggregation final extent at each assessment points

Statistical methods

All Pharmacodynamics, Pharmacokinetics and safety data will be summarised descriptively by treatment group and region (Japan, Non-Japan).

Inhibition of Platelet Aggregation (final extent) at 2, 4, 8, 12 and 24 hours post-dose on Day 28 will be analysed separately based on ANOVA model including treatment group (AZD6140 45mg, 90mg and clopidogrel) and the difference between AZD6140 dose groups and its 2-sided 95% confidence interval will be estimated. In addition, the difference between each AZD6140 dose group and clopidogrel group and its 2-sided 95% confidence interval will be estimated.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACS	Acute coronary syndromes
ADP	Adenosine diphosphate
AE	Adverse event (see definition in Section 6.4.1)
ASA	Acetyl salicylic acid (aspirin)
$AUC_{0\text{-}tau}$	Area under the plasma concentration curve from time zero to dosing interval
CABG	Coronary artery bypass graft
CEC	Clinical Endpoint Committee
C_{max}	Maximum plasma (peak) drug concentration
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IPA	Inhibition of platelet aggregation
ISF	Investigator's study file
IWRS	Interactive Web Response System
LOQ	Lower Limit of Quantification
LMWH	Low Molecular Weight Heparin
MedDRA	Medical Dictionary for Regulatory Activities
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
SAE	Serious adverse event (see definition in Section 6.4.2).
TIA	Transient ischemic attack
t_{max}	Time to reach peak or maximum concentration or maximum response following drug administration
$t_{½}$	Half-life
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). Thus the development of new ADP receptor antagonists with improved efficacy and/or safety profiles is desirable.

The Phase III study (PLATO/D5130C05262) is an international, multicenter, double-blind, randomized, two-arm parallel group, comparative trial. In this study, we compared AZD6140 (180 mg loading dose, 90 mg bid thereafter) and clopidogrel (300-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 often end up being fatal cases, which is still a major issue in these days where Percutaneous coronary intervention (PCI) has been commonly performed. 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

Research hypothesis to be tested is that IPA increases with dose level of AZD6140 in Japanese patients with stable coronary artery disease in the similar way to the results from DISPERSE.

1.3 Rationale for conducting this study

Data from Phase I studies in human volunteers demonstrate acceptable tolerability of AZD6140 over an orally administered dose range of up to 900mg 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 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 2 hours while not until after 24 hours with clopidogrel. 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 but not until after 24 hours with clopidogrel. After the initial dose there was a 10-15% higher degree of platelet inhibition with the 400 mg dose compared to the 100 and 200mg doses. However, during maintenance treatment there was no significant difference in platelet inhibition between the 100 mg, 200 mg twice daily or 400mg 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 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 75mg 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, 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 myocardial infarction 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 significantly 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 coronary-artery bypass grafting (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).

Holter monitoring and dyspnoea was investigated in detail in the PLATO, 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 2907 patients. The number of patients with ventricular pause (> 3sec) 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).

Percentage of patients who complained of any type of dyspnea 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 dyspnea, leading to discontinuation was 0.8% and 0.1% in the AZD6140 group and the clopidogrel group, respectively. However, most cases of dyspnea associated with AZD6140 were of mild to moderate intensity, and dyspnea 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 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 conserved (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 CV death (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 conserved 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 (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. As in the whole PLATO, the Asian patients exhibited a consistent tendency to higher bleeding event rates in the AZD6140 than in the clopidogrel group but the differences were not statistically significant. In conclusion, 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 (CV death, 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 excellent efficacy and risk/benefit balance when compared to clopidogrel. The AZD6140 90 mg twice daily dose and 45 mg twice daily dose have been selected as the dose for this study in phase 2 since equivalent doses were used in DISPERSE and therefore will offer the data of IPA and safety profile in the studied patients with stable coronary artery disease.

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 (cardiovascular death, 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 result from the 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 Major bleeding risk.

Ideally, it is preferable to recruit patients in a Phase II Asian collaboration study who are as closer to the target population for which AZD6140 will be ultimately indicated as possible. However, 90 mg bid is to be the therapeutic dose and 45 mg bid may not be clinically effective enough, it is considered inappropriate to enrol patients to whom dual antiplatelet therapy with ASA is essential.

Therefore, we intend to conduct a Phase II study in patients with stable target disease, i.e. those who underwent PCI or were diagnosed as having ACS more than 3 months prior to randomisation. Platelet aggregation capability is enhanced in these patients, compared to healthy volunteers, which means that the pathology is similar to that in patients with ACS, the ultimate target population. Thus, we judged it appropriate to enroll these patients.

In overseas, DISPERSE was conducted in patients with atherosclerosis to choose an optimal dose by comparing IPA of AZD6140 with clopidogrel. Subsequently, DISPERSE was conducted in patients with ACS to make similar comparisons. Although there was a slight difference in absolute IPA value of AZD6140 between two studies, the results were similar in terms of comparison with clopidogrel, suggesting that there was no obvious difference in the antiplatelet effects of AZD6140 between two patient populations.

In summary, we believe it appropriate to conduct a Phase II Asian collaboration study in patients with a history of ischemic heart disease whose disease is currently stable to investigate the correlation of IPA and PK with the dose in Asian populations including Japanese.

2. STUDY OBJECTIVES

2.1 Primary objective

To investigate effect of two doses of AZD6140 (45 mg and 90 mg bid) on IPA in Japanese patients with Stable Coronary Artery Disease.

- IPA final extent at each assessment points

2.2 Secondary objectives

1. To evaluate overall safety and tolerability (especially in Bleeding) of two doses of AZD6140 (45 mg and 90 mg bid) in Japanese and Non-Japanese Asian patients.

   - AEs, laboratory values, physical examination, 12-lead ECG, Holter ECG and vital signs.
   - Bleeding events (to be adjudicated using DISPERSE and PLATO definitions)

2. To evaluate overall safety and tolerability (especially in Bleeding) of two doses of AZD6140 (45 mg and 90 mg bid) in Japanese patients.

   - AEs, laboratory values, physical examination, 12-lead ECG, Holter ECG and vital signs.
   - Bleeding events (to be adjudicated using DISPERSE and PLATO definitions)

3. To investigate PK profile of AZD6140 in Japanese patients in comparison with Non-Japanese Asian patients.

   - Exposure of AZD6140 and AR-C124910XX (C_{max}, $AUC_{0\text{-}tau}$, t_{max}, $t_{1/2}$ for AZD6140 and its active metabolite AR-C124910XX, accumulation ratios)

4. To compare relationship of AZD6140 and AR-C124910XX plasma concentrations and IPA between Japanese and Non-Japanese Asian patients.

   - Relationship of mean exposure of AZD6140/AR-C124910XX and IPA final extent at each assessment points.

5. To compare the safety and tolerability of two doses of AZD6140 (45 mg and 90 mg bid) plus ASA with clopidogrel 75 mg qd plus ASA in Japanese and Non-Japanese Asian patients.

   - AEs, laboratory values, physical examination, 12-lead ECG, Holter ECG and vital signs.
   - Bleeding events (to be adjudicated using DISPERSE and PLATO definitions)

6. To investigate IPA of AZD6140 in Japanese patients by visual comparison with IPA from study D5130C00008 (DISPERSE)

   - IPA final extent at each assessment points

7. To investigate PK profile in Japanese patients in comparison with profile from studyD5130C00008 (DISPERSE)

- Exposure of AZD6140 and AR-C124910XX (C_{max}, $AUC_{0\text{-}tau}$, t_{max}, $t_{1/2}$ for AZD6140 and its active metabolite AR-C124910XX, accumulation ratios)

8. To compare relationship of AZD6140 and AR-C124910XX plasma concentrations and IPA between Japanese patients and study D5130C00008 (DISPERSE)

   - Relationship of mean exposure of AZD6140/AR-C124910XX and IPA final extent at each assessment points

9. To assess the pharmacodynamic effects of two doses of AZD6140 (45 mg and 90 mg bid) in the presence of ASA compared to clopidogrel 75 mg qd plus ASA, in Japanese patients

   - IPA final extent at each assessment points

2.3 Safety objective

See Section 2.2.

2.4 Exploratory objective - Not applicable

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

This is a randomised, double-blind, parallel group, Asian, multicenter trial, to assess efficacy of 2 doses of AZD6140 on low dose ASA therapy on platelet aggregation in Japanese and Non-Japanese Asian patients with stable coronary artery disease.

This study consists of a 2-week run-in period , 4-week treatment period and the follow-up examinations 4 weeks after completion of study medication(Figure 1, Table 1). Eligible patients will be randomised to one of the three arms; AZD6140 45 mg bid + ASA 81-100 mg/day, AZD6140 90 mg bid + ASA 81-100 mg/day or clopidogrel 75 mg qd + ASA 81-100 mg/day. Forty-five patients, at least 34 Japanese patients and 7 Non-Japanese Asian patients, will be randomised to each arm, totally 135 patients will be randomised to this trial.

At Visits 2 and 5 there will be detailed PD and PK sampling and analysis over 12-hour and 24 hour period following the morning dose of investigational product. The final dose of investigational product will be taken at Visit 5. The time interval between visits will be as follows:

Visit 3 will take place 7 days (±1 days) from Visit 2

Visit 4 will take place 14 days (±2 days) from Visit 2

Visit 5 will take place 28 days (±2 days) from Visit 2

Follow-up visit will take place 28 days (±4 days) from Visit 5 or discontinuation visit

Investigational product will be dispensed to the subject at Visit 2.

Concomitant medications will be recorded from 14 days prior to Visit 2 to Follow-up visit. AEs will be recorded after obtaining the written informed consent until the follow up visit.

Two-week run-in period (between Visit 1 and Visit 2)

Visit 1 (enrolment) will take place 3 to 14 days prior to Visit 2. The minimum 3 day interval will ensure that Visit 1 blood results from the central laboratory will be available to assess exclusion criteria at Visit 2.

At or before Visit 1, the investigator will obtain the written informed consent from the patient before study-related procedure will be performed.

The eligibility tests will be performed in line with the inclusion/exclusion criteria listed in Sections 4.1 and 4.2, respectively. The following enrolment assessments will be performed and recorded on electric case report form(eCRF): demographics (birth day, sex, body weight and height), smoking and alcohol habit, medical history, current disease, surgical history, premedication, laboratory tests (blood), 12-lead ECG , vital signs (blood pressure and pulse rate), and physical examination and pregnancy test for possible childbearing female. The AEs will be recorded.

After obtaining the written informed consent, 24-hour Holter ECG will performed as a baseline examination.

Four-week randomised treatment period (between Visit 2 to Visit 5)

At Visit 2 the subjects' eligibility will be re-confirmed. To be eligible all subjects must be receiving concomitant ASA 81 to 100 mg od for at least 2 weeks prior to Visit 2. In addition subjects will continue with concomitant ASA 81 to 100 mg od (administered as a constant daily dose) during the 28 day treatment period.

The subjects will be randomised to one of three treatment groups by Interactive web response system (IWRS).

At Visit2, before study medication, the following assessments will be performed and recorded on eCRF: physical examination, measurement of vital signs (blood pressure and pulse rate), 12-lead ECG, laboratory tests (blood and urine), PD and PK assessments. The concomitant medication and AEs will be recorded.

The investigator(s) will instruct the subjects on how to take the study medication. The first dose of investigational product will be taken in the clinic at Visit 2, and the detailed PD and PK assessment will commence and continue over the next 12 hours.

Subjects who do not fulfil the inclusion/exclusion criteria will not be randomised in the study and will not receive any investigational product.

At Visit 3 the following assessments will be performed and recorded on eCRF: vital signs (blood pressure and pulse rate), physical examination. The concomitant medication and AEs will be recorded.

At Visit 4 the following assessments will be performed and recorded on eCRF: physical examination, measurement of vital signs (blood pressure and pulse rate), 12-lead ECG, laboratory tests (blood). The concomitant medication and AEs will be recorded. The 24-hour Holter ECG will be carried out.

At Visit 5 or discontinuation visit the following assessments will be performed and recorded on eCRF: physical examination, measurement of vital signs (blood pressure and pulse rate), 12-lead ECG, laboratory tests (blood and urine). The concomitant medication and AEs will be recorded.

The subject will visit the clinic without intake of the study drug and will take the last dose of investigational product in the clinic at Visit 5, and the detailed PD and PK assessment will commence and continue over the next 24 hours. The subjects will not take the evening dose of the investigational product.

Four-week follow-up (Visit 6)

The following assessments will be performed and recorded on eCRF: physical examination, measurement of vital signs (blood pressure and pulse rate), 12-lead ECG. The concomitant medication and AEs will be recorded.

Figure 1 shows the study flow chart and Table 1 shows the study parameters and the schedule.

Table 2 shows the schedule for the PD and PK assessment.

Figure 1 Study flow chart

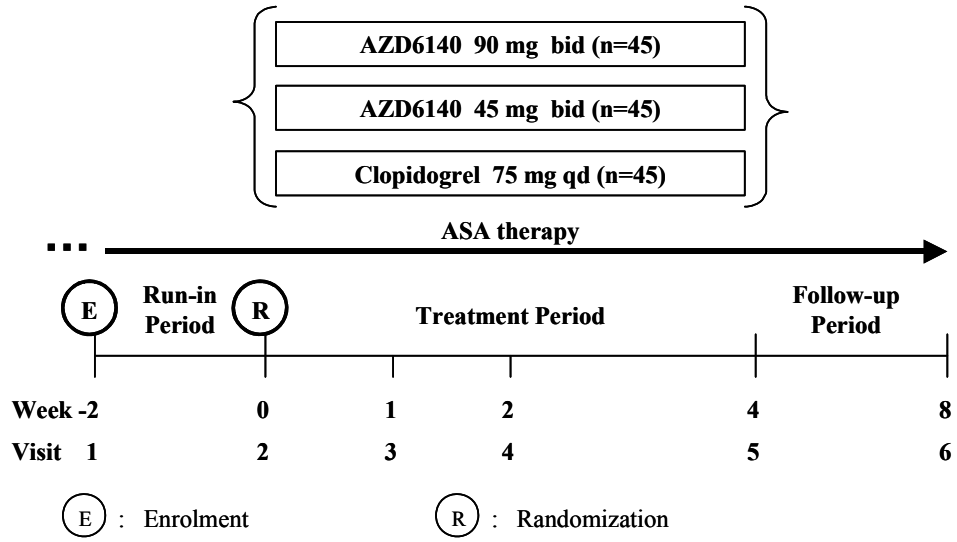

Table 1 Study parameters and schedule

Visit	1	2	3	4	5	Follow Up	Discontinuation
Week	**-2-0**	**0**	**1**	**2**	**4**	**8**	
Day	**-14--3**	**0**	**7**	**14**	**28**	**28 day aft. discont.**	
Informed consent	X						
Eligibility criteria	X	X					
Randomisation		X					
Demographics	X						
Concomitant medication	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
12-lead ECG	X	X		X	X	X	X
Holter ECG	X			X			
Study medication dispensing		X					
Compliance/ Drug accountability			X	X	X		X
AE/SAE reporting	X	X	X	X	X	X	X
Laboratory test (blood)	X	X		X	X		X
Laboratory test (urine)		X			X		X
Pregnancy test*	X						
Plasma concentrations		X			X		X
IPA		X			X		X

* For childbearing female only

Table 2 PK/PD assessment schedule

Assessment	**Visit 2 Randomisation (Day 0)**						**Visit 5 (or Discontinuation) Week4 (Day 28)**					
Hours (relative to dose)	**Pre**	**1**	**2**	**4**	**8**	**12**	**Pre**	**2**	**4**	**8**	**12**	**24**
PK blood sample	X	X	X	X	X	X	X	X	X	X	X	X
PD blood sample	X	X	X	X	X	X	X	X	X	X	X	X

3.2 Rationale for study design, doses and control groups

Research hypothesis to be tested is that IPA increases with dose level in Japanese patients with stable coronary artery disease in the similar way to the results from DISPERSE.

Primary endpoint

The DISPERSE result shows AZD6140 has a favourable antiplatelet potency with regard to IPA compared to clopidogrel sulphate. This study will evaluate IPA as primary endopoint.

AZD6140 dosing regimen

The objective of this study is to investigate IPA of AZD6140 and the correlaiton of IPA and PK with the dose in Japanese patients with stable coronary artery disease. Also, we plan to visually compare PK and IPA data obtained from this study with those from DISPERSE conducted in overseas. In DISPERSE, a total of 4 doses of AZD6140 (50mg bid, 100mg bid, 200mg bid and 400mg qd as the old formulation, which corresponds to 45mg bid, 90mg bid, 180mg bid and 360mg qd as the new formulation, respectively) were used.

Both the DISPERSE2 and the PLATO suggested that 90 mg should be the clinically recommended dose. Results from a Japanese Phase I repeated dose study showed about 40% higher exposure to AZD6140 in Japanese, compared to Caucasians. Therefore we considered it inappropriate to investigate a higher dose than 90 mg bid in this study. The AZD6140 90mg twice daily dose and 45 mg twice daily dose have been selected as the dose for this study since equivalent doses were used in DISPERSE.

Since the secondary objective of this study is to compare the results with those from DISPERSE, it is considered necessary to adopt the same administration method as DISPERSE, therefore, we decided that no loading dose, which was given as the initial dose in PLATO, is employed in this study.

Control group and background therapy

Since one of the objectives of a Phase II study is to visually compare the results with those from DISPERSE to assess similarities in IPA and PK between two studies, we set clopidogrel as a reference drug and the dosage to be 75 mg qd in this study as well as DISPERSE. Also, it is considered necessary to adopt the same administration method as DISPERSE also for a reference, therefore, we decided that no loading dose is employed in this study.

Both AZD6140 and clopidogrel may be administered against a background of ASA therapy, unless contraindicated, since ASA is standard therapy for prevention of thrombotic events and new therapies will be adjunctive (Chen ZM et al 2005, Sabatine MS et al 2005, Yusuf S et al 2001) A once daily ASA dose of 81 to 100mg is recommended in this study considering medical circumstance since previous manuscripts (Peters RJG et al 2003, Patrono C et al 2004) have indicated 75 to 100 mg as a suitable daily dose range for ASA in combination therapy to protect against thrombotic events.

Study design

This study is mirror study of DISPERSE in Asian patients. However, this is not a confirmative study of DISPERSE. A duration of 4 weeks has been selected based on DISPERSE.

Study committees and organisation

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

The bleeding events will be reported and centrally adjudicated by an Clinical Endpoint Committee (CEC) (See Section 6.4.9 and 12.5).

An independent, external DSMB will monitor data on an ongoing basis to ensure that patient safety is not compromised and will make recommendations for early safety, or efficacy termination (See section 12.4).

Study patient population

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

The sites selected in this study will represent a range of treatment practices, however, a particular emphasis will be placed on selecting sites with experienced cardiologist.

It is expected that the sex distribution in this study will be approximately the same as in the ACS population (60% male and 40% female), as patients will be enrolled into the study without taking into account the sex of the patients. The intention is to include patients with a sex distribution as close to the ACS population as possible. The only reason to believe the sex distribution in this study may be different from the ACS population is that women of childbearing potential are required to use 2 methods of reliable contraception, one of which must be barrier method (See Section 4.1). However, this requirement is not expected to have an important effect on recruitment.

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 written informed consent prior to any study specific procedures

2. Male and female with age between 20 and 80 years of age.

3. For inclusion in the study, patients have to fulfil the following criteria:

   – Any PCI, more than 3 months prior to Visit 2

   Or

   – Previous documented ACS, more than 3 months prior to Visit 2

4. ASA therapy 81 to 100mg qd at least 2 weeks prior to Visit 2

5. 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.

4.2 Exclusion criteria

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

1. ACS, transient ischaemic attack (TIA) or stroke within the 3 months prior to Visit 2.

2. Known concurrent disease of Stroke or TIA with atrial fibrillation

3. Concomitant antiplatelet therapy other than ASA within the 14 days prior to Visit 2.

4. Full dual antiplatelet treatment required according to clinical judgment

5. Fibrinolytic therapy within 2 weeks prior to Visit 2 or is planned to be administered for any conditions during the study.

6. Patients who implanted Drug-eluting stent

7. Any percutaneous intervention (eg, coronary, peripheral or cerebral), carotid endoatherectomy or surgical operation that is planned to occur during the course of the study.

8. Chronic atrial fibrillation (constant or paroxysmal), rheumatic valve disease, prosthetic heart valves or valve surgery

9. Any contraindications for ASA and/or clopidogrel treatment (also refer to the prescribing information of the concomitant medication)

10. The following conditions associated with increased risk of bleeding:

    (a) History of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding

(b) Gastrointestinal bleeding within the 12 months prior to Visit 2

(c) Gastric or duodenal ulcer disease verified by endoscopy or barium meal-double contrast technique within the 3 months prior to Visit 2

(d) Uncontrolled hypertension: systolic 180 mm Hg and higher or diastolic 100 mm Hg and higher (with or without anti-hypertensive treatment) as measured at Visits 1 and 2

(e) Hemorrhagic disorder

(f) Required concomitant therapy with nonselective NSAIDs

(g) Major surgical procedure or trauma within the 30 days prior to Visit 2.

11. Increased risk of bradycardic events (e.g. 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)

12. Patient with renal failure requiring dialysis

13. Platelet count less than 10 x $10^4/\mu L$

14. Hemoglobin (Hb) level less than 10 g/dL

15. Pregnancy or lactation

16. Anticoagulant therapy within the 14 days prior to Visit 2.

17. Any other condition which in the opinion of the investigator(s), may either put the patient at risk or inappropriately influence the result of the study , or the subject's ability to participate in the study (eg, cardiogenic shock or severe hemodynamic instability, active cancer, risk for non-compliance, risk for being lost to follow up)

18. Patient with moderate or severe liver disease

19. Concomitant oral or intravenous therapy (see examples below) with strong CYP3A inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers which cannot be stopped for the course of the study

- Strong inhibitors: ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, erythromycin, nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atanazavir, over 1 litre daily of grapefruit juice.

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

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

20. Participation in another investigational drug or device study in the last 30 days prior to Visit 2

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

22. Previous enrolment or randomisation of treatment in the AZD6140 studies.

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.

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

Females of child-bearing potential (ie, females who are not chemically or surgically sterilised or females who are not post-menopause) must use 2 methods of reliable contraception, one of which must be a barrier method from the enrolment until 1 month after the last dose.

Restrictions regarding concomitant medications are described in Section 5.6.

5.2 Subject enrolment and randomisation

The Principal Investigator will:

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

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

3. Determine subject eligibility. See Sections 4.1 and 4.2

4. Assign eligible subject unique randomisation code.

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

5.2.1 Procedures for randomisation

After signing the written informed consent, each subject will be allocated a strictly sequential enrolment code (E-code). If a subject discontinues from the study, the subject number will not be reused, and the subject will not be allowed to re-enter the study.

Subject eligibility will be established before treatment randomisation. At Visit 2, subjects who fulfil all the eligibility requirements will be allocated a randomisation code strictly sequentially from a randomisation list. The randomisation list will be generated in blocks of a predefined size to ensure all 3 treatment groups are equally represented. Following randomisation the first dose of investigational product will be administered. If a subject discontinues from the study after randomisation, the randomisation code will not be reused, and the subject will not be allowed to re-enter the study.

5.3 Procedures for handling subjects incorrectly enrolled or randomised

Subjects who fail to meet the inclusion criteria or who meet the 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.

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

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

This study will be conducted under double-blind fashion. The closest attention should be paid to make the appearance, package and labelling of the investigational products indistinguishable. The investigational product will be allocated by the responsible person who is not related to this study.

5.4.2 Methods for unblinding the study

Individual treatment codes in the sealed envelope, indicating the treatment randomisation for each randomised subject, will be provided to the investigator(s) or pharmacist by AstraZeneca representative with investigational products.

For Japan, replace the above paragraph with the paragraph below

Individual treatment codes in the sealed envelope, 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 by AstraZeneca representative with investigational products.

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 serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

5.5 Treatments

5.5.1 Identity of investigational product(s)

AZD6140 45 mg and 90mg tablets and their matching placebo tablets will be used in the study together with clopidogrel 75mg tablets that have been over-encapsulated and their matching placebo capsules.

Investigational product	Dosage form and strength	Manufacturer
AZD6140 45 mg	Plain, round, yellow, film-coated tablet	AstraZeneca
AZD6140 90 mg	Plain, round, yellow, film-coated tablet	AstraZeneca
AZD6140 45 mg placebo	Plain, round, yellow, film-coated tablet, placebo to match 45 mg	AstraZeneca
AZD6140 90 mg placebo	Plain, round, yellow, film-coated tablet, placebo to match 90 mg	AstraZeneca

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

5.5.2 Doses and treatment regimens

At Visit 2 (randomisation) eligible patients will be randomly assigned to one of three treatment arms, AZD6140 45mg, 90mg twice daily or clopidogrel 75mg once daily, taken orally.

Randomisation and treatment pack assignment will be managed via the IWRS and the first dose of study medication should be taken directly after randomisation at Visit 2. Subsequent maintenance doses should be taken morning and evening, at approximately 12-hourly intervals, for the remainder of the treatment period.

Study medication should be swallowed whole with water. Study medication should not be altered (eg, crushed, put in another vehicle) and should not be given by nasogastric tube or other routes.

5.5.3 Concomitant ASA

In addition to randomised study medication all patients should be treated with concomitant ASA 81 to 100mg daily for at least 2 weeks prior to Visit2 and during the treatment period according to local practice. This medication will be open label and obtained locally.

5.5.4 Labelling

Labelling of the investigational products will be carried out by AstraZeneca or a Contract Research Organization in accordance with current Good Manufacturing Practice (GMP). The labels will be translated into local languages and in accordance with local regulations for each participating country. The labels will fulfil GMP Annex 13 requirements and/or local regulatory guideline.

All investigational products will be labelled. Information from the labels will be transferred to suitable forms in the Investigator's Study File (ISF).

5.5.5 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 the above paragraph 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 (defined as ASA and ongoing prescriptions) will be recorded from 14 days prior to Visit2 and throughout the study until the follow-up visit.

5.6.1 Parenteral anticoagulants

Treatment with approved parenteral anticoagulants (eg. unfractionated heparin (UFH), LMWH, bivalirudin, fondaparinux) is not allowed during the study. If treatment with parenteral anticoagulant drugs is considered essential during the study, study medication must be discontinued.

5.6.2 Oral anticoagulants

Concomitant treatment with anticoagulant drugs is not allowed during the study. If treatment with anticoagulant drugs is considered essential during the study, study medication must be discontinued.

5.6.3 Oral antiplatelet therapies and NSAIDs

ASA: All patients should take open label ASA at a dose of 81 to 100mg once daily throughout the study. ASA for pain relief should where possible be discouraged and paracetamol (acetaminophen) given.

Clopidogrel sulphate and Ticlopidine: Patients who are currently taking clopidogrel are not eligible to enter the study.

Dipyridamole and cilostazol: Patients who are currently taking any of these drugs are eligible to enter the study but treatment must be discontinued at least 14 days prior toVisit2. Further dosing of any of these drugs in addition to study medication is not allowed during the study.

Other oral antiplatelets: Clinical experience with other drugs with antiplatelet effect (e.g., 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.

5.6.4 Fibrinolytic therapy

A patient is not eligible for inclusion into the study if fibrinolytic therapy has been given within 2 weeks prior to Visit 2 or is planned to be administered for any conditions during the study.

Clinical experience of fibrinolytics in combination with AZD6140 is not available at this time. If treatment with fibrinolytic therapy is required during the study, study medication must be discontinued. .

5.6.5 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.

5.6.6 CYP3A interactions

5.6.6.1 CYP3A inhibitors

AZD6140 and AR-C124910XX (active metabolite) are metabolised by CYP3A. Therefore strong inhibitors of this enzyme (e.g. ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, erythoromycin, nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atanazavir or over 1 litre daily of grapefruit juice) are not permitted during the study as plasma levels of AZD6140 would be substantially increased (coadministration of AZD6140 with ketoconazole causes a 7.3-fold mean increase in area under the curve of AZD6140). If treatment with such therapies is necessary study medication dosing must be discontinued.

5.6.6.2 CYP3A substrates or inducers

Non-clinical data shows AZD6140 has different effects from activation through no effect to inhibition of CYP3A depending on the substrate studied. The *in vivo* effects of AZD6140 on the metabolism of the CYP3A substrates midazolam, simvastatin and atorvastatin have been examined.

In healthy volunteers midazolam levels were lowered by about 30% in the presence of AZD6140.

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 40mg 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). Monitoring of patients for possible statin associated myopathy should be performed according to local practice.

The magnitude of these interactions would classify AZD6140 as a mild inhibitor or activator of CYP3A.

Treatment with CYP3A substrates with a narrow therapeutic index (e.g., cyclosporine, and quinidine) is not allowed during the study due to the observed changes with midazolam and simvastatin noted above. Treatment with CYP3A substrates with strong inducers of CYP3A also is not allowed during the study (e.g., phenytoin, rifampin/rifampicin, carbamazepine, phenobarbital). If treatment with such therapies is necessary study medication dosing must be discontinued.

5.6.7 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 in the eCRF. Prescribing information of concomitant medication should be considered.

5.6.8 Treatment after study completion

After the patient has completed or discontinued the study they will be treated according to local medical practice. At Follow up Visit (Visit 6), 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.

5.7 Treatment compliance

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

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

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.

For studies where study drugs are destroyed at site:

Study site personnel, if applicable, or the AZ monitor will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction should be signed.

For studies where study drugs are returned to AZ:

Study site personnel, if applicable, or the AZ monitor will account for all received study drugs and return all unused study drugs to AstraZeneca. Certificates of delivery and return should be signed.

For Japan, replace the above paragraph 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.

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 (e.g clinically significant ventricular pauses, syncope related to bradycardia, persistent increase in serum creatinine level of clinical relevance, persistent, unexplained anaemia (e.g. Hb <10 g/dL) or thrombocytopenia (e.g. platelet count <10 x10^4/μL)
- 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) and the discontinuation is decided by the discussion (see Section 5.3)
- Pregnancy
- Development of a condition or an acute event (eg, MI or stroke) that necessitates treatment with one or more prohibited medications

Once randomised into the study all patients will be assessed until study closure unless informed consent is withdrawn for study participation.

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).

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) and the presence of any AEs. If possible, the subject should be seen and assessed by the investigator(s) at discontinuation visit and follow up visit as planned in Table 1. AEs will be followed up (See Sections 6.4.3 and 6.4.4), and all study drugs should be returned by the subject.

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

For Japan, replace the above paragraph with the paragraph below

A subject that discontinues will always be asked about the reason(s) for discontinuation and the presence of any AEs. 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. AEs will be followed up (See Sections 6.4.3 and 6.4.4), and study drug should be returned by the subject.

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 AEs. If possible, they will be seen and assessed by an investigator. AEs will be followed up (See Sections 6.4.3 and 6.4.4); and all study drugs should be returned by the subject.

Withdrawn subjects will not be replaced.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The Rave 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 eCRFs 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 eCRFs. A copy of the completed eCRFs 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 eCRFs 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

The primary efficacy variable of this study is the final extent IPA (%) induced by a 20 μM ADP. Maximal extent IPA (%) will be calculated to ensure the findings using the final extent IPA.

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 and alcohol history, family history of coronary heart disease
- Safety laboratory blood analyses (clinical chemistry and haematology)
- Blood pregnancy test (for females of child bearing potential)
- Relevant medical and surgical history (including PCI, if any)
- Current concomitant medications
- Targeted physical examination including vital signs (pulse rate and BP), weight and height
- 12-lead ECG
- 24-hour Holtor ECG

6.2.1 Follow-up procedures

Follow-up is planned for 28 days after Visit 5 or discontinuation visit

6.3 Efficacy - Not applicable

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 AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). 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 paragraph below

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 SAE 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 above bullet with the bullet below

Requires in-patient hospitalisation or prolongation of existing hospitalisation (including hospitalisation for tests related to AEs), except hospitalisation that has been planned before enrolment.

- 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 AEs

AEs will be recorded after obtaining the written informed consent until the follow-up visit.

Follow-up of unresolved AEs

Any AEs that are unresolved at the subject's last AE assessment 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 collected 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 SAE
- Date Investigator became aware of SAE
- 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:

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

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

Causality collection

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

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

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

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the 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 (CSR). Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, 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 should be reported using the standard procedures for assessing severity, causality and seriousness.

Bleeding AEs will be further classified as described in Section 6.4.9.

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

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

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

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

For Japan, Replace the above paragraphs with the paragraphs below.

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.

Investigators and other site personnel should inform (emergency report) appropriate AstraZeneca representatives of any SAE that occurs at his or her site in the course of the study within 1 day (in this section, within 1 day is defined as 'immediately but no later than the end of the next business day') of when he or she becomes aware of it (initial SAE report). This should apply whether or not the SAE is considered causally related to the study treatment or to the study procedure(s). The Principal Investigator should provide detailed information to AstraZeneca in writing within 4 calendar days of the initial report. The Principal Investigator should notify the SAEs in writing to the head of the study site immediately.

