Clinical Study Protocol

Drug Substance	Ticagrelor
Study Code	D5130L00012
Edition Number	1
[redacted]	[redacted]

A Randomized, Open-Label, Multiple Dose, Crossover, Multiple Center Study of the Antiplatelet Effects of Ticagrelor versus Clopidogrel in Hispanic Patients with Stable Coronary Artery Disease

Sponsor:

AstraZeneca LP, Wilmington, DE 19850

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

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

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

AstraZeneca

PROTOCOL SYNOPSIS

A Randomized, Open-Label, Multiple Dose, Crossover, Multiple Center Study of the Antiplatelet Effects of Ticagrelor versus Clopidogrel in Hispanic Patients with Stable Coronary Artery Disease

International Co-ordinating Investigator or Principal Investigator or National Co-ordinating Investigator

[redacted]

Study centre(s) and number of subjects planned

The study plans to randomise approximately 34 male and female patients with documented stable coronary artery disease (CAD) in approximately 4 to 6 study centers in the United States (US).

Study period		Phase of development
Estimated date of first subject enrolled	[redacted]	IV
Estimated date of last subject completed	[redacted]	

Objectives

Primary

The primary objective of the study is to compare ticagrelor's versus clopidogrel's on-treatment platelet reactivity at the 2 hour time point after a loading dose of each as measured by $P2Y_{12}$ Reaction Units (PRU) using VerifyNow™ in Hispanic patients with stable coronary artery disease on chronic low dose ASA.

Secondary

The secondary objectives of this study are to:

- Compare ticagrelor's versus clopidogrel's on-treatment platelet reactivity at the 0.5 and 8 hour time point after a loading dose of each as measured by $P2Y_{12}$ Reaction Units (PRU) using VerifyNow™ in Hispanic patients with stable coronary artery disease on chronic low dose ASA.

- Compare ticagrelor's versus clopidogrel's on-treatment platelet reactivity at the 2 hr, 8 hr on Day 7 and end of dosing interval (12 hours after last evening dose of ticagrelor and 24 hours after the last morning dose of clopidogrel) on Day 8 as measured by $P2Y_{12}$.Reaction Units (PRU) using VerifyNow™ in Hispanic patients with stable coronary artery disease on chronic low dose ASA.

- To evaluate plasma concentration of ticagrelor and its active metabolite AR – C124910XX at times of the VerifyNow™ assessment.

Safety Objective

To assess the safety of ticagrelor by assessment of AEs, physical examination, and vital signs.

Exploratory Objectives

To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to ticagrelor and clopidogrel.

Study design

This is a multiple center, randomised, open-label, multiple dose, crossover study of the onset and repeated doses antiplatelet effect of ticagrelor compared with clopidogrel with chronic low dose acetylsalicylic acid (ASA) as background therapy in approximately 34 Hispanic patients with stable coronary artery disease.

This study will consist of 2 treatment periods. During each period patients will receive 1 of 2 possible treatments. There will be a 10-14 day washout period between 2 treatments.

Treatment A: Clopidogrel 600 mg loading dose followed by 75 mg once daily (od) for 7, 8 or 9 days.

Treatment B: Ticagrelor 180 mg loading dose followed by 90 mg twice daily (bd) for 7, 8 or 9 days.

All treatments will be administered in an open-label design. All patients will continue to receive 75-100 mg daily ASA, which will be maintained at a constant dose throughout the study period.

Thirty-four patients will be randomized to receive study drug in order to ensure 28 evaluable patients. The study will be conducted at approximately 4 to 6 centers and will consist of 8 visits. The study duration for each subject will be up to 11 weeks.

Target subject population

The male and female Hispanic patients aged 18 years and over, with documented stable CAD (defined as any of the following: stable angina pectoris (current or history of) with objective evidence of CAD; previous MI history; or previous revascularization history) will be eligible for study participation. Patients with a history of acute coronary syndromes (ACS) within 12 months of study enrolment will be excluded from participation. The planned sample size is approximately 34 randomised patients.

Investigational product, dosage and mode of administration

Ticagrelor: Ticagrelor 180 mg loading dose followed by 90 mg bd for 7, 8 or 9 days

Comparator, dosage and mode of administration

Clopidogrel 600 mg loading dose followed by 75 mg od for 7, 8 or 9 days

Duration of study

Study duration is approximately 11 weeks, consisting of 8 Visits. The screening period will be up to 21 days prior to receiving the first dose of study medication. The total duration of treatment will be approximately 14 days. Each treatment sequence will be 7 days with a 10 to 14 day washout period in between treatment sequences. A follow-up visit will be conducted 7 to 10 days after discharge from the study at visit 7.

Outcome variable(s):

Pharmacodynamic

– **Primary outcome variables:**

- Inhibition of the $P2Y_{12}$ receptor at 2 hours after loading dose with ticagrelor compared with clopidogrel as measured by PRU from Verify Now™ in Hispanic patients.

– **Secondary outcome variables:**

-Inhibition of the $P2Y_{12}$ receptor at 0.5 and 8 hours after loading dose with ticagrelor compared with clopidogrel as measured by PRU from Verify Now™ in Hispanic patients.

-Inhibition of the $P2Y_{12}$ receptor at 2 hours, 8 hours and end of dosing interval after 7 days of administration with ticagrelor compared with clopidogrel as measured by PRU from Verify Now™ in Hispanic patients.

-Percent reduction in platelet $P2Y_{12}$ receptor activity measured by VerifyNow™ on $P2Y_{12}$ reaction units (PRU), represented as percentage change from baseline (pre-treatment)

$$\% \text{ Reduction from baseline} = \left(1 - \left[\frac{\text{PRU after study drug}}{\text{PRU at baseline}}\right]\right) \times 100\%$$

- Percentage inhibition of platelet aggregation as measured by Verify Now™ measured as change from BASE (on-treatment)

– **Safety**

- Adverse events, physical examination and vital signs

Statistical methods

All data from patients included in the pharmacodynamics (PD) analysis set will be summarized using descriptive statistics by sequence, treatment, period and time relative to dose. The primary analysis of the difference between ticagrelor and clopidogrel in PRU at 2 hours will be analyzed using a mixed effect model with terms for period (I/II), treatment (A/B), pre-dose PRU, and a random effect for patient within sequence. Treatment level means will be estimated using least squares means and 2-sided 95% confidence intervals. Tests will be evaluated with a 2-sided alpha level of 0.05. Distribution assumptions underlying the analysis will be assessed by residual plots. If the assumptions are violated, a Wilcoxon signed rank test will be used.

Secondary analyses of PRU at other time points will be analyzed with similar mixed effects models. Analyses will be done at 0.5, and 8 hours after the loading dose. Separate analyses will be done for pre-dose, 2, 8 hours after last morning dose of both drugs, and 12 hours after last evening dose for ticagrelor or 24 hours after last dose of clopidogrel. There will be secondary analyses of reduction in platelet $P2Y_{12}$ receptor activity as measured by percent change from baseline (pre-treatment) in PRU. There will also be a secondary analysis of percent inhibition of platelet aggregation from BASE on treatment.

Safety will be evaluated using the safety analysis set. Adverse events will be reported as proportions of subjects with adverse events. Adverse events that lead to discontinuation will be summarized. Vital signs will be reported using descriptive statistics by treatment and protocol time point.

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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
AE	Adverse event (see definition in Section 6.4.1)
ACS	Acute Coronary Syndromes
ADP	Adenosine diphosphate
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASA	Aspirin
AST	Aspartate aminotransferase
BD	Twice daily
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
CYP	Cytochrome P450
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
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation

Abbreviation or special term	Explanation
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational Product
IRB	Investigational Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LIMS	Laboratory Information Management System
LLOQ	Lower Limit of Quantification
LSLV	Last Subject Last Visit
LTA	Light transmittance aggregometry
MI	Myocardial Infarction
NDA	New Drug Application
NSAID	Non-steroidal anti-inflammatory drug
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
OD	Once Daily
PCI	Percutaneous coronary intervention
PD	Pharmacodynamics
PGx	Pharmacogenetic research
PGI_2	Prostacyclins
PI	Principal Investigator
PK	Pharmacokinetics
PLATO	A study of PLATelet inhibition and Patient Outcomes
PRBCs	Packed red blood cells
PRU	$P2Y_{12}$ Reaction Units
SAE	Serious adverse event (see definition in Section 6.4.2).
SBP	Systolic Blood Pressure
SUSAR	Suspected Unexpected Serious Adverse Reactions
$T_{1/2}$	Half-life
ULN	Upper Limit of Normal
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 ACS. Ticagrelor was recently approved in the USA. However, the database of the NDA for ticagrelor was limited in the inclusion of various ethnic groups. A well controlled pharmacodynamic study in Hispanics has not been conducted. This study explores the platelet inhibiting effects of ticagrelor and clopidogrel in Hispanic patients with stable coronary artery 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 a potent, reversibly binding, selective $P2Y_{12}$-receptor antagonist (antiplatelet agent). It 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 ($t_{½}$) of the parent compound is approximately 7 hours and one of the primary metabolites, AR-C124910XX, is considered equipotent to the parent drug *in vitro*. Refer to the investigator brochure for further details.

The FDA has recently approved Ticagrelor. 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 Research hypothesis

When ticagrelor compared with clopidogrel is administered to Hispanic patients with stable coronary artery disease on chronic low dose ASA therapy, the ticagrelor administered patients will have a faster onset of platelet inhibition and achieve a greater inhibition of platelets after the first dose and maintain this difference on day 7.

1.3 Rationale for conducting this study

The Phase 3 pivotal efficacy and safety study (PLATO) evaluated ticagrelor mediated reduction of clinical thrombotic events compared with clopidogrel in patients with acute coronary syndrome using a ticagrelor dosing regimen of a 180 mg loading dose followed by a 90 mg twice daily (bd) maintenance dose. However, the Phase III study enrolled few Hispanics. A well controlled trial of the platelet inhibiting effects of ticagrelor in Hispanics has not been conducted. Therefore the present study will determine the antiplatelet effects of ticagrelor compared with clopidogrel in Hispanic patients with stable coronary artery disease.

The primary objective of the study is to compare ticagrelor's versus clopidogrel's inhibition of the $P2Y_{12}$ receptor at the 2 hour time point after a loading dose of each as measured by the $P2Y_{12}$ Reaction Units (PRU) using VerifyNow™ in Hispanic patients with stable coronary artery disease on chronic low dose ASA. There is a paucity of data regarding the antiplatelet effect of ticagrelor in Hispanics, therefore the primary objective is to compare the 2 hour time point after the first dose of either drug to determine onset of ticagrelor compared with clopidogrel.

A secondary objective of the study is to compare ticagrelor's versus clopidogrel's on-treatment platelet reactivity at the 0.5 and 8 hour time point after a loading dose of each as measured by $P2Y_{12}$ Reaction Units (PRU) using VerifyNow™ in Hispanic patients with stable coronary artery disease on chronic low dose ASA. The rationale is to understand the effect of the onset of the antiplatelet effect in the first eight hours after the loading dose of ticagrelor and clopidogrel in Hispanic patients.

Once pharmacokinetic steady state is obtained, $P2Y_{12}$ Reaction Units (PRU) by VerifyNow™ from ticagrelor and clopidogrel at the 2 hr, 8 hr, and end of dosing interval from the last dose on day 7 (12 hours after last evening dose of ticagrelor and 24 hours after the last dose of

clopidogrel) will be compared. The rationale is to determine the antitplatelet effect of ticagrelor and clopidogrel after multiple days of dosing in the Hispanic population.

1.4 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 Hispanic 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. Hemorrhage was judged to be life-threatening in 3% of cases secondary to a procedure and in 1% of gastrointestinal bleeds.

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.

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. The incidence of gout did not differ between ticagrelor and clopidogrel in trials comparing the two treatments

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.

Procedures in case of medical emergency or other special situations are covered in details in Section 13.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to compare ticagrelor's versus clopidogrel's on-treatment platelet reactivity at the 2 hour time point after a loading dose of each as measured by $P2Y_{12}$ Reaction Units (PRU) using VerifyNow™ in Hispanic patients with stable coronary artery disease on chronic low dose ASA.

2.2 Secondary objectives

The secondary objectives of this study are to:

- Compare ticagrelor's versus clopidogrel's on-treatment platelet reactivity at the 0.5 and 8 hour time point after a loading dose of each as measured by $P2Y_{12}$ Reaction Units (PRU) using VerifyNow™ in Hispanic patients with stable coronary artery disease on chronic low dose ASA.

- Compare ticagrelor's versus clopidogrel's on-treatment platelet reactivity at 2 hr, 8 hr on Day 7 and end of dosing interval (12 hours after last evening dose of ticagrelor and 24 hours after the last morning dose of clopidogrel) on Day 8 as measured by $P2Y_{12}$.Reaction Units (PRU) using VerifyNow™ in Hispanic patients with stable coronary artery disease on chronic low dose ASA.

- To evaluate plasma concentration of ticagrelor and its active metabolite AR –C124910XX at times of the VerifyNow™ assessment

2.3 Safety objective

The safety objective of this study is to assess the safety of ticagrelor by assessment of AEs, physical examination and vital signs.

2.4 Exploratory objectives

To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to ticagrelor and clopidogrel.

The exploratory analysis will be reported separately.

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This is a multiple center, randomised, open-label, multiple dose, crossover study of the onset and repeated dose administration antiplatelet effect of ticagrelor compared with clopidogrel with chronic low dose acetylsalicylic acid (ASA) as background therapy in approximately 34 Hispanic patients with stable coronary artery disease.

This study will consist of 2 treatment periods. During each treatment period patients will receive 1 of 2 possible treatments. There will be a 10 to 14 day washout period between the 2 treatments.

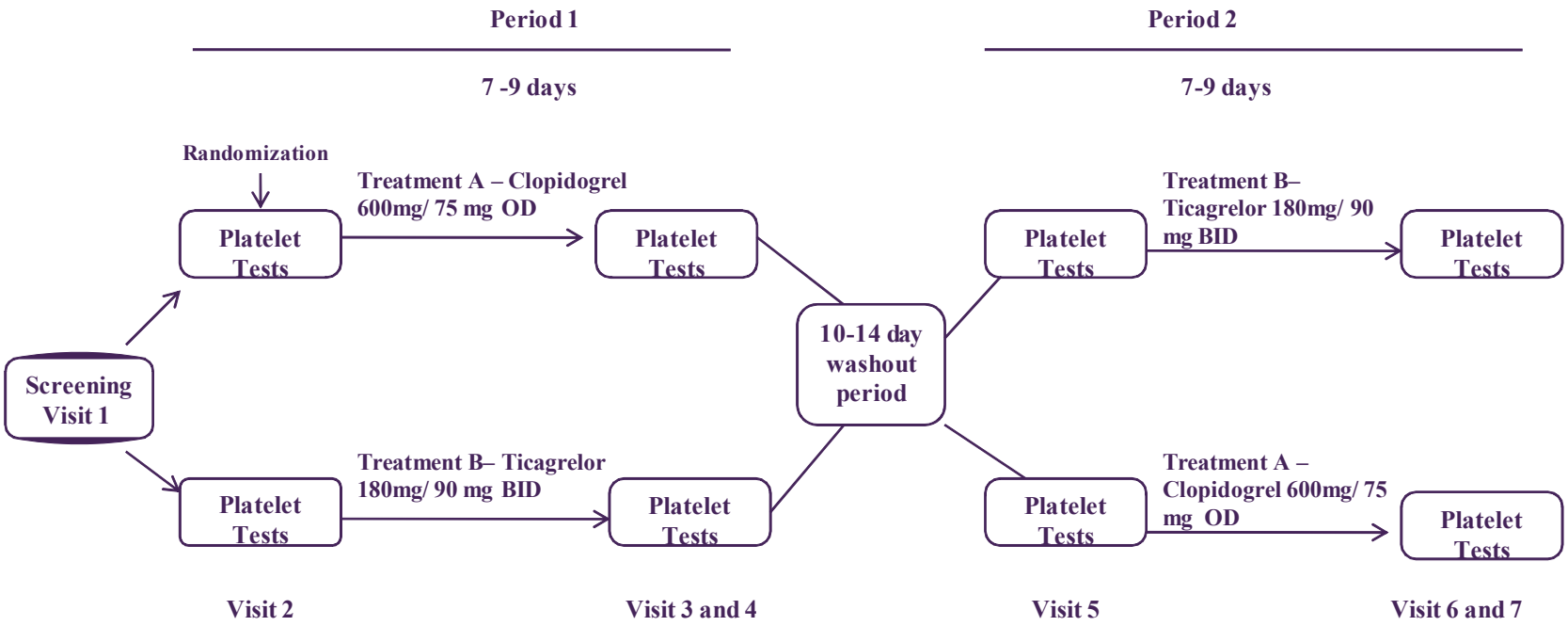
Treatment A: Clopidogrel 600 mg loading dose followed by 75 mg once daily (od) for 7days + 2 days.

Treatment B: Ticagrelor 180 mg loading dose followed by 90 mg twice daily (bd) for 7 days + 2 days.

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

Thirty-four patients will be randomized in order to ensure 28 patients are evaluable. The study will be conducted at approximately 4-6 centers and will consist of 8 visits. The study duration for each subject will be up to 11 weeks.

Figure 1 Study Flow Chart



Platelet Assessments and PK samples will be assessed at Visit 2, Visit 3, Visit 4 in Treatment Period 1 and Visit 5, Visit 6 and Visit 7 in Treatment Period 2

Table 1 Study Plan

Visit Description	Screening/ Washout	Treatment Period 1			Washout Period	Treatment Period 2			Follow Up Period
Visit	**1**	**2**	**3**	**4**		**5**	**6**	**7**	**8**
Visit Schedule	**Day -21 to Day -1**	**Day 1**	**Day 7[a]**	**Day 8**		**Day 1**	**Day 7***	**Day 8**	**7-10 days after Visit 7**
Informed consent	X				10-14 Day Washout Period				
Inclusion/Exclusion criteria	X								
Demographics	X								
Medical/Surgical history	X								
Cardiovascular history	X								
Complete physical examination	X								
Targeted physical examination		X				X			X
Vital signs	X	X	X	X		X	X	X	X
12-lead electrocardiogram (ECG)	X								
Clinical laboratory tests	X								
Pregnancy test (serum or urine)	X								
Randomisation		X							
Dispense study drug/diary		X				X			
Retrieve study drug/diary				X				X	
Pharmacokinetic blood samples[b]		X	X	X		X	X	X	
Platelet function blood tests [b]		X	X	X		X	X	X	X

Table 1 Study Plan

Visit Description	**Screening/ Washout**	**Treatment Period 1**			**Washout Period**	**Treatment Period 2**			**Follow Up Period**
Visit	**1**	**2**	**3**	**4**		**5**	**6**	**7**	**8**
Visit Schedule	**Day -21 to Day -1**	**Day 1**	**Day 7[a]**	**Day 8**		**Day 1**	**Day 7***	**Day 8**	**7-10 days after Visit 7**
Adverse events (including vascular assessment)	X	X	X	X		X	X	X	X
Concomitant medications	X	X	X	X		X	X	X	X

a The visit 3 and visit 6 will be on Day 7, 8 or 9 of each treatment period
b Refer to Table 2 for the protocol scheduled time of the PK/PD assessments at each scheduled visit

Table 2 Timing of pharmacokinetic and platelet function samples

Parameter	Time
PK samples (ticagrelor, AR-C124910XX)	• Visits 2 and 5: 0 (pre-dose), 0.5, 2 and 8 hours after loading dose • Visits 3 and 6: 0 (pre-dose), 2, and 8 hours after the last morning dose • Visits 4 and 7: End of dosing interval from Day 7 (12 hours after last evening dose of ticagrelor and 24 hours after the last dose of clopidogrel
VerifyNow™ $P2Y_{12}$ assay[ab]	• Visits 2 and 5: 0 (pre-dose), 0.5, 2 and 8 hours after loading dose • Visits 3 and 6: 0 (pre-dose), 2, and 8 hours after the last morning dose • Visits 4 and 7: End of dosing interval from Day 7 (12 hours after last evening dose of ticagrelor and 24 hours after the last dose of clopidogrel.

a VerifyNow™ $P2Y_{12}$ assay will measure $P2Y_{12}$ reaction units and percentage inhibition of $P2Y_{12}$ receptor.
b Visit 2 occurs on Day 1; Visit 3 occurs on Day 7, 8 or 9 (treatment period 1); Visit 4 occurs 1 day after Visit 3 (treatment period 1); Visit 5 occurs 10-14days after Visit 4 (treatment period 2);Visit 6 occurs on Day 7, 8 or 9 (treatment period 2); Visit 7 occurs 1 day after Visit 6 (treatment period 2)

3.2 Rationale for study design, doses and control groups

The primary objective of the study is to compare ticagrelor's versus clopidogrel's on-treatment platelet reactivity at the 2 hour time point after a loading dose of each as measured by $P2Y_{12}$ Reaction Units (PRU) using VerifyNow™ in Hispanic patients with stable coronary artery disease on chronic low dose ASA. As the number of Hispanics enrolled in clinical trials has been limited, this study will add to understanding the onset and repeated dose effect of ticagrelor and clopidogrel in this ethnic population.

The study design is a randomized, two way crossover study as each subject will be their own control. The study will be open-label, however, the operator of the VerifyNow™ test will be blinded to treatment. The comparator in this study will be clopidogrel. As the washout period is 10 to 14 days, sufficient time exists to completely washout the effects of both drugs prior to receiving the alternative drug.

Treatment of 7 days allows each drug to attain steady state, and hence allow day 7 results to be compared with the initial dose of each drug.

Guidelines to assess and assure patient safety are presented in Section 6.4 of this protocol.

Ticagrelor dosing regimen

The approved loading dose of ticagrelor is 180 mg in patients with ACS. This dose was well tolerated and showed significantly greater and consistently higher levels of IPA compared to clopidogrel 600 mg loading dose (Gurbel PA et al 2009) in non-Hispanic population. The ticagrelor 90 mg bd dose, following the loading dose of 180 mg, has been selected as the maintenance dose for this study since it is the approved dose.

Comparator group

A 600 mg clopidogrel loading dose was chosen for its common use in clinical practice (particularly before PCI). The clopidogrel 75 mg daily dose has been selected as the maintenance dose for this study since it is the approved dose.

Background therapy

Ticagrelor and clopidogrel 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.

Platelet function variables

The primary measure of platelet aggregation is optical aggregometry designed to measure the $P2Y_{12}$ receptor blockade expressed as PRU by the VerifyNow™ device. The simplicity of this technique makes it promising for research purposes compared to the technically demanding LTA. There have been several publications exploring the use of this assay versus LTA and there are also substantial data correlating the results of VerifyNow™ with clinical outcomes in patients with ACS and those undergoing PCI.

4. SUBJECT SELECTION CRITERIA

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

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

4.1 Inclusion criteria

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

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

2. Female and/or male aged 18 years or older

3. Documented stable CAD fulfilling any of the following, and taking 75-100mg ASA daily treatment:

   - Stable angina pectoris (current or history of) with objective evidence of CAD
   - Previous MI history
   - Previous revascularization history, (i.e., PCI or coronary artery bypass graft [CABG])

4. Females must be post menopausal or surgically sterile

   – Post Menopausal Women – Women over 50 years of age will be considered post menopausal if they are amenorrheic for 12 months without and alternative medical cause following cessation of all exogenous hormonal treatment

5. Women must have a negative urine pregnancy test

6. Self-identified as Hispanic

For inclusion in the genetic research, patients must sign the informed consent for genetic research.

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

The patient should be excluded from this genetic research if a previous bone marrow transplant has been performed.

4.2 Exclusion criteria

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

1. Any indication for oral anticoagulant (e.g., atrial fibrillation, mitral stenosis or prosthetic heart valve) or dual antiplatelet treatment (e.g., clopidogrel, prasugrel, ASA dose other than 75 to 100 mg daily) during study period

2. Concomitant therapy with strong CYP3A inhibitors, CYP3A substrates with narrow therapeutic index, or strong CYP3A inducers within 14 days and during study treatment and during:

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

   - Substrates with narrow therapeutic index: cyclosporine, quinidine.

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

   – The sponsor should be consulted for enrolment with any concomitant medicines which are suspected of undergoing strong drug-drug interaction

3. Increased bleeding risk including:

   - Recent (within 30 days) GI bleeding

   - Any history of intracranial, intraocular, retroperitoneal, or spinal bleeding

   - Recent (within 30 days of dosing) major trauma

   - Sustained uncontrolled hypertension (systolic blood pressure [SBP]>180mmHg or diastolic blood pressure [DBP]>100mmHg)

   - History of hemorrhagic disorders that can increase the risk of bleeding, e.g., haemophilia, von Willebrand's disease.

- Inability to discontinue required concomitant therapy with non-steroidal anti-inflammatory drug (NSAID) at screening
- Patients that have used within 30 days of screening, any oral or parenteral antithrombotic agent (Section 5.5)
- Platelet count less than 100,000 mm^3 or hemoglobin <10 g/dL

4. Diabetic patients with HbA1c≥10%
5. Contraindication or other reason that clopidogrel, ASA, or ticagrelor should not be administered (e.g., hypersensitivity, active bleeding, major surgery within 30 days of dosing, any bleeding tendency [coagulation defects], acute or chronic liver disease etc.)
6. History of drug addiction or alcohol abuse in the previous 2 years
7. Patient requires dialysis
8. Participation in another investigational drug or device study within 30 days of dosing
9. Recent (within 30 days of dosing) blood donation
10. Patients that are scheduled for revascularization (e.g., PCI, CABG) during the study period
11. 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 (e.g., active cancer, risk for non-compliance, risk for being lost to follow-up)
12. History of moderate or severe hepatic impairment
13. Patients who in the opinion of the investigator would be at risk for bradycardia
14. Involvement in the planning and conduct of the study (applies to AstraZeneca or delegate staff, and study site staff)
15. Previous enrolment or randomization of treatment in the present study
16. Current smokers, including the use of tobacco containing products in the past 1 month
17. Patients who had ACS or stent placed within 12 months of screening

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

19. Aspartate aminotransferace (AST), alanine aminotransferase (ALT) or total bilirubin > 1.5 x upper limit of the reference range

20. Currently taking ticlopidine and cilostazol

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

Procedures for withdrawal of incorrectly enrolled subjects see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

Patients must fast for at least 8 hours prior to the pre-dose PK and platelet function blood samples collected at Visit 2 through 7 (Table 2). Diabetic patients should fast for at least 4 hours, however clear fruit juices, crackers, or hard candy will be permitted if necessary to maintain patient safety.

A meal may be provided to patients following the 2 hour sample collection. Patients will again fast for 2 hours prior to the 8 hour sample collection.

Patients should not donate blood or bone marrow at any time during the study period. Patients will refrain from scheduling surgery, including dental surgery, at any time following the screening visit and through the completion of the follow-up visit.

Restrictions regarding concomitant medications are described in Section 5.5.

5.2 Subject enrolment and randomisation

The Principal Investigator will:

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

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

3. Determine subject eligibility. See Sections 4.1 and 4.2

4. Assign eligible subject unique randomisation code (subject number), beginning with 101.

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

5.2.1 Procedures for randomisation

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

5.3 Procedures for handling subjects incorrectly enrolled or randomised

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

Where patients not meeting the study criteria are enrolled in error, incorrectly randomised, or where they subsequently fail to meet the criteria for the study post-enrolment, they will be discontinued from further study participation. The end of study/early termination procedures (Section 5.8) should be followed for these patients.

5.3.1 Procedures for discontinuation from genetic aspects of the study

Patients who discontinue from the main study should always be asked specifically whether they are withdrawing or continuing their consent for this genetic research. It must be established whether the patient agrees with one of the following:

- Agrees to the genetic sample and any DNA extracted from the sample being kept for genetic research in the future.
- Withdraws consent for the sample to be kept for genetic research in the future and wishes the sample to be destroyed. Destruction of the sample (or the DNA extracted from the sample) will only be possible so long as the particular sample is traceable. In the event that genetic research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons, but these will not be used in any subsequent analyses.

Refer to Appendix D for more information.

5.4 Treatments

5.4.1 Investigational product(s)

AstraZeneca will provide the site with bottled study medication. The study medication provided will be ticagrelor and clopidogrel for the open label study.

5.4.2 Doses and treatment regimens

This study will consist of 2 treatment periods. During each period patients will receive 1 of 2 possible treatments. There will be a 10-14 day washout period between the 2 treatments.

Treatment A: Clopidogrel 600 mg loading dose followed by 75 mg once daily (od) for 7, 8 or 9 days

Treatment B: Ticagrelor 180 mg loading dose followed by 90 mg twice daily (bd) for 7, 8 or 9 days

5.4.3 Additional study drug

5.4.3.1 Concomitant ASA

In addition to randomized study drug, all patients are to be treated with concomitant ASA 75 mg to 100 mg (obtained locally by the investigator) daily during the treatment period according to local practice. The dose is to remain constant throughout the study, and patients will be instructed to make every effort to administer ASA at approximately the same time each day.

5.4.4 Interruptions to study drug

In the event a dose is missed the patients will be told to contact the investigator for instructions. Missed doses of ticagrelor or clopidogrel study drug should not be made up (ie, if a dose is missed, the next regularly scheduled dose should be taken and should not be doubled). If a patient cannot take oral medication, then study treatment should be interrupted until oral therapy can be resumed. For those who stopped the study drug, patients will need to follow-up with the site investigator.

Any temporary interruption of investigational products >24 hours should be recorded in the eCRF.

5.4.5 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines.

5.4.6 Storage

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

5.5 Concomitant and post-study treatment(s)

All medications (defined as ASA and ongoing prescriptions) will be recorded from Visit 1 through Visit 8. All individual medications will be recorded per-event for any SAE and discontinuation due to an AE.

The following medications as noted are prohibited:

- Treatment with approved parenteral or oral anticoagulants (e.g., unfractionated heparin, low molecular weight heparin, bivalirudin, fondaparinux, warfarin, rivaroxaban, dabigatran, lepirudin, desirudin) is not allowed 10 days prior to randomization and during the study
- Glycoprotein IIb/IIIa receptor antagonists are not allowed 30 days prior to randomization and during the study.
- Oral antiplatelet therapies and NSAIDs are not allowed 10 days prior to randomization and during the study
- St. John's Wort within 21 days prior to randomization and during the study
- ASA for pain relief is not permitted during the study
- Prostacyclins (PGI_2) are prohibited due to their effect on the function of platelets from 10 days prior to randomization and during the study
- Simvastatin and lovastatin more than 40mg/day during the study

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

5.6 Treatment compliance

Compliance will be monitored at each visit after randomisation. Any patient found to be taking less than 86% or more than 110% of the assigned study drug at visits 4 and 7 will be considered non-compliant. Subjects must not have missed any of the previous 6 doses immediately preceding visits 3 and 6. The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the Case Report Form.

5.6.1 Accountability

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

Patients will be asked to return all unused investigational products to the investigational center at Visits 4 and 7. The investigator will make an assessment in the eCRF regarding patient treatment compliance (see Section 5.6).

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

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

5.7 Discontinuation of investigational product

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient from this study are:

- Development of a condition or an acute event (eg, vascular event, MI, or stroke) that necessitates treatment with one or more prohibited medications, or disables the patient from following study procedures
- Voluntary discontinuation by the patient who is at any time free to discontinue participation in the study, without prejudice to further treatment
- Safety reasons as judged by the investigator, AstraZeneca or their delegate (eg, clinically significant ventricular pauses, life threatening bleeding)
- Severe non-compliance to protocol as judged by the investigator, AstraZeneca or their delegate
- Incorrect enrolment (ie, the patient does not meet the required inclusion/exclusion criteria for the study)
- Pregnancy

Once randomized into the study, all patients will be assessed until the final follow-up visit unless informed consent is withdrawn for study participation.

A patient will be classified as lost to follow-up only if he/she has failed to return for the required study visits and his/her vital status remains unknown despite multiple attempts to contact him/her via telephone, fax, email, or certified letter.

Temporary and permanent treatment discontinuations should be kept to a minimum, as this will reduce the ability to detect differences between the treatments.

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

5.7.1 Procedures for discontinuation of a subject 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 6.4.3 and 6.4.4); and all study drugs should be returned by the subject. Patients who discontinue should be seen and assessed by an investigator(s), if possible, at an End of Treatment Visit.

At this visit see Section 6.2.2 for the end of treatment assessments to be performed.

If a subject is withdrawn from study, see Section 5.8.

Telephone contact should be made 7 days after the Follow up Visit to follow-up on any ongoing or new AEs (Section 6.2.2).

Patients who are lost to follow-up should be contacted to request return to the study center to complete the end of study procedures. Methods, date, and time of contact should be recorded on the source document regardless of whether the patient agrees to return to the study center or not.

5.8 Withdrawal from study

Subjects are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); and the subject should return all study drugs.

Withdrawn subjects may be replaced with the approval of the sponsor.

6. COLLECTION OF STUDY VARIABLES

The following study measurements will be obtained. The timing of these measurements is detailed in the study plan (Table 1 and Table 2).

6.1 Recording of data

A 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 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 at enrolment and follow-up

6.2.1 Enrolment procedures

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

- Informed consent
- Review of inclusion/exclusion criteria
- Review of medical and surgical history, including determination of medication history (including current medications)
- Physical examination
- Demographics (including sex, date of birth, race, ethnic group)
- Vital signs (seated blood pressure [BP], pulse, respiratory rate, oral temperature)
- Cardiovascular history
- 12-lead ECG
- Laboratory assessments: haematology, clinical chemistry, urine/blood pregnancy test, urinalysis as outlined in Section 6.4.7.

6.2.2 Follow-up procedures

Each patient will have follow-up procedures performed during Visit 8, at the completion of the treatment period. Data will be collected for the following procedures performed in the eCRF:

- Targeted physical examination
- Vital signs (seated blood pressure [BP], pulse, respiratory rate, oral temperature)
- Platelet function test (VerifyNow™ $P2Y_{12}$ test)
- Assessment of adverse events and concomitant medications

6.3 Efficacy

Not applicable.

6.4 Safety

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

6.4.1 Definition of adverse events

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

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

6.4.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that 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 subject or may require medical intervention to prevent one of the outcomes listed above.

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

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse Events will be collected from the time of signature of the informed consent throughout the treatment period and including the follow-up period, Visit 8.

SAEs will be recorded from the time of informed consent.

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

Vascular events are assessed at each visit and may be reported by patients at anytime during the study. Non-serious vascular events will be reported as AEs. Any vascular events meeting the criteria for serious as outlined in section 6.4.2 will be reported.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the patients last AE assessment at Visit 8 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 subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- AE caused subject'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
- Causality assessment in relation to Additional Study Drug
- Description of AE.

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

The intensity will be rated according to the following definition:

- Mild (awareness of sign or symptom, but easily tolerated);
- Moderate (discomfort sufficient to cause interference with normal activities);
- Severe (incapacitating, with inability to perform normal activities).

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 subject or reported in response to the open question from the study personnel: 'Have you/the child 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 vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated 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 vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated vital sign will be considered as additional information. In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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

6.4.4 Reporting of serious adverse events

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

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

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

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

The Investigator or other study site personnel is to report a SAW to the appropriate AstraZeneca representative or delegate by telephone.

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.

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

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

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

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

In addition AstraZeneca will provide details of any *unexpected* serious adverse drug reactions reported with regard to the test product in this study to the Head of the study site, Principal Investigator and the regulatory agency. The Head of the study site should submit a written report to the IRB providing the details of all adverse event case(s) reported by AstraZeneca.

6.4.5 Reporting of suspected vascular events as adverse events

Non-serious suspected vascular events are reported as AEs. They are part of the natural history of the condition under investigation and therefore may be expected.

Once an event has been identified, using their clinical judgement, investigators must determine if the event is an acute vascular event (including the clinical terms for ACS, MI, UA, etc). All events will be recorded in the eCRF.

6.4.6 Bleeding assessments

For all bleeding events, the investigator will complete information on the eCRF specific to that bleeding event, including classification of the event as described in Section 6.4.6.1 below and a determination of whether it is an AE.

6.4.6.1 Definition of bleeding events

Bleeding events will be classified as shown below:

For patients experiencing a bleeding event that fulfils criteria in more than one category, the event will be assigned to the most severe category. This classification is a modification of the CURE definitions (Jneid H et al 2003).

Major bleed – fatal/life threatening

Any one of the following:

- Fatal
- Intracranial
- Intrapericardial bleed with cardiac tamponade
- Hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery
- Clinically overt or apparent bleeding associated with a decrease in Hb of more than 50 g/L[a] (3.1 mmol/L[b]; 0.775 mmol/L[c])[d]
- Transfusion of 4 or more units (whole blood or packed red blood cells [PRBCs]) for bleeding.

Major bleed- other

Any one of the following:

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

Minor bleed

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

Minimal bleed

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

Definitions of Terms

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

b Reference range Hb tetramer 8.1 to 11.2 mmol/L (males); 7.4 to 9.9 mmol/L (females).
c Reference range Hb monomer 2.02 to 2.80 mmol/L (males); 1.85 to 2.47 mmol/L (females).
d To account for transfusions, Hb measurements will be adjusted for any PRBCs or whole blood given between 2 blood measurements. A transfusion of one unit of blood will be assumed to result in an increase of 10 g/La; 0.62 mmol/Lb; 0.155 mmol/Lc in Hb. Therefore, to calculate the true change in Hb if there has been an intervening transfusion between 2 blood measurements, the following calculations should be performed: Δ Hb = [baseline Hb – post-transfusion Hb] + [number of transfused units x conversion factor in Hbe].
e Conversion factor = 10 g/La; 0.62 mmol/Lb; 0.155 mmol/Lc.

All blood product transfusions during the study will be recorded in the eCRF. In addition, all haemoglobin (haematocrit) values obtained in the 7 days preceding, during and for 7 days after a bleeding event will be recorded in the eCRF. Bleeding event data will be collected in sufficient detail so that categorisation according to other previously published scales (eg, TIMI) will be possible.

Information regarding the relationship of any bleed (excluding minimal) will be recorded on the eCRF.

6.4.7 Laboratory safety assessment

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

The following laboratory variables will be measured:

Table 3 Laboratory Variables

Clinical chemistry (Serum)	Haematology (Whole Blood)	Urinalysis
Creatinine	Haemoglobin	Glucose
Alkaline phosphatase	Haematocrit	Haemoglobin
Aspartate aminotransferase (AST)	Platelet Count	Protein
Alanine aminotransferase (ALT)	White blood cells	
Total Bilirubin	Erythrocytes (RBCs)	
Blood Urea Nitrogen (BUN)		
Glucose		
Total Protein		
Albumin		
Sodium		
Potassium		
Bicarbonate		
Phosphate		
Chloride		
Pregnancy		

For blood volume see Section 7.1.

6.4.8 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.

The targeted examination will be performed by medically qualified individuals and include skin, cardiovascular, lung, abdomen, and neurological evaluations.

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

6.4.9 ECG

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

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

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

6.4.10 Vital signs

6.4.10.1 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)

6.4.10.2 Body temperature

Body temperature will be measured in degrees Celsius using an automated thermometer at the times indicated in the Study Plan and Time Schedule (see Table 1)

6.5 Pharmacokinetics

6.5.1 Collection of samples

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

The tolerance window for the scheduled blood sample draw is 10% from the scheduled time. For example, 1 hour samples have a tolerance window of +/- 6 minutes from the scheduled time.

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

For blood volume see Section 7.1.

Table 4 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	Ticagrelor/AR-C124910XX	Pre-dose[a]	1
	Ticagrelor/AR-C124910XX	0.5 hr	2
	Ticagrelor/AR-C124910XX	2 hr	3
	Ticagrelor/AR-C124910XX	8 hr	4
Visit 3	Ticagrelor/AR-C124910XX	Pre-dose[a]	5
	Ticagrelor/AR-C124910XX	2 hr	6
	Ticagrelor/AR-C124910XX	8 hr	7
Visit 4	Ticagrelor/AR-C124910XX	12 hr post evening dose	8
Visit 5	Ticagrelor/AR-C124910XX	Pre-dose[a]	9
	Ticagrelor/AR-C124910XX	0.5 hr	10
	Ticagrelor/AR-C124910XX	2 hr	11
	Ticagrelor/AR-C124910XX	8 hr	12
Visit 6	Ticagrelor/AR-C124910XX	Pre-dose[a]	13
	Ticagrelor/AR-C124910XX	2 hr	14
	Ticagrelor/AR-C124910XX	8 hr	15
Visit 7	Ticagrelor/AR-C124910XX	12 hr post evening dose	16

a Blood sample must be drawn no more than 15 minutes hour prior to dose administration.

The date and time of collection will be recorded on the appropriate eCRF. Disposable needles and disposable lithium heparinized tubes shall be used and ordered by the site (22-040-017 Greiner VACUETTE North America No. 454089 for the 2 mL samples for assessment of total concentration). Individual venipunctures for each time point may be performed or an indwelling catheter may be used. If an indwelling catheter is used, the catheter should be kept patent with isotonic saline; the saline will be withdrawn (1 mL) and discarded prior to the blood sample being taken.

Blood samples (2 mL) will be collected into a lithium-heparinized tube. The heparin and blood will be carefully mixed. The sample will be labelled as described below, and placed on ice, until centrifugation, which will begin within 30 minutes after the sample is obtained. The sample will be centrifuged for 10 minutes at 4°C at a relative centrifugal force of 1500 g. The resulting plasma for ticagrelor and AR-C124910XX concentration will be transferred into a 1.8 mL polypropylene tube (Nunc Cryovial, Fisher Scientific No 12-565-163N, NNI No. 375418) with screw caps and immediately frozen upright at -20°C or below in a non-frost-free freezer and kept frozen at this temperature before, during and after transport to

the designated laboratory. Samples should be frozen within 60 minutes after the corresponding venipuncture.

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. Results from analyses stored longer than the period stated will not be reported.

Labelling of Ticagrelor and AR-C124910XX plasma samples

The pre-printed labels will clearly designate collection for total drug concentration assessment and will be supplied by AstraZeneca R & D, Wilmington, DE or their delegate. The labels must be applied to the plasma sample tubes and should include the following information:

- Study Code: D5130C00012
- Randomisation number
- Tube number
- Scheduled time and visit
- Analyte: Ticagrelor/AR-C124910XX
- Matrix: PLASMA.

Prior to shipment, all sample tubes for each patient from each study period will be placed in a separate bag and labelled with the study code, randomization number, study period, analyte, and the matrix (plasma). The sample will be shipped as detailed below.

Shipment of Ticagrelor and AR-C124910XX plasma samples

All PK plasma samples accompanied by the specimen shipment logs will be shipped via an agreed-upon overnight courier (World Courier). The frozen samples must be packed securely to avoid breakage during transit, and contact with other tubes, which would jeopardise the legibility of identifying labels. The samples should be double bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure they remain frozen for at least 72 hours to allow for delays in shipment. The samples from each volunteer will be placed in separate bags and labelled as instructed above. A specimen inventory will accompany the shipments and document any samples not processed according to the protocol's specifications. All applicable shipping regulations must be followed. Documentation sufficient to identify each sample must be included in the shipment.

For safety reasons, it is imperative that samples are not shipped until confirmation/consent has been received from the designated laboratory. Once completed, the primary contact at AstraZeneca, and the designated laboratory must be notified by e-mail or fax at the time samples are shipped. The fax notification must include a copy of the specimen shipment log and the courier tracking number (World Courier). Refer to the laboratory manual for analysis laboratory sample shipment information.

Samples should only be shipped on Monday through Wednesday. Do not ship within 3 days of a local holiday.

Notification to Clinical Pharmacology Sciences Group; Sweden:

[redacted]

6.5.2 Determination of drug concentration

Pharmacