Clinical Study Protocol

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An Open Label, Single Centre, Randomised, Phase IV, Pharmacokinetic, Pharmacodynamic, and Safety Study to Evaluate Single and Multiple Doses of 45, 60, and 90 mg of Ticagrelor in Chinese Patients with Stable Coronary Heart Disease

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

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

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PROTOCOL SYNOPSIS

An Open Label, Single Centre, Randomised, Phase IV, Pharmacokinetic, Pharmacodynamic, and Safety Study to Evaluate Single and Multiple Doses of 45, 60, and 90 mg of Ticagrelor in Chinese Patients with Stable Coronary Heart Disease

Principal Investigator

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Study centre(s) and number of patients planned

This study will be conducted at 1 study centre. Up to 36 patients (male and female) with stable coronary heart disease will be enrolled, with 12 patients will enter each of three treatment groups, to ensure at least 10 evaluable patients per treatment group.

Study period		**Phase of development**
Estimated date of first patient enrolled	Q1 2014	Phase IV
Estimated date of last patient completed	Q4 2014	

Objectives

Primary Objective

- To determine the Inhibition of Platelet Aggregation (IPA) profiles of single and multiple doses of ticagrelor 45, 60, and 90 mg in Chinese patients with stable coronary heart disease (CHD) on chronic low dose ASA (75-100mg daily).

Secondary objectives

- To determine the $P2Y_{12}$ Reaction Units (PRU) (VerifyNow) profiles of single and multiple doses of ticagrelor 45, 60, and 90 mg in Chinese patients with stable coronary heart disease on chronic low dose ASA.
- To determine the Pharmacokinetics of ticagrelor after single and multiple doses of 45, 60, and 90 mg in Chinese patients with stable coronary heart disease on chronic low dose ASA.

- To assess the safety of ticagrelor in Chinese patients with stable coronary heart disease on chronic low dose ASA.

Study design

This is an open label, single centre, randomised, Phase IV, pharmacokinetic, pharmacodynamic, and safety study to evaluate single and multiple doses of 45, 60, and 90 mg of ticagrelor in Chinese patients with stable coronary heart disease.

Patients will be recruited sequentially and randomized into one of following treatments:

Treatment A: A single dose of ticagrelor 45 mg on Day 1 followed by 45 mg twice daily (bid) on Days 3-6 and a 45mg single dose on Day 7.

Treatment B: A single dose of ticagrelor 60 mg on Day 1 followed by 60 mg twice daily (bid) on Days 3-6 and a 60mg single dose on Day 7.

Treatment C: A single dose of ticagrelor 90 mg on Day 1 followed by 90 mg twice daily (bid) on Days 3-6 and a 90mg single dose on Day 7.

Up to 36 patients will be randomized in order to ensure 10 patients per treatment are evaluable.

Target patient population

Male and female patients aged 18 years or older, with documented stable coronary heart disease.

Investigational product, dosage and mode of administration

Ticagrelor will be supplied as 45 mg, 60mg, and 90mg tablets.

Following an 8-hour fast on single dose Day 1 and Day 7, patients will be administered the tablets and must swallow them with 240 mL of water; On multiple doses Day 3-6, the patients will take ticagrelor tablets bid at least one hour before food.

Study treatment will be administered under the supervision of investigator site personnel.

The oral cavity of each patient will be examined following dosing to assure the study medication was taken.

Duration of treatment

Prior to the first dose of study drug there will be a screening period of maximum 19 days. Patients will report to the clinical pharmacology unit (CPU) on Day -2 and will remain confined there until completion of study procedures on Day 7, the patients will be discharged on Day 8. In addition, patients will return to the CPU for a follow up visit 2-5 days after the last dose. Each patient's participation, including the screening period, will take approximately 33 days.

Outcome variable(s):

Primary outcome variables:

- **Pharmacodynamic**
  - IPA (final extent) induced by 20μM adenosine diphosphate (ADP) at each assessment point after single and multiple doses of ticagrelor measured by Light-Transmittance Aggregometer (LTA)

Secondary outcome variables:

- **Pharmacodynamic:**
  - The time to peak IPA ($TIPA_{max}$) and the area-under-the-effect curve (AUEC) will be estimated for ADP-induced final extent IPA.
  - Inhibition of the $P2Y_{12}$ receptor at each assessment point after single and multiple doses of ticagrelor as measured by PRU from VerifyNow™ in stable coronary heart disease (CHD) patients.
  - Percent reduction in platelet $P2Y_{12}$ receptor at each assessment point activity measured by VerifyNow™ on $P2Y_{12}$ reaction units (PRU), represented as percentage change from baseline (pre-treatment) after single and multiple doses of ticagrelor.
- **Pharmacokinetic**
  - Day 1:

    C_{max}, t_{max}, $AUC_{(0\text{-}12h)}$, $AUC_{0\text{-}t}$ AUC, and $t_{½}$ of ticagrelor and AR-C124910XX, metabolite: parent C_{max} and AUC ratios
  - Day 7:

C_{max}, t_{max}, and $AUC_{(0\text{-}12h)}$ of ticagrelor, AR-C124910XX, metabolite: parent C_{max} and AUC ratios and accumulation ratio (AR) for ticagrelor and AR-C124910XX.

- **Safety**
  - Safety will be assessed by physical examination, clinical laboratory tests, vital signs, and adverse events.

Statistical methods

IPA(%), absolute PRU and percent reduction of PRU from baseline will be presented descriptively and plotted by treatment group and time point. The time to peak IPA ($TIPA_{max}$) and the area-under-the-effect curve (AUEC) will be presented descriptively by treatment group and study Day 1 and 7.

Plasma concentrations of ticagrelor and AR-C214910XX will be summarized by treatment group and time point. PK parameters will be summarized by treatment group and study Day 1 and 7.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ADME	Absorption/Distribution/Metabolism/Excretion
ACS	Acute Coronary Syndromes
ADP	Adenosine diphosphate
AE	Adverse event (see definition in Section 6.3.1)
ALP	Alkaline phophatase
ALT	Alanine aminotransferase
ASA	Aspirin
AST	Aspartate aminotransferase
AR	Accumulation ratio
ASA	Acetylsalicylic acid
AUC	Area under plasma concentration-time curve from zero to infinity
$AUC_{(0-12)}$	Area under plasma concentration-time curve from zero to 12 hours
AUC_{τ}	Area under plasma concentration-time curve during a dosing interval
AUEC	Area-under-the-effect curve
AUMC	Area under the first moment-time curve
BD/bid	Twice daily
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C_{max}	Maximum plasma (peak) drug concentration after single dose administration
CABG	Coronary Artery Bypass Graft
CHD	Coronary heart disease
CL	Total body clearance of drug from plasma
CPU	Clinical Pharmacology Unit
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CYP	Cytochrome P450

Abbreviation or special term	**Explanation**
DAE	Discontinuation of Investigational Product due to Adverse Event
DBP	Diastolic Blood Pressure
DNA	Deoxyribonucleic acid
DUS	Disease under Study
ECG	Electrocardiogram
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
ICH	International Conference on Harmonisation
ICF	Informed consent form
IP	Investigational Product
IPA	Inhibition of platelet aggregation
IRB	Investigational Review Board
LIMS	Laboratory Information Management System
LLOQ	Lower Limit of Quantification
LSLV	Last Subject Last Visit
LTA	Light-Transmittance Aggregometer
MI	Myocardial Infarction
MTD	Maximum tolerated dose
NDA	New Drug Application
NSAID	Non-steroidal anti-inflammatory drug
NSTEMI	Non ST segment elevation myocardial infarction
OAE	Other Significant Adverse Event (see definition in Section 11.1.1)
OD	Once Daily
PCI	Percutaneous coronary intervention

Abbreviation or special term	**Explanation**
PD	Pharmacodynamics
PE	Physical Examination
PI	Principal Investigator
PK/PD	Pharmacokinetic/pharmacodynamic
PLATO	A study of PLATelet inhibition and Patient Outcomes
PRBCs	Packed red blood cells
PRU	$P2Y_{12}$ Reaction Units
QD	Once daily
SAE	Serious adverse event (see definition in Section 6.3.2).
SBP	Systolic Blood Pressure
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reactions
STEMI	ST segment elevation myocardial infarction
UA	Unstable angina
ULN	Upper limit of normal
γ	Shape factor in concentration-response relationship
$TIPA_{max}$	Time to peak IPA
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

Ticagrelor is an oral, reversible ADP receptor antagonist acting via the $P2Y_{12}$ receptor, which has been developed for the prevention of thrombotic events in patients with Acute Coronary Syndromes (ACS). Ticagrelor has been approved in many countries. However, the database of the New Drug Application (NDA) for ticagrelor was limited in the inclusion of various ethnic groups. A well controlled pharmacodynamic study in Chinese patients with stable coronary heart disease has not been conducted. This study explores the platelet inhibiting effects of ticagrelor in Chinese patients with stable coronary heart disease, specifically looking at Day 1 and Day 7 platelet inhibiting effects.

1.1 Background

Atherothrombotic disorders of the coronary, cerebrovascular and peripheral arterial circulation are the leading cause of death and disability in the developed world. The increasing prevalence and significant under-treatment of this disorder underscore the need for better methods of prevention.

The central role of platelets in the pathogenesis of arterial thrombosis has been demonstrated. Platelet activation and aggregation, via the expression of surface adhesion glycoproteins, are currently considered essential components for the development of thrombi, leading to the evolution of ischemic thrombotic complications in susceptible individuals. Platelet inhibitors have been proven as effective agents for the treatment of both chronic and acute diseases of the arterial vessel wall. Low dose acetylsalicylic acid (ASA) reduces ischemic outcomes in patients but often is insufficient to prevent ischemic events in high-risk patients. While ASA inhibits the cyclo-oxygenase pathway, it has no known effect on the adenosine diphosphate $P2Y_{12}$ platelet receptor. Adenosine diphosphate (ADP) is one of the primary mediators of platelet activation and aggregation. Inhibition of ADP-mediated platelet activation and aggregation by ticlopidine and clopidogrel has been shown to provide improved efficacy for treatment of thrombotic ischemic events, compared to ASA therapy alone, while demonstrating a favorable bleeding profile (Jneid H et al 2003).

However, both ticlopidine and clopidogrel have a slow onset of action at the platelet ADP receptor, and their pharmacologic inhibition of platelet aggregation has been reported as irreversible and incomplete. Approximately 15% to 30% of patients treated with clopidogrel were reported as non-responders to clopidogrel therapy (Gurbel PA et al 2003, Järemo et al 2002, Muller et al 2003). Nonresponders have a higher rate of ischemic events during clopidogrel treatment (Aleil B et al 2005, Barragan P et al 2003, Matetzky S et al 2004, Price MJ et al 2006). In addition, the slow offset of clopidogrel's effect is problematic in the current strategy of administering clopidogrel therapy before percutaneous coronary intervention (PCI) in patients with undefined, diseased coronary anatomy, as these patients have an increased risk of bleeding if administered clopidogrel within 5-7 days of undergoing coronary artery bypass graft surgery (Hongo RH et al 2002). Therefore, the development of new ADP receptor antagonists with improved efficacy and/or safety profiles is desirable.

Ticagrelor is orally active and does not require metabolic activation. Ticagrelor binds to plasma proteins (>99.7%), is extensively metabolised by cytochrome P450 3A (CYP3A), the elimination half-life ($t_{1/2}$) of the parent compound is approximately 7 hours and the primary metabolite, AR-C124910XX, is considered equipotent to the parent drug *in vitro*. Additional information on ticagrelor is available in the investigator's brochure.

Ticagrelor is approved with low doses of ASA (75-100 mg daily). Therefore, the current study will limit the dose of ASA to 75 to 100mg daily.

1.2 Rationale for conducting this study

Previous exposure of ticagrelor in China includes healthy patients (D5130C00054) and ACS patients (D5130C05262), but not stable coronary heart disease. This study will examine three doses of ticagrelor (45, 60, and 90 mg) in single and multiple doses in the stable coronary heart disease (CHD) population.

1.3 Benefit/risk and ethical assessment

The Investigator's Brochure for ticagrelor 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, non-clinical and clinical findings with ticagrelor.

Though there may not be direct benefit to patients participating in this study, the data generated, e.g., drug effect on platelet reactivity, will improve the understanding of this effect in the Chinese population.

Ticagrelor, like other inhibitors of platelet-aggregation, increases the risk of bleeding. Up to 30% of patients with ACS exposed to Ticagrelor have been reported to have at least 1 bleeding event, usually mild to moderate in intensity and non-fatal. In the PLATO study, life threatening bleeding in ACS patients occurred in 5.8% of ticagrelor treated patients and 5.8% of clopidogrel treated patients.

Dyspnea is a dose-dependent adverse event in up to about 15% of ticagrelor-treated patients, characterized by a feeling of shortness of breath that is mostly mild to moderate in intensity and is usually observed at the initiation of treatment. In the PLATO study, dyspnea was observed in 13.8% of ticagrelor treated patients and 7.8% of clopidogrel treated patients.

Up to 30% of patients may have an abnormal serum uric acid value during treatment with ticagrelor. Gout or hyperuricemia has been reported in up to 1% of ticagrelor-treated patients. However, in the PLATO trial, the incidence of gout did not differ between ticagrelor (2.9%) and clopidogrel (2.8%).

Cardiac arrhythmias, predominantly supraventricular but also ventricular arrhythmias occurred more frequently in ticagrelor-treated patients with ACS (up to 5%). Ventricular

pauses detected via Holter monitoring in the acute phase of ACS occurred in 6% of ticagrelor-treated patients and 3.5% of clopidogrel treatment patients (PLATO).

Increase in serum creatinine levels was observed in 7.4% of ticagrelor-treated patients compared with 5.9% of clopidogrel treated patients.

Mild to moderate diarrhea, nausea, vomiting, abdominal pain, dyspepsia, and constipation occurred in 5-10% of ticagrelor-treated patients. Hypotension, insomnia, anxiety, dizziness, headache, and pyrexia have occurred in up to 10% of ticagrelor-treated patients. These have been non-serious, mostly mild AEs. Complete information for ticagrelor may be found in the Single Reference Safety Document which, for this study, is the Investigator's Brochure.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective is to determine the Inhibition of platelet aggregation (IPA) profiles of single and multiple doses of ticagrelor 45, 60, and 90 mg in Chinese patients with stable coronary heart disease on chronic low dose ASA (75-100mg daily).

2.2 Secondary objectives

The secondary objectives of this study are to:

- To determine the $P2Y_{12}$ Reaction Units (PRU)(measured by VerifyNow) profiles of single and multiple doses of ticagrelor 45, 60, and 90 mg in Chinese patients with stable coronary heart disease on chronic low dose ASA.
- To determine the PK of ticagrelor after single and multiple doses of 45, 60, and 90 mg in Chinese patients with stable coronary heart disease on chronic low dose ASA.
- To assess the safety of ticagrelor in Chinese patients with stable coronary heart disease on chronic low dose ASA.

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 an open label, single centre, randomised, Phase IV, pharmacokinetic, pharmacodynamic, and safety study to evaluate single and multiple doses of 45, 60, and 90 mg of ticagrelor in Chinese patients with stable coronary heart disease.

The timing of study assessments is outlined in the Study Plan (Table 1). Patients will undergo screening assessments during the maximum 19-day period preceding administration of the first dose of study drug on Day 1. Patients will report to the CPU on Day -2 and will remain confined there until Day 8 for the fully completion of study procedures of Day 7. In addition, patients will return to the CPU for a follow up visit 2-5 days after the last dose. Each patient will participate in the study for approximately 33 days.

Approximately 36 patients with stable coronary heart disease will enter this study, with 12 patients randomly enter into each of three treatment groups (Treatment A, Treatment B and Treatment C). Patients will receive ticagrelor as a single dose on Day 1, followed by a bid dose for 4 days (Day 3 to Day 6), and a single dose on Day 7. On Day 2, no treatment will be given, but blood samples will be obtained.

Treatment A: A single dose of ticagrelor 45 mg on Day 1 followed by 45 mg twice daily (bid) on Days 3-6 and a 45mg single dose on Day 7.

Treatment B: A single dose of ticagrelor 60 mg on Day 1 followed by 60 mg twice daily (bid) on Days 3-6 and a 60mg single dose on Day 7.

Treatment C: A single dose of ticagrelor 90 mg on Day 1 followed by 90 mg twice daily (bid) on Days 3-6 and a 90mg single dose on Day 7.

Safety assessments including physical examinations, laboratory assessments, AE and vital sign measurements will be performed according to the schedule in the Study Plan (Table 1). PK and PD blood samples will be obtained at the times noted in the Blood Sampling schedule (Table 2).

All treatment will be administered in an open-label design. To be included in the study the patients must stay on ASA, 75-100mg, which will be maintained at a constant dose throughout the study period.

Figure 1 Study Flow Chart

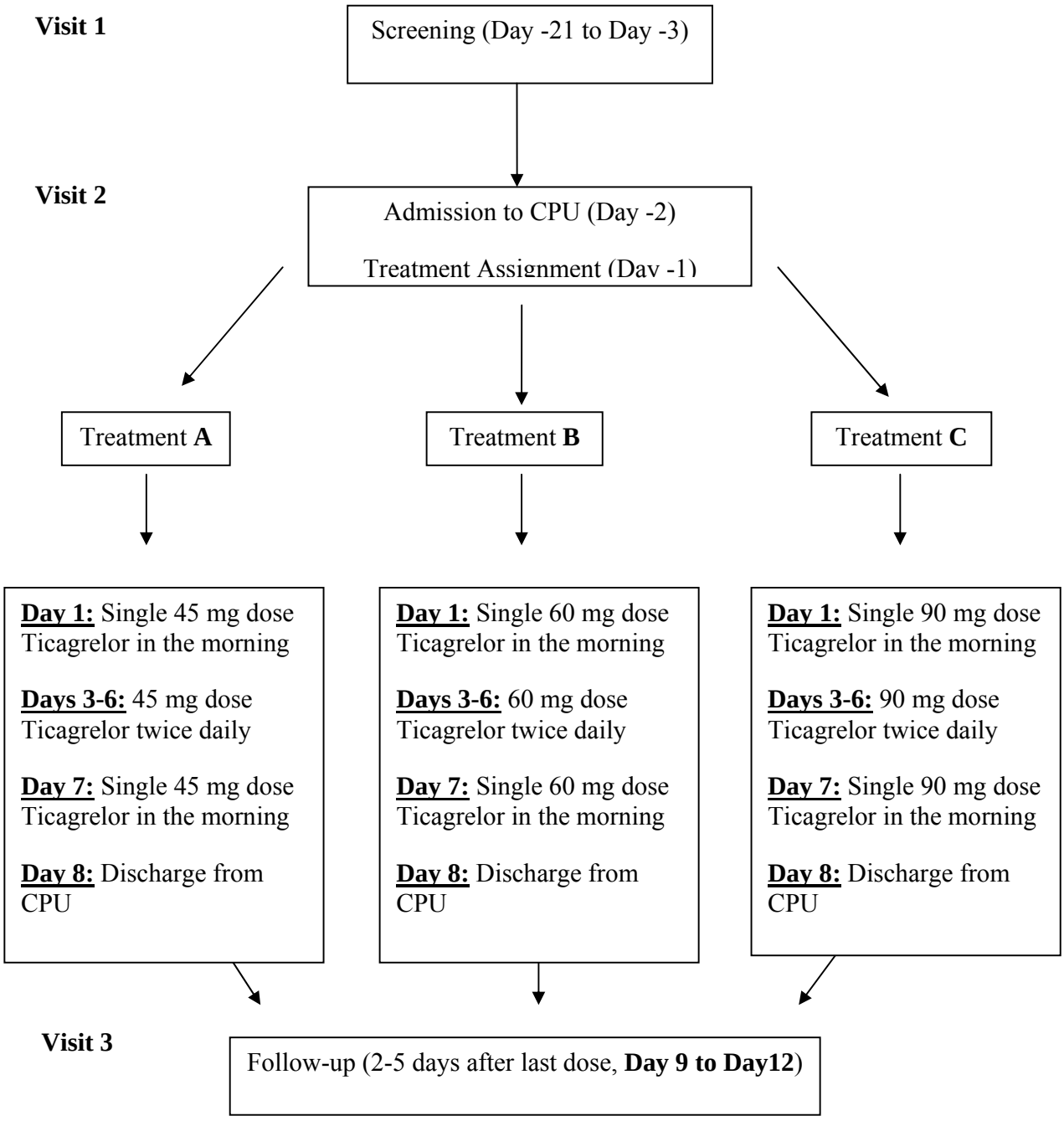

Table 1 Study Plan

Assessment/ Activity		Visit 1	Visit 2									Visit 3
		Screening			Study Day							Follow Up
		Day –21 to -3	-2	-1	1	2	3	4	5	6	7	8	2-5 days after Last Dose[11]
Informed Consent		X[1]											
Inclusion/Exclusion Criteria		X		X									
Admission to CPU			X										
Relevant Medical and Surgical History		X		X									
Demographics		X											
Vital Signs (BP, pulse)		X		X	X	X	X	X	X	X	X		X
Physical Examination[2]		X		X									X
Weight and Height		X											
Urine Drugs of Abuse Screenings [3]		X		X									
Alcohol Breath Test		X		X									
Safety Laboratory	Hematology	X[4]		X[4]									X
	Blood Chemistry												
	Urinalysis												

Assessment/ Activity	Visit 1	Visit 2									Visit 3
	Screening			Study Day							Follow Up
	Day –21 to -3	-2	-1	1	2	3	4	5	6	7	8	2-5 days after Last Dose[11]
Serology Test (Hepatitis B surface antigen; Anti HCV IgG; HIV)	X											
Coagulation test (PT, TT, aPTT)			X									
12-Lead ECG	X											
Ultrasonic cardiogram			X									
24h Holter[5]		←	→									
Pregnancy test[6]	X		X									
FSH[7] (Females)	X											
Randomization			X									
Blood Sample for IPA and $P2Y_{12}$ assessment[8]				X	X	X				X		
Blood Sample for PK[8]				X	X	X				X		
Administration of Investigational product (IP)[9]				X		X	X	X	X	X		
Compliance/Drug Accountability				X		X	X	X	X	X		
Adverse Event Monitoring	X[10]	X[10]	X[10]	←	—	—	—	—	—	—	→	
Concomitant Medication		←	—	—	—	—	—	—	—	—	—	→

Assessment/ Activity	Visit 1	Visit 2										Visit 3
	Screening			Study Day								Follow Up
	Day –21 to -3	-2	-1	1	2	3	4	5	6	7	8	2-5 days after Last Dose[11]
Discharge from CPU											X	

AE: adverse event; BP: blood pressure; ECG: electrocardiogram; IP: investigational product; IPA: inhibition of platelet aggregation; PRU: platelet reaction units; CPU: Clinical Pharmacology Unit; SAE: serious adverse event; PT: prothrombin time; TT: thrombin time; aPTT: activated partial thromboplastin time.

1. Informed Consent must be completed before any study related procedures are performed.
2. For scheduled physical examinations (PE): a full PE including weight and height should be performed either at Screening and the end of the study. Frequency can be increased if clinically indicated. Full exam at Screening may be performed on Day -1 at the discretion of the PI.
3. Urine will be tested for following drugs of abuse at screening and admission: amphetamines, barbiturates, tricyclic antidepressants, cocaine, methadone, 3,4-Methylenedioxymethamphetamine (MDMA [ecstasy]), benzodiazapines, morphine, phencyclidine, tetrahydrocannabinol, and opiates. If the Screening urine drug test is performed on Day -3, it is at the discretion of the PI if it needs to be repeated on Day -1.
4. The test may not need to be repeated on Day -1 if the tests are performed on Day -3.
5. 24h Holter will be performed on Day -2 and last for 24 hours till Day -1.
6. For females of childbearing potential: a urine β-HCG pregnancy test must be performed at the screening visit and Day-1. Since urine tests may miss a pregnancy in the first days after conception, relevant sexual history, including methods of contraception, should be considered. Any patient whose sexual history suggests the possibility of early pregnancy should be excluded.
7. Female patients who reported post-menopause, but have not had a hysterectomy, bilateral oophorectomy or bilateral salpingectomy will be required to have serum testing at Screening.
8. See Table 2
9. A single dose will be given on Day 1 in the morning, and bid will be given on Days 3 to 6, and another single dose will be given on Day 7, which is administered on the same time as Day 1.
10. Only SAE which occur after informed consent but prior to dosing will be reported during this time period.
11. Visit 3 will be Day 9 through Day 12 (2 to 5 days after last dose)

Table 2 Blood Sampling

Assessment	Day 1	Day2	Day3	Day 7
Samples for PK	0, 0.5, 1, 2, 3, 6, and 12 h	24 and 36 h	48 h	0, 0.5, 1, 2, 3, 6, 12 h
Samples for IPA and $P2Y_{12}$ measured by VerifyNow	0, 0.5, 1, 2, 3, 6, and 12 h	24 and 36 h	48 h	0, 0.5, 1, 2, 3, 6, 12 h

3.2 Rationale for study design, doses and control groups

The primary objective is to determine the IPA profiles of single and multiple doses of ticagrelor 45, 60, and 90 mg in Chinese patients with stable coronary heart disease on chronic low dose ASA. The primary variable is IPA, final extent (20μM ADP). Previous exposure of ticagrelor in China includes healthy patients (D5130C00054) and ACS patients (D5130C05262), but not stable coronary heart disease. This study will explore three doses of ticagrelor in order to determine the IPA, PRU and pharmacokinetic profile in Chinese patients with stable coronary heart disease. The VerifyNow System is a commercially available system to measure inhibition of $P2Y_{12}$ receptor and is considered appropriate for this study. Holter monitoring and an echocardiogram will be obtained prior to dosing in order to rule out those at risk for bradyarrhytmias and potential indications for anticoagulation. See Section 4.2

This is an open label, single centre, randomised, Phase IV, pharmacodynamic, pharmacokinetic, and safety study. There is no control group.

Treatment for 4 days with bid dosing of the study allows ticagrelor to reach steady-state, and hence allows Day 7 results to be compared with the Day 1 dose of each drug dose level.

Ticagrelor dosing regimen

The approved loading dose of ticagrelor is 180 mg followed by 90 mg bid in patients with ACS. There is no approved dose for chronic coronary heart disease. Therefore, this study will examine 45, 60 and 90 mg doses of ticagrelor in order to determine the IPA and PK profile in Chinese patients with stable coronary heart disease.

Background Therapy

Ticagrelor will be administered against a background of ASA therapy, since ASA is standard therapy for the prevention of thrombotic events and new therapies will be adjunctive in this patient population (Matetzky S et al 2004, Hongo RH et al 2002, Aleil B et al 2005, Barragan P et al 2003). A once daily ASA dose of 75 mg to 100 mg is being used as that is the dose that has been approved for chronic therapy with ticagrelor. The ASA dose of 75 to 100 mg has been recommended since previous clinical studies (Chen ZM 2005, Peters RJG et al 2003, Price MJ et al 2006, Sabatine MS et al 2005) have indicated this as a suitable daily dose range for ASA in combination therapy to protect against thrombotic events. Each patient's ASA dose should remain constant throughout the study. As ticagrelor has not been approved with doses of ASA above 100mg, doses greater than 100mg will not be studied. Patient requiring greater than 100mg ASA will not be enrolled in the study.

4. PATIENT SELECTION CRITERIA

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

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

4.1 Inclusion criteria

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

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

2. Female or male Chinese (as defined by Chinese Regulatory) patients aged 18 years or older with suitable veins for cannulations or repeated venipunctures.

3. Documented stable coronary heart disease (CHD) fulfilling all of the following, and taking 75-100 mg ASA daily treatment:

   Diagnosed stable angina pectoris per the guidance of Chinese Society of Cardiology published in 2007, patients with angina severity classified as I and II of Canadian Cardiovascular Society grading of angina pectoris.

4. Female patients must meet one of the following conditions:

   - Post-menopausal defined as amenorrhoea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle-stimulating hormone (FSH) levels in the laboratory defined post-menopausal range.

   - Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.

   - Women of childbearing potential must have a negative urine pregnancy test

4.2 Exclusion criteria

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

1. Any indication for oral anticoagulant (eg, atrial fibrillation, mitral stenosis or prosthetic heart valve) or dual antiplatelet treatment (eg, clopidogrel, prasugrel, or ASA). Also, chronic ASA with doses greater than 100 mg/day.

2. Concomitant therapy with strong CYP3A inhibitors, CYP3A substrates with narrow therapeutic index, or strong CYP3A inducers within 14 days preceding the first dose of study medication and during study treatment:

   - Strong inhibitors: ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir.

- Substrates with narrow therapeutic index: cyclosporine, quinidine
- Strong inducers: rifampin/rifampicin, phenytoin, carbamazepine
- Doses of lovastatin or simvastatin >40mg/day.

3. Increased bleeding risk including:

   - Recent (within 30 days preceding the first dose of study medication) GI bleeding
   - Any history of intracranial, intraocular, retroperitoneal, or spinal bleeding
   - Recent (within 30 days of first dosing) major trauma
   - Sustained uncontrolled hypertension (systolic blood pressure [SBP] >180 mmHg or diastolic blood pressure [DBP] >100 mmHg)
   - History of hemorrhagic disorders that can increase the risk of bleeding, eg, haemophilia, von Willebrand's disease
   - Inability to discontinue required concomitant therapy with non-steroidal anti-inflammatory drug (NSAID) at screening. (Washout of NSAID, if currently taking, for at least 7 days or 5 half lives of the medication, whichever is longer)
   - Patients that have used within 30 days of screening, any oral or parenteral anticoagulant, including low molecular weight heparin.
   - Platelet count less than 100,000 mm^3 or hemoglobin <10 g/dL

4. Contraindication or other reason that ASA or ticagrelor should not be administered (eg, hypersensitivity, active bleeding, major surgery within 30 days of dosing, any bleeding tendency [coagulation defects], acute or chronic liver disease etc)
5. History of drug addiction or alcohol abuse in the previous 1 year
6. Positive screen for urine drugs of abuse
7. Positive screen for alcohol abuse (by alcohol breath test)
8. Current smokers, however, if <5 cigarettes per week, then not defined as smoker, and allow in study
9. Patient requires dialysis

10. Participation in another investigational drug or device study within 30 days prior to first dosing

11. Blood donation within 30 days of first dosing or any blood/plasma loss >500 mL during the 3 months prior to enrolment

12. Patients that are scheduled for revascularization (eg, PCI, CABG) during the study period

13. Any acute or chronic unstable condition in the past 30 days or other condition which, in the opinion of the investigator, may either put the patient at risk or influence the result of the study (eg, active cancer, risk for non-compliance, risk for being lost to follow-up)

14. History of moderate or severe hepatic impairment

15. Patients who in the opinion of the investigator would be at risk for bradycardia or have a HR≤50.

16. Involvement in the planning and conduct of the study (applies to AstraZeneca or delegate staff, and study site staff

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

18. Patients who had ACS or stent placed within 12 months of screening

19. A suspected/manifest infection according to the World Health Organization (WHO) risk categories 2, 3, and 4

20. Currently taking ticlopidine or cilostazol

21. History of intolerance or allergy to ASA, clopidogrel, prasugrel, ticagrelor

22. Clinically significant deviation in physical findings or laboratory values as judged by the investigator.

23. Positive Serology (Hepatitis B surface antigen, Hepatitis C IgG, HIV Ab)

24. Concern for the inability of the patient to comply with study procedures and/or follow-up.

Procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

1. Fast (except for water) for at least 8 hours before dosing for the morning dose on Day 1 and Day 7, and remain fasting until 2 h post-dose. Water is allowed until 1 h before, and from 1 h after dosing. Water (240 mL) needed for drug administration is allowed.

2. Eat and drink only the standardised meals and drinks provided (apart from water) during the residential period in the unit.

3. Abstain from consuming any of the following:

   – Alcohol from 72 h prior to enrolment visit, during the residential period and until the follow-up visit

   – Grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade or other products containing grapefruit or Seville oranges and grapefruit from 7 days prior to initiation of investigational product (IP) until end of the treatment period

   – Refrain from taking any new medication (including traditional Chinese medication) during the 2 weeks prior to the first administration of IP until the follow-up visit, unless the investigator has given prior consent.

   – Abstain from blood or plasma donation until 3 months after the last dose of IP

   – Refrain from drugs of abuse from time of consent until after the final medical examination at the study follow-up

4. Stay at the study unit from Day -2 until 12 to 24 hours after Day 7 dosing of Visit 2. The stay might also be prolonged for safety reasons, if judged necessary by the investigator.

5. Patients of child bearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception throughout their participation in the study and for three months after last dose of study drug(s), including:

   - Condom with spermicide

   And one of the following:

   - Oral contraceptive or hormonal therapy (e.g. hormone implants)

- Placement of an intra-uterine device

Appendix E provides details of acceptable birth control methods to be used within the study.

5.2 Patient enrolment and randomisation

The Investigator will:

- Obtain signed informed consent from the potential patients before any study-specific procedure is performed.
- Assign potential patient a unique enrolment number, beginning with 'E0001001'.
- Determine patient eligibility. See Sections 4.1 and 4.2.
- Assign eligible patient a unique patient number, beginning with '1001'.

Patients will be randomized into the study provided they have satisfied all patient selection criteria.

If patients have withdrawn their participation in the study after dosing they cannot re-enter into the study.

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

5.2.1 Procedures for randomisation

A randomization list will be produced by using the global randomization system (GRand). Patients will be allocated to one of the three different dose level treatments. The randomization will be done using consecutive randomization codes (patient numbers).

Randomisation codes will be assigned strictly sequentially as patients become eligible for randomisation.

5.3 Procedures for handling patients incorrectly enrolled or randomized

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

Where a patient, who does not meet the selection criteria, is randomized in error and this is identified before dosing, the patient should be withdrawn from the study. A discussion should occur between the AstraZeneca Study Team Physician and the investigator regarding whether a replacement may be considered.

Where a patient, who does not meet the selection criteria, is randomized in error and started on treatment, or where a patient subsequently fails to meet the study criteria post initiation, a discussion should occur between the AstraZeneca Study Team Physician and the investigator regarding whether to continue or discontinue the patient from treatment. If treatment is discontinued the patient should be advised to continue assessments to ensure their safety. In situations where an agreement cannot be reached, the patient should have their study treatment discontinued.

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

5.4 Blinding and procedures for unblinding the study

This is an open-label study.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Table 3 Identity of Investigational Product(s)

Investigational Product	Dosage Form and Strength	Manufacturer
Ticagrelor	Tablet 45 mg	AstraZeneca
Ticagrelor	Tablet 60 mg	AstraZeneca
Ticagrelor	Tablet 90 mg	AstraZeneca

Ticagrelor will be supplied in one bottle containing 14 tablets for each patient.

Ticagrelor tablets will be manufactured and packaged as open-label, patient specific supplies for oral use. The supplies will be labelled in accordance with Good Manufacturing Practice (GMP) and local regulatory requirements.

5.5.2 Doses and treatment regimens

Each patient will receive the following treatments during the treatment visit (Visit 2):

Day 1: ticagrelor (single dose)

Day 3-6: ticagrelor (twice daily/bid)

Day 7: ticagrelor (single dose)

On the morning of Day 1, the patients will receive a single 45mg or 60mg or 90 mg dose of ticagrelor (as assigned) under fasting conditions, i.e., patients will fast overnight for at least 8 hours prior to dosing, with water permitted freely except for one hour prior to and following dosing; the patients will take ticagrelor tablets bid on Day 3-6 at least one hour before food. On Day 7, patients will fast overnight for at least 8 hours prior to dosing with water permitted freely except for one hour prior to and following dosing. Patients will receive a single 45 mg or 60 mg dose or 90 mg of ticagrelor in the morning only.

The oral tablet dose will be administered with 240 mL of room temperature water while the patient is sitting in an upright or in a semi-recumbent position. The tablets must not be crushed, chewed, or divided. Meals will be provided on a fixed schedule at the CPU's discretion.

Any patient that vomits within 2 hours after dosing in single dosing days will be considered non-evaluable for PK analysis.

5.5.3 Labelling

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

5.5.4 Storage

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

5.6 Concomitant and post-study treatment(s)

Patients are not allowed to take the following medication during the study:

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

2. Chronic oral anticoagulant therapy or chronic low-molecular-weight heparin.

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

   - Strong inhibitors: ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin (but not erythromycin or azithromycin), nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atanazavir.

   - Substrates with narrow therapeutic index: cyclosporine, quinidine.

– Simvastatin or lovastatin at doses >40 mg daily.

– Strong inducers: rifampin/rifampicin, rifabutin, phenytoin, carbamazepine, Phenobarbital.

Patients are permitted to take non-NSAID analgesics, including acetaminophen / paracetamol up to 4 g/day as needed for pain relief. ASA for pain relief is prohibited.

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the Case Report Form. Patients should continue with their prior medications post-study.

5.7 Treatment compliance

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

Treatment compliance will be assured by supervised administration of the IP by the investigator or delegate. The oral cavity of each patient will be examined following dosing to assure the study medication was taken.

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 patient.

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 and destruction should be signed.

5.8 Discontinuation of investigational product

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

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Safety reasons as judged by the investigator and/or AstraZeneca.
- Severe non-compliance to study protocol as judged by the investigator and/or AstraZeneca

- Incorrect enrolment (ie, the patient does not meet the required inclusion or exclusion criteria) or if the patient is not allocated study drug as described in the protocol.

5.8.1 Procedures for discontinuation of a patient from investigational product

A patient that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (See Sections 6.3.3 and 6.3.4); and all study drugs should be returned by the patient.

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

5.9 Withdrawal from study

Patients are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (See Sections 6.3.3 and 6.3.4); and all study drugs should be returned by the patient.

Patients who are withdrawn from the study by the investigator due to AEs after dosing will not be replaced. Patients who withdraw for any reason before dosing or for reasons other than AEs after dosing may be replaced following a discussion between the investigator and AstraZeneca.

6. COLLECTION OF STUDY VARIABLES

The study assessments are described in the sections below and the timing of assessments are detailed in the Study Plan (Table 1).

For the study period described below, when multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, where possible.

- ECG recordings
- Vital signs: obtain as close as possible to scheduled time, but prior to blood specimen collection.
- Pharmacodynamic blood specimens: obtain at scheduled time.
- Pharmacokinetic blood specimens.
- Blood sampling for safety laboratory assessments

- Other procedures: obtain all other procedures as close as possible to the scheduled time, but may be obtained before or after blood specimen collection

The actual time for all assessments will be recorded in the eCRF.

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 *electronic* Case Report Forms (eCRF) as specified in the study protocol and in accordance with the instructions provided.

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

6.2 Data collection during the study

6.2.1 Screening procedures (D -21 to D -3)

Each patient will undergo the screening procedures during Visit 1, prior to randomization. Data will be collected for the following procedures performed in the eCRF:

- Obtain written Informed Consent before performing any study related activities.
- Review of inclusion/exclusion criteria
- Review of medical and surgical history, including determination of medication history (including current medications)
- Physical examination
- Weight and Height
- Demographics (including sex, date of birth, race)
- Vital signs (seated blood pressure [BP], pulse)
- 12-lead ECG
- Urine drugs of abuse screening
- Alcohol abuse screening (by alcohol breath test)
- Haematology and Clinical Chemistry
- Serology (Hepatitis B surface antigen, Hepatitis C IgG, HIV Ab)

- Urinalysis
- Pregnancy test (For Female patients of childbearing potential)
- FSH (For Female patients of non childbearing potential who have not had a hysterctomy or bilateral oophorectomy will be required to have serum FSH testing at Screening)
- Serious adverse events must be captured from time of consent

The Principal investigator/sub-investigator should adhere to the study plan (Section Table 1), procedures and perform tests/observations in accordance with the protocol.

6.2.2 Baseline procedures (D -2 and D -1)

Data will be collected on baseline for the following procedures and entered in the eCRF:

D -2

- 24h Holter
- Serious adverse events must be captured

D -1

- Review of inclusion/exclusion criteria
- Review of medical and surgical history, including determination of medication history (including current medications)
- Physical examination
- Vital signs (seated blood pressure [BP], pulse)
- Urine drugs of abuse screening
- Alcohol abuse screening (by alcohol breath test)
- Haematology and Clinical Chemistry
- Urinalysis
- Coagulation test
- Ultrasonic cardiogram
- Pregnancy test (For Female patients of childbearing potential)

- Randomization
- Serious adverse events must be captured

6.2.3 Follow-up procedures (2-5 days after last dose of study medication)

Each patient will have follow-up procedures performed during Visit 3, at the completion of the treatment period. Data will be collected for the following procedures performed in the eCRF:

- Vital signs (seated blood pressure [BP], pulse)
- Physical examination
- Haematology, Clinical Chemistry, and Urinalysis
- Assessment of adverse events and concomitant medications

6.3 Safety

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

6.3.1 Definition of adverse events

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

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

6.3.2 Definitions of serious adverse event

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

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

- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

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

6.3.3 Recording of adverse events

Time period for collection of adverse events

Adverse events will be collected from administration of the first dose of IP throughout the treatment periods and including the follow-up visit (Visit 3).

SAEs will be recorded from the time of informed consent up to and including the follow-up visit.

Follow-up of unresolved adverse events

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

Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date and time when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- AE caused patient's withdrawal from study *(*yes or no*)*
- Outcome

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE
- The following intensity ratings will be used:
    - 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 6.3.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Causality collection

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

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

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

Adverse Events based on signs and symptoms

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

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs 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).

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

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

NB. Cases where a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, please refer to Appendix D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

6.3.4 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 CRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

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

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** 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.

6.3.5 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 (Table 1).

The following laboratory variables will be measured:

Table 4 Laboratory Assessment

Clinical chemistry (Serum)	**Haematology (Whole Blood)**
Creatinine	Haemoglobin
Alkaline phosphatase	Haematocrit
Aspartate aminotransferase (AST)	Platelet Count
Alanine aminotransferase (ALT)	White blood cells
Total Bilirubin	Erythrocytes (RBCs)
Blood Urea Nitrogen (BUN)	
Glucose	**Urinalysis**
Total Protein	Glucose
Albumin	Haemoglobin
Sodium	Protein
Potassium	**Urine pregnancy test**[b]
Bicarbonate	Human chorionic gonadotropin
Phosphate	
Chloride	**Urine drug screen**
FSH[a]	Amphetamines; Barbiturates; Tricyclic antidepressants; Cocaine; Methadone
Serology	3,4-Methylenedioxymethamphetamine; Benzodiazapines; Morphine
Hepatitis B surface antigen	Phencyclidine; Tetrahydrocannabinol
Anti HCV IgG	Opiates
HIV antibodies	
Coagulation test	
Prothrombin Time (PT)	
Thrombin Time (TT)	
Activated Partial Thromboplastin Time (aPTT)	
Other	
Alcohol abuse screen (breath test)	

[a] Female patients who reported post-menopause, but have not had a hysterectomy, bilateral oophorectomy or bilateral salpingectomy will be required to have serum FSH testing at Screening.

[b] For females of childbearing potential: a urine β-HCG pregnancy test must be performed at the screening visit and Day -1.

For blood volume see Section 7.1.

NB. In case a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN please refer to Appendix D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

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

Samples with laboratory values outside the reference ranges suspected to be of any clinical significance will be retaken. Patients, in whom suspected clinical significance is confirmed, will either not be included or, if already randomized, will be followed until normalization or for as long as the investigator considers it necessary. Additional laboratory values may be performed for safety reasons if judged appropriate by the investigator.

Samples will be collected in tubes according to standard practices. The safety laboratory samples will be analysed using routine methods at each clinical site.

6.3.6 Physical examination

Refer to Study Plan, Table 1. For the visits when a physical exam will be performed.

Medically qualified individual will perform a physical examination and include an assessment of the following: general appearance, skin, head and neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular, lungs, abdomen, and neurological systems.

Results will be recorded in the eCRF as an overall normal or abnormal with a listing of abnormalities.

6.3.7 ECG

For timings of assessments, refer to the Study Plan and Time Schedule (Table 1).

Standard 12-lead ECGs will be recorded after a 10-minute supine rest at Visit 1 (the pre-entry visit) only. Electrocardiograms will be evaluated by the investigator.

The date, time and whether the ECG was normal or abnormal, as well as reason for abnormalities will be recorded. All ECGs will be evaluated by the investigator, or, if necessary, a qualified cardiologist, who will judge the overall interpretation as normal or abnormal. If abnormal, a decision will be made on whether or not the abnormality is clinically significant.

6.3.8 Ultrasonic cardiogram

For timings of assessments, refer to the Study Plan and Time Schedule (Table 1).

The date, time and whether the Ultrasonic cardiogram was normal or abnormal, as well as reason for abnormalities will be recorded. The result will be evaluated by the investigator, or, if necessary, a qualified cardiologist, who will judge the overall interpretation as normal or abnormal. If abnormal, a decision will be made on whether or not the abnormality is clinically significant.

6.3.9 24h Holter

For timings of assessments, refer to the Study Plan and Time Schedule (Table 1).

The date, time and whether the 24Holter was normal or abnormal, as well as reason for abnormalities will be recorded. The result will be evaluated by the investigator, or, if necessary, a qualified cardiologist, who will judge the overall interpretation as normal or abnormal. If abnormal, a decision will be made on whether or not the abnormality is clinically significant.

6.3.10 Vital signs

6.3.10.1 Pulse and blood pressure

Blood pressure and pulse rate will be measured after 5 minutes rest in a sitting position. For timings of assessments refer to the Study Plan and Time Schedule (see Table 1).

6.4 Pharmacokinetics

6.4.1 Collection of samples

Blood samples (2 mL) for determination of ticagrelor and its metabolite AR-C214910XX in plasma will be taken at the times presented in the study plan Table 2.

On Days 1, 2, 3, blood samples for pharmacokinetic analysis of ticagrelor and its metabolite AR-C214910XX will be obtained of each treatment group at the following time points:

- Pre-dose (within 120 minutes prior to dosing), 0.5, 1, 2, 3, 6, 12, 24, 36, and 48 hours post dose.

On Day 7, blood samples for pharmacokinetic analysis of ticagrelor and its metabolite AR-C214910XX will be obtained of each treatment period at the following time points:

- Pre-dose (within 5 minutes prior to dosing), 0.5, 1, 2, 3, 6, and 12 hours post dose.

Table 5 Schedule of Ticagrelor/AR-C124910XX Pharmacokinetic Blood Sampling for Measurement of Drug Concentration

Study visit	Analyte	Scheduled time relative to ticagrelor dose (h)	Tube number
Visit 2/Day1	Ticagrelor/AR-C124910XX	Pre-dose	1
	Ticagrelor/AR-C124910XX	0.5 hr	2
	Ticagrelor/AR-C124910XX	1 hr	3

Study visit	Analyte	Scheduled time relative to ticagrelor dose (h)	Tube number
	Ticagrelor/AR-C124910XX	2 hr	4
	Ticagrelor/AR-C124910XX	3 hr	5
	Ticagrelor/AR-C124910XX	6 hr	6
	Ticagrelor/AR-C124910XX	12 hr	7
Visit 2/Day 2	Ticagrelor/AR-C124910XX	24 hr	8
	Ticagrelor/AR-C124910XX	36 hr	9
Visit 2 Day 3	Ticagrelor/AR-C124910XX	48 hr	10
Visit 2.Day 7	Ticagrelor/AR-C124910XX	0 hr	11
	Ticagrelor/AR-C124910XX	0.5 hr	12
	Ticagrelor/AR-C124910XX	1 hr	13
	Ticagrelor/AR-C124910XX	2 hr	14
	Ticagrelor/AR-C124910XX	3 hr	15
	Ticagrelor/AR-C124910XX	6 hr	16
	Ticagrelor/AR-C124910XX	12 hr	17

Individual venipunctures for each time point may be performed or an indwelling catheter may be used.

Samples for the measurement of concentration should be analysed within the timeframe after collection for which the stability in the samples has been validated and found acceptable.

Samples will be collected, labelled stored and shipped as detailed in Laboratory Manual.

For blood volume see Section 7.1.

6.4.2 Determination of drug concentration

Samples for determination of ticagrelor and its active metabolite (AR-C124910XX) concentrations in plasma will be analysed by Covance on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

6.5 Pharmacodynamics

6.5.1 Collection of pharmacodynamic markers

Pharmacodynamic measurements will include IPA (final extent, 20µm ADP) and the VerifyNow™ $P2Y_{12}$ assay. Blood samples for pharmacodynamics measurements will be collected at the time points outlined in Table 2. The PD sample should always precede the PK sample, should difficulty occur obtaining PK or PD blood samples, the PD blood sample takes priority.

The actual times of every sample drawn may change but the number of samples will remain the same. All efforts will be made to obtain the pharmacodynamics and pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, eCRF).

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume see Section 7.1.

6.5.2 IPA by LTA

6.5.2.1 Methods of assessment

4.5 mL Blood samples for pharmacodynamics measurements will be drawn through the same cannula used for the PK sampling and will be collected at the time points outlined in Table 2.

The samples will be maintained at room temperature until centrifugation. The study specific laboratory manual contains a detailed description of the process and procedure.

6.5.3 VerifyNow™ $P2Y_{12}$ assay

6.5.3.1 Methods of assessment

A 2 mL blood sample will be collected for $P2Y_{12}$ assay. The VerifyNow™ System (Accumetrics, San Diego, CA) is a turbidimetric based optical detection system that measures platelet aggregation in whole blood (Aleil B et al 2005, Barragan P et al 2003). The assay device contains a lyophilised preparation of human fibrinogen-coated beads, platelet activators, and buffer. The assay is based upon the ability of activated platelets to bind fibrinogen. Fibrinogen-coated micro-particles aggregate in whole blood in proportion to the number of expressed platelet GPIIb/IIIa receptors. The rate of micro-bead aggregation is more rapid and reproducible if platelets are activated; therefore, the reagent adenosine-5-diphosphate (ADP/PGE_1) is incorporated into the assay channel to induce platelet activation without fibrin formation.

For blood volume see Section 7.1.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

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

Table 6 Volume of Blood

Volume of Blood to be Drawn from Each Patient				
Assessment		**Sample Volume[a] (mL)**	**No. of Samples**	**Total Volume (mL)**
Safety	Clinical chemistry	4	3	12
	Haematology	2	3	6
Serology[b]		4	1	4
Pharmocokinetic		2	17	34
VerifyNow™ $P2Y_{12}$		2	17	34
Discard sample prior to PD/PK sample[c]		1	17	17
Platelet Aggregation (LTA)		4.5	17	76.5
FSH		4	1	4
Coagulation test		2	1	2
Total (approximately)				**189.5**

[a]The sample volume for safety assessments, Serology, serum β-HCG are approximate volumes that are patient to site-specific change.

[b]The Serology test includes: Hepatitis B surface antigen; Anti HCV IgG; HIV. The blood taken for Serology will be combined with chemistry at screening.

[c]This discarded blood from predraws used to remove fluid from flushed catheters, the discarded volume is not expected to exceed 1 mL for each PK or PD draw point.

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses and the clinical study report has been finalized.

7.2.1 Pharmacokinetic samples

Pharmacokinetic samples will be disposed of or anonymised by pooling after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses. Pooled, anonymised samples may be used for analytical method and/or validation.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the Clinical Study Report but separately in a Bioanalytical Report.

7.2.2 Pharmacodynamic samples

Samples will be disposed of after the clinical study report has been finalised.

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 patient 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 patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

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

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

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already 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 patient is withdrawn from further study participation.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented

- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site

- Ensures that the patient and AstraZeneca are informed about the sample disposal.

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

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Patient data protection

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

8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients.

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

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

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

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

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

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

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

8.4 Informed consent

The Principal Investigator(s) at each centre will:

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

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the 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.

8.6 Audits and inspections

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

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

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

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

9.2 Training of study site personnel

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

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

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

9.3 Monitoring of the study

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

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, 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 CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

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

9.3.1 Source data

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

9.4 Study agreements

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

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

9.4.1 Archiving of study documents

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

9.5 Study timetable and end of study

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

The study is expected to start in Q1, 2014 and to end by Q4, 2014.

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

10. DATA MANAGEMENT BY ASTRAZENECA

Data management will be performed by Cognizant.

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

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at the Cognizant Data Management Centre.

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

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

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

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

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

11.1 Calculation or derivation of safety variable(s)

Where appropriate, change-from-baseline variables will be calculated for the continuous variables as the post-treatment value minus the value at baseline.

Baseline for Haematology and Clinical Chemistry will be defined as the value measured Day-1. If a patient is missing the baseline collection, the previous non-missing evaluation will become the baseline value. If no baseline or previous-to-baseline evaluation exists then the baseline value will be treated as missing.

11.1.1 Other significant adverse events (OAE)

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

11.2 Calculation or derivation of pharmacokinetic variables

Pharmacokinetic analyses will be performed by AstraZeneca R&D.

Plasma concentrations of ticagrelor and its metabolite AR-C124910XX will be listed and depicted graphically as a function of time relative to dose. The following pharmacokinetic parameters will be estimated by non-compartmental analysis:

- Single dose: C_{max}, t_{max}, $t_{1/2}$ and AUC_{0-t}, and AUC of ticagrelor and AR-C124910XX.
- Multiple doses: C_{max}, t_{max} of ticagrelor and AR-C124910XX.

Ticagrelor and AR-C124910XX C_{max} will be estimated as the highest measured concentration and t_{max} will be the time to maximum concentration following dosing. The terminal phase elimination constant (λ_z) will be calculated by log-linear regression of the terminal portion of the concentration-time profile using at least 3 time points. The terminal elimination half-life ($t_{1/2}$) will be calculated as $0.693/\lambda_z$. AUC will be calculated using the linear trapezoidal method up to the last measurable concentration (AUC_{0-t}) and thereafter by extrapolation of the terminal elimination phase to infinity. The ratio of AR-C124910XX C_{max} to ticagrelor C_{max} ratio and, AR-C124910XX AUC to ticagrelor AUC ratio will be calculated. Accumulation ratio (AR) of ticagrelor and AR C124910XX will be estimated as a ratio of Day 7 $AUC_{(0-12h)}$ to Day 1 $AUC_{(0-12h)}$.

11.3 Calculation or derivation of pharmacodynamic variable(s)

ADP-induced inhibition of platelet aggregation

The inhibition of platelet aggregation, (IPA), from pre-dose baseline will be calculated at each time post-dose using the following formula for ADP-induced aggregation (final extent):

$$IPA(\%) = 100 \times \frac{(PA_{BL} - PA_T)}{PA_{BL}}$$

Where PA_T is the response at any post treatment time 'T', and PA_{BL} is the response at pre-dose baseline on Day 1. Percentage inhibition will be restricted to the closed interval [0,100]; any data falling outside this range will be truncated to the appropriate limit.

The area under the time-effect curve (AUEC) for IPA will be calculated over the dosing interval from the respective IPA vs. time curves using the linear trapezoidal rule.

Time to peak IPA ($TIPA_{max}$) will be the time of the maximum final extent IPA within a dosing interval.

PRU

$P2Y_{12}$ reaction units (PRU) will be measured by VerifyNow™ $P2Y_{12}$ assay. The PRU data will be presented as the absolute PRU at each timepoint and percent reduction of the $P2Y_{12}$ receptor from baseline. Percent reduction will be calculated as percent change from baseline (pre-treatment) PRU versus each timepoint post treatment using the following formula

$$\% \text{ Reduction from baseline} = 100 \times \frac{(PRU_{BL} - PRU_T)}{PRU_{BL}}$$

Where PRU_T is the response at any post treatment time 'T', and PRU_{BL} is the response at pre-dose baseline on Day 1.

11.3.1 Calculation or derivation of the relationship between pharmacokinetic and pharmacodynamic variables

Relationship between ticagrelor plasma concentration and effect on PD variables will be presented graphically. If appropriate, concentration-effect relationships will be explored.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

The statistical analysis will be performed by Biostatistics Group using SAS® Version 9.1, or higher.

12.1 Description of analysis sets

Throughout the analyses, erroneously treated patients (eg, those randomised to treatment A but actually given treatment B) will be accounted for in the actual treatment group. Patient inclusion in each of the analysis sets will be determined from database lock.

12.1.1 Safety analysis set

All patients who receive at least 1 administration of the investigational product and for whom any post-dose data are available will be included in the safety analysis set.

12.1.2 Pharmacodynamic analysis set

All randomized patients who received at least one dose of investigational product with post-dose PD measurements available and no protocol deviation considered to significantly affect the integrity of PD results (eg, non-compliance with study drug) will be included in the PD analysis set.

12.1.3 Pharmacokinetic analysis set

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

12.2 Methods of statistical analyses

12.2.1 General principles

Quantitative variables will be summarized by treatment using descriptive statistics, including n, mean, standard deviation (SD), median, minimum, and maximum values.

Missing data will result in a reduced sample size for that parameter. No action will be taken to handle missing data.

A patient who withdraws prior to the last planned observation will be included in the analysis up to the time of discontinuation.

12.2.2 Patient characteristics

Demographics and relevant medical and surgical history will be listed by patient and summarized by treatment group.

Categorical variables will be summarized by treatment, and time point in frequency tables (frequency and proportion). Quantitative variables will be summarized by treatment using descriptive statistics, including n, mean, standard deviation (SD), median, minimum, and maximum values.

12.2.3 Pharmacodynamic data

IPA(final extent), absolute PRU and percent reduction of PRU from baseline will be listed by patient and time, and summarized by treatment group at each time point using n, arithmetic mean, SD, median, minimum and maximum $TIPA_{max}$ and AUEC for final extent IPA will be summarized descriptively by treatment group and study Day 1 and 7.

Profiles of IPA (final extent), percent inhibition and percent reduction of PRU will be plotted per patient for Day 1 (0-48h post dose) and Day 7 (0-12h post dose). The corresponding arithmetic mean (± SD) by time point and treatment group will be plotted in one graph with treatment group indicated.

12.2.4 Plasma concentrations of ticagrelor and AR-C124910XX

All plasma concentrations will be listed by patient and time, and summarized by treatment group at each time point using n, number of samples ≤ LOQ, geometric mean, CV, arithmetic mean, SD median, minimum and maximum. The CV is calculated as

$100 \cdot \sqrt{(\exp(s^2) - 1)}$, where s is the SD of log transformed values. (Shen H et al 2006)

Individual plasma concentrations and mean by treatment group will be plotted over time by study day (Day1 and 7).

12.2.5 PK parameters

All PK parameters will be listed by patient.

All PK parameters will be summarized by treatment group and study day using n, number of samples, CV (calculated as above), arithmetic mean, SD, median, minimum and maximum.

Box plots of the PK parameters by treatment group and study day will be presented.

12.2.6 Safety Analyses

All safety data will be listed by patient and summarized by treatment group.

Adverse events will be summarized by Preferred Term and System Organ Class using Medical Dictionary for Regulatory Activities (MedDRA) vocabulary. Listings of SAEs and AEs that lead to withdrawal will be presented. The number of patients who had any AEs, SAEs, AEs that led to withdrawal, AEs with severe intensity and AEs judged as causally related to IP by the investigator will be summarized by treatment group. Where appropriate AEs will be summarized by SOC and Preferred Term by treatment group.

Serious adverse events that occur before administration of first dose will be reported separately

For continuous safety variables, the observed values and change from baseline at each time point will be summarized by treatment, and time point using descriptive statistics (n, mean, SD, minimum, median, maximum). The baseline will be defined as the last value measured prior to randomization. Shift plots of maximum value post dose versus baseline with reference limits indicated will be presented.

If a patient has more than one measurement at the same post dose occasion, then the first measurement will be used in the summaries. The extra measurement will be included in data listings. Laboratory values outside the reference limits will be listed.

For qualitative safety variables (physical examination and urinalysis) shift tables vs baseline assessment will be presented at each time point.

12.3 Determination of sample size

The study data will be presented descriptively and sample size has not been determined based on statistical testing. The sample size is based on the desire to obtain adequate safety, PK, PD data to achieve the objectives of the study whilst exposing as few patients as possible to the study procedures

12.4 Data monitoring committee

A data monitoring committee will not be used for this study.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

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.** In the case of a vascular event, the patients should be discontinued from the study if administration of a prohibited concomitant medication treatment with PCI or CABG or other major surgery is needed.

The AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that the appropriate AstraZeneca Patient Safety Department receives a report by Day one for all fatal and life-threatening cases and by Day five for all other SAEs.

All Serious Adverse Events (SAE) must be reported to Clinical Patient Safety, AstraZeneca Marketing Company within one day (that is immediately but not later than the end of the next business day) by fax. Clinical Drug Safety will forward the SAE report to the applicable AstraZeneca R&D. The monitor should also be informed when an SAE has occurred.

Follow-up information on SAEs must also be reported by the investigator within the same time frames.

The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

For Serious Adverse event reporting, complete the SAE report and fax the report to the appropriate Patient Safety department.

There is no known antidote to reverse the effects of ticegrelor. The average half-life of ticegrelor is approximately 12 hours, so blood levels of ticegrelor should be low by 48 to 72 hours (ie, 4 to 6 half-lives) after discontinuation. Platelet transfusions may be given. It is not known if new platelets may be inhibited by ticagrelor as long as it is circulating in blood.

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.3.4**

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

Table 7 AstraZeneca contacts

Name	Role in the study	Address & telephone number
	Study Delivery Team (SDT) Leader responsible for the protocol at central R&D site	35/F CITIC Square, 1168 Nanjing West Road, Shanghai 200041, China.
	SDT Physician responsible for the protocol	AstraZeneca Pharmaceuticals Room C3B-718,1800 Concord Pike PO Box 15437, Wilmington, DE 19850-5437, United States

13.2 Overdose

There is no known antidote to ticagrelor. In the event of overdose, adverse events should be monitored and ECG monitoring may be required. The expected effect of overdose is prolonged duration of bleeding risk. If bleeding occurs appropriate supportive measures should be taken. An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

- An overdose without associated symptoms is only reported on the Overdose CRF module.
- If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** 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 6.3.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

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

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without

complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** 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 6.3.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

13.3.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for three months following the last dose.

Pregnancy of the patient's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

The outcome of any conception occurring from the date of the first dose until three months after the last dose should be followed up and documented.

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