Follow-up information on SAEs should also be reported to AstraZeneca by the investigator(s) within the same time frames. If a non-serious AE becomes serious, this and other relevant follow-up information should also be provided to AstraZeneca within 1 day as described above.

The following information is required in the initial SAE report to AstraZeneca from the investigator(s); study code, site number, Enrolment code, AE, seriousness, start date. The following detailed information should be sent to AstraZeneca as soon as it becomes available;

Severity, outcome (including stop date, if available), causality (investigational product and if applicable any other concomitant drug), date when a non-serious AE became serious, withdrawal of study treatment, treatment ofAE, concurrent therapy (except for treatment of AE), concurrent medication (including pre-study medication if the causality of the AE cannot be assessed), date of birth, sex, other current illnesses, relevant medical history and if applicable, date and course of death.

In addition AstraZeneca will provide the information on the serious adverse drug reactions collected domestically and abroad regarding the investigational product to the Head of the study site, Principal Investigator and the regulatory agency as per local requirements. The Head of the study site must submit a written report to the IRB providing the information reported by AstraZeneca.

Reporting Procedure of SAEs using WBDC system.

The investigator(s) and other site personnel will access WBDC system and report SAE information by entering it into the relevant eCRF module. Upon entry of the SAE information, an automated email alert will be sent to the designated AstraZeneca representative. If the system is unavailable, the investigator(s) should take other appropriate measures to provide SAE report to the AstraZeneca representative immediately, recognising that the same reporting time frames still apply. The investigator(s) is responsible for completing the eCRF as soon as the system becomes available again.

If initial or the subsequent reports are made by means other than WBDC, necessary information on any SAEs should finally be entered into eCRF via WBDC system by the investigator(s).

6.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be taken at the times indicated in the Study Plan (see Table 1).

The following laboratory variables will be measured:

Clinical chemistry	**Haematology**
S-Creatinine	B-Haemoglobin
S-Alkaline phosphatase	B-Haematocrit
S-Aspartate aminotransferase (AST)	B-Platelets
S-Alanine aminotransferase (ALT)	B-White blood cells
S-Total Bilirubin	B-Red blood cells
S-Albumin (elevated values to be fractionated)	B-White blood cells (differential)
S-Uric acid	
B- Haemoglobin A1c	**Urinalysis (U denotes Urine)**
S-Gamma glutamyltransferase (GGT)	U-Glucose
S-Total protein	U-Protein
S-Lactate dehydrogenase	U-Blood
S-Blood urea nitrogen	
S-Sodium	
S-Potassium	
S-Chloride	
S-Total calcium	
S-pregnancy test (females of child bearing potential only at visit 1)	

*S denotes serum and B denotes whole blood.

For blood volume see Section 7.1

6.4.6 Physical examination

At Visit 1, 2, 3, 4 and 5 or at the time of withdrawal and Follow up a physical examination will be performed and include an assessment of the following: general appearance ,respiratory, cardiovascular, abdomen

6.4.7 ECG

6.4.7.1 Resting 12-lead ECG

The following variables will be measured and assessed.

- Heart rate (beats/min)
- QT interval (ms)
- QRS duration (ms)
- PR interval (ms)
- RR interval (ms)
- Sinus rhythm (yes/no)
- Extrasystoles (yes/no)
- AV conduction (normal/abnormal)
- ST-T change (yes/no), if yes, the details will be recorded.

At Visit 1, 2, 4and 5 or at the time of withdrawal and Follow up visit, ECGs will be recorded in the supine position after the patient has rested in this position for 5 minutes and assessed locally.

ECGs should be standard 12-lead ECG with a lead II rhythm strip and a paper speed of 25 mm/second, covering at least 5 complexes.

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

6.4.7.2 Holter ECG

The holter recordings are analysed centrally using an automated arrhythmia detection program followed by cardiologist review. 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.

Before randomisation and at Visit 4, 24-hour holter ECG will be recorded.

6.4.8 Vital signs

6.4.8.1 Pulse and blood pressure

Pulse rate, systolic BP and diastolic BP will be assessed using the equipment used in the normal practice after the patient has been at rest for 5 minutes.

6.4.9 Other safety assessments

For all bleeding events the investigator will complete information on the eCRF specific to that bleeding event, including classification of the event as described in section 6.4.9.1 below and

a determination of whether it is an AE. For all bleeding events (excluding minimal) relevant additional source information will be compiled into a 'Bleeding 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 bleeding events (excluding minimal) as described in the CEC Charter.

6.4.9.1 Definitions of bleeding events

In this study bleeding events will be classified as shown below (both criteria in PLATO and DISPERSE):

PLATO

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 bleeding – fatal/life-threatening

Any one of the following:

- Fatal bleeding
- Intracranial bleeding
- 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 5 g/dL[a]
- Transfusion[b] of 4 or more units (whole blood or packed red blood cells (PRBCs)) for bleeding.

Major bleeding – 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 3g/dL[a] to 5 g/dL[a]
- Transfusion[b] of 2-3 units (whole blood or PRBCs[b]) for bleeding.

Minor bleeding

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

Minimal bleeding

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

DISPERSE

Bleeding events will be evaluated using the criteria in DISPERSE and classified as major or minor. A major bleeding event is one that meets any of the following criteria:

- Is fatal
- Occurs in a critical site (eg, intracranial, intraocular, spinal, pericardial, joint or retroperitoneal)
- Clinically overt bleeding leading to transfusion [b] of 2 or more units (whole blood or PRBCs)
- Clinically overt bleeding is associated with a decrease in Hb of more than 2 g/dL[a] .

All other bleeding events will be considered minor.

Definitions of Terms

[a] Reference range 13 to 18 g/dL (males); 12 to 16 g/dL (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 1 g/dL 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 = 1 g/dL

All blood product transfusions during the study will be recorded in the eCRF. In addition all haemoglobin (haematocrit) 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 appendix of CEC charter and provided separately to investigators.

Main analysis regarding bleeding events will be performed using the judgement of CEC.

6.5 Patient reported outcomes (PRO) – Not applicable

6.6 Pharmacokinetics

Blood samples for determination of AZD6140 and AR-C124910XX concentrations in plasma will be collected at Visit 2 (day 1) and Visit 5 (day 28). If patients discontinue participation in the study, blood samples will be collected at the discontinuation visit instead of Visit 5.

Instructions for collection, labelling, storage and shipment of PK samples are given below 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 for blood sampling, 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. Handling, storage and destruction of biological samples should be referred to Section 7.2.1.

6.6.1 Collection of samples

Blood samples (3 mL) for determination of AZD6140 and AR-C124910XX in plasma will be taken at the times presented in the study plan Table 2.

For blood volume see Section 7.1.

6.7 Pharmacodynamics

Blood samples for ADP-induced platelet aggregation will be collected at Visit 2 (day 1) and Visit 5 (day 28). If patients discontinue participation in the study, blood samples will be collected at the discontinuation visit instead of Visit 5.

Instructions for collection and handling of PD samples are given below and further details will be provided in the Appendix D. At visits for blood sampling, the date and time of sample collection will be correctly recorded.

6.7.1 Collection of pharmacodynamic markers

Blood samples (10 mL) for ADP-induced platelet aggregation will be taken at the times presented in the study plan Table 2.

For blood volume see Section 7.1.

6.8 Pharmacogenetics – Not applicable

6.9 Health economics – Not applicable

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

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

Table 3 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	4	4	16
	Haematology	2	4	8
PK		3	12	36
PD		10	12	120
Total				180

7.2 Handling, storage and destruction of biological samples

The long-term stability of the analyte(s) should be described in validation report of bioassay established 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 certain should not be reported unless complementary analyte(s) stability data is acquired and amended to the relevant validation report. The time period for which stability has been demonstrated should be documented by the AstraZeneca R&D DMPK department prior to the first patient gives informed consent to take part in the study.

7.2.1 Pharmacokinetic samples

Samples will usually be taken by direct venipuncture. A 3mL 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. A log recording daily temperature readings of the freezer used to store samples at the investigational centre must be maintained.

Individual venepunctures for blood collection at each time point are highly recommended to avoid contamination of saline and heparin by using indwelling venous cannulla.. 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 , venepuncture should be done for further sample collection.

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 Pharmacodynamics samples

Samples for the measurement of platelet aggregation will be drawn through the same cannula used for PK sampling. 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.

At each time point specified in the study plan in Table 2, one 10 mL venous blood sample will be collected into a plain syringe. From this 9.0 mL will be transferred into a tube containing 1 mL trisodium citrate dihydrate.

Pre-dose samples should be obtained shortly (within 30 minutes) before dosing with the investigational product. The pre-dose sample at Visit 2 is a critical baseline sample and enough time should be allowed for a repeat sample and analysis should the first aggregometry analysis fail eg, the sample clots, prior to the first dose of investigational product. The date and time of each sample collection will be recorded in the appropriate section of the eCRF.

The samples will be prepared to produce platelet rich plasma (PRP) that will then be assessed using optical aggregometry. Full details of the methodology are given in Appendix D.

Preparation of PRP will start within 15 minutes of blood samples being obtained so that aggregation studies can start one hour (±10 minutes) after blood sampling to ensure consistency in methodology. Appropriately trained laboratory personnel at each centre will perform all analyses.

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 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.

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 International Conference on Harmonisation (ICH) /Good Clinical Practice (GCP), 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/GCP, applicable regulatory requirements,The applicable regulatory requirements in Japan are 'GCP for Trials on Drugs (MHLW Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications and the AstraZeneca policy on Bioethics and Human Biological Samples.

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).

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 investigator should submit the written approval to AstraZeneca before enrolment of any subject into the study. 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.

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

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 and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

8.4 Informed consent

The 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
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the 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 9.5). 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 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 is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

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

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

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

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, GCP, guidelines of the 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 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).

Laboratory technicians who will perform the optical aggregometry at each centre will receive training in the aggregometry method used in this study and complete a pre-study aggregometry exercise prior to the recruitment of subjects. The training log should be recorded and kept in ISF. An aggregometry manual will provide guidance on all aspects of aggregometry in the study.

9.3 Monitoring of the study

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

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs 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 staff at the centre needs information and advice about the study conduct.

9.3.1 Source data

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

For Japan, replace the above paragraph with the paragraph below

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 eCRFs 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 eCRFs against source data before collecting the eCRFs to ensure accuracy and completeness of documentation, and assure that the Principal Investigator/sub-investigator has submitted the eCRFs to AstraZeneca. If the investigator wishes to amend the collected eCRFs, 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 (e.g. 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, e.g. 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 2010 and to end by 2nd Quarter 2011.

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: February 2010 - April 2011

Registration period: April 2010 – February 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 BY AS COGNIZANT DMC

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 eCRFs. 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 reguratory 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 (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) - Not applicable.

11.2 Calculation or derivation of safety variable(s)

Following variables will be calculated:

- Bleeding events (to be adjudicated using PLATO criteria)
  - Major, Minor, and Minimal bleeding events.
- Bleeding events (to be adjudicated using DISPERSE criteria)
  - Major and Minor bleeding events.
- AEs, laboratory values, physical examination, 12-lead ECG, and vital signs, Holter ECG.

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

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

11.3 Calculation or derivation of patient reported outcome variables - Not applicable

11.4 Calculation or derivation of pharmacokinetic variables

The PK analyses will be performed at AstraZeneca R&D. The actual sampling times will be used in the PK calculations. PK parameters will be determined using standard non-compartmental methods. The following PK parameters will be determined:

Maximum plasma concentration (C_{max} and $C_{ss,max}$), time to C_{max} or $C_{ss,max}$ (t_{max} and $t_{ss,max}$, respectively), minimum plasma concentration (C_{min} and $C_{ss,min}$), average plasma concentration (C_{av} and $C_{ss,av}$), half-life ($t_{1/2}$), area under the plasma concentration-time curve from zero to

dosing interval (AUC_{τ}), and accumulation ratio (R_{ac}) at Visit 2 and 5 for AZD6140 and AR-C124910XX. Oral clearance (CL/F) will be calculated at steady-state.

11.5 Calculation or derivation of pharmacodynamic variable(s)

Maximum and final extent IPA from pre-dose baseline at Visit 2 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 Population analysis of pharmacokinetic/pharmacodynamic variables

AZD6140 and its active metabolite AR-C124910XX concentrations in plasma, which will be measured for the studied population in this study, will be served for population PK analysis.

The result of population analysis of PK/PD will be reported separately from CSR.

11.7 Calculation or derivation of pharmacogenetic variables – Not applicable

11.8 Calculation or derivation of health economic variables – Not applicable

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

Statistical analyses will be performed by Statistics & Programming Department, AstraZeneca KK using SAS. The SAP will provide further details of the analyses and presentation of the data. The SAP 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. Throughout the analyses, erroneously treated subjects (eg, those randomised to treatment A but actually given treatment B) will be accounted for in the actual treatment group.

12.1.1 Pharmacodynamic analysis set

All randomised patients who received at least one dose of investigational product with post-dose PD measurements available and no protocol deviation/violation considered to significantly affect PD of AZD6140 will be included in PD analysis set

12.1.2 Pharmacokinetic analysis set

All randomised patients who received at least one dose of investigational product with post-dose PK measurements available and no protocol deviation/violation considered to significantly affect PK of AZD6140 and its metabolite, AR-C124910XX, will be included in PK analysis set.

12.1.3 Safety analysis set

All subjects who received at least one dose of randomised investigational product will be included in the safety analysis set.

12.2 Methods of statistical analyses

12.2.1 Pharmacodynamic data

All PD data will be listed by patient and summarised by region (Japan, non-Japan) and treatment group.

At each time point, all PD variables will be summarised using the following descriptive statistics.

- N
- Arithmetic mean
- SD
- Median
- Minimum
- Maximum

The mean and individual plots of PD variables over time by day will be presented.

IPA (final extent) at 2, 4, 8, 12 and 24 hours post-dose on Day 28 will be analysed separately based on ANOVA model including treatment group (AZD6140 45mg, 90mg and clopidogrel) and the difference between AZD6140 dose groups and its 2-sided 95% confidence interval will be estimated. In addition, the difference between each AZD6140 dose group and clopidogrel group and its 2-sided 95% confidence interval will be estimated.

The plots of IPA against plasma concentration of AZD6140 and AR-C124910XX will be made. Exploratory analyses based on non-linear models such as sigmoid E-max model will be made to investigate the relationship between PK and PD.

12.2.2 Plasma concentration of AZD6140 and AR-C124910XX

All plasma concentration data will be listed by patient and summarised by region and treatment group.

At each time point, all plasma concentrations will be summarised using the following descriptive statistics.

- N
- Number of samples ≥ Lower limit of quantification (LOQ)
- Geometric mean
- CV (calculated as $100\times\sqrt{(\exp(s^2)-1)}$, where s is the standard deviation of log transformed sample values)
- Arithmetic mean
- SD
- Median
- Minimum
- Maximum

The handling of plasma concentrations below LOQ will be specified in the SAP.

The mean and individual plots of plasma concentration of AZD6140 and AR-C124910XX over time by day will be presented.

12.2.3 PK parameters

All PK parameters will be listed by patient and summarised by region and treatment group.

All PK parameters except for t_{max} will be summarised by day using the following descriptive statistics.

- N
- Geometric mean
- CV (calculated as $100\times\sqrt{(\exp(s^2)-1)}$, where s is the standard deviation of log transformed sample values)
- Arithmetic mean

- SD
- Median
- Minimum
- Maximum

For t_{max}, the following descriptive statistics will be presented.

- N
- Median
- Minimum
- Maximum

12.2.4 Safety data

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

All AEs will be listed and summarised by the System Organ Class and Preferred Terms assigned to the events using MedDRA vocabulary. Furthermore, listings of SAEs and AEs that led to withdrawal will be made and the number of patients who had any AEs, SAEs, AEs that led to withdrawal, and AEs with severe intensity will be summarised. If appropriate, adverse drug reactions will be summarised by the System Organ Class and Preferred Term assigned to the event using the MedDRA.

For the bleeding events adjudicated by CEC, the number of patients with bleeding event along with percentage will be presented.

For the quantitative safety variables, the observed value and the changes from baseline at each time point will be summarised using the following descriptive statistics.

- N
- Arithmetic mean
- SD
- Minimum
- Median
- Maximum

For all quantitative safety variables, the baseline will be the pre-dose value at Day 1. If a patient has more than 1 observation on the same measurement occasion, the results from the earliest draw should be used in all summaries.

For qualitative safety variables, shift tables at each time point will be presented.

Laboratories values outside the reference range will be listed.

12.3 Determination of sample size

The sample size is not based on formal statistical tests. As a measure of study precision, with 34 Japanese patients per group, the expected width of the 2-sided 95% confidence interval of the difference between 90mg and 45mg dose groups in IPA is approximately ± 12%, assuming the SD for the final IPA of 25% based on DISPERSE.

In order to obtain PK and PD data in non-Japanese Asian patients and to make exploratory comparison between Japanese and non-Japanese Asian, 7 non-Japanese Asian patients per group will be included. Based on DISPERSE, the difference between the higher dose (90mg) and lower dose (45mg) in final IPA at 12 hours post-dose at Week 4 was predicted to be at least 12%. With 7 non-Japanese Asian patients per group, $P(D_{NJP}>0)$, where D_{NJP} is estimate of difference between 90mg and 45mg dose groups in IPA for non-Japanese Asian is more than 0.8. Therefore, 7 non-Japanese Asian patients per group is considered sufficient to obtain consistent result in terms of point estimates.

Assuming that there are approximately 10% premature discontinuations due to informed consent withdrawal and/or AE, 45 patients per group to be randomized in total.

12.4 Data safety monitoring board

In this study, a single joint DSMB will be established for this study and the clinical Phase III study (D5130C00027), 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.

In this study, the DSMB will review all cardiac ischaemic events and all AEs/SAEs (including stroke) under an unblind fashion at least every 3 months to determine the appropriateness of continuing the study.

In addition to the periodical review during this study, the DSMB will discuss whether a Phase III study can be initiated, based on the data from this study. Also, after the Phase III study is initiated, the DSMB will review the data from the Phase III study together with the data from this study, and perform a comprehensive safety assessment similar to the periodical review in

accordance with the time point defined for the Phase III study 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

In this study, a single joint CEC will be established for this study and the clinical Phase III study (D5130C00027), which are conducted separately.

The CEC is independent of AstraZeneca, study sites and DSMB, and the CEC is to independently review and interpret the bleeding events that are reported by the investigator as defined in Section 6.4.9.1. 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	Tel: Fax: Mobile:
	SDT Physician responsible for the protocol at central R&D site	Tel: Fax: Mobile:
(For Japan) 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 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 6.4.9.1, study medication should be discontinued.

13.1.2 Minor bleeding events

If a patient experiences a minor bleeding event as defined in Section 6.4.9.1, study medication may be continued, interrupted temporarily or discontinued permanently at the discretion of the investigator.

13.1.3 Treatment with Percutaneous coronary intervention

Subjects who have ischemic symptom during the study period might be considered invasive therapy such as PCI or CABG. And, Study medication should be terminated. Subjects should be treated appropriately according to the judgement by investigational doctor. Details of PCI procedures should be undertaken according to local clinical practice and established methods.

13.1.4 Uric acid management

AZD6140 90mg 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.

13.1.5 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 (> 3sec) 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.

13.1.6 Dyspnoea management

A dose dependent increase in dyspnoea was observed in patients exposed to AZD6140 in the 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, Body Mass Index, 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 (e.g chronic heart failure)
- Asthma
- Chronic Obstructive Pulmonary Disease
- Pulmonary Vascular Disease (pulmonary hypertension, pulmonary embolism)
- Parenchymal Lung Disease
- Infection (e.g pneumonia or bronchitis)
- Metabolic Disorder
- Anxiety Disorder
- Other known cause
- Unexplained

13.2 Overdose

An overdose is defined as any intake of study medication more than defined in the protocol.

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 eCRF module.

- An overdose without associated symptoms is only reported on the Overdose eCRF 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 AE 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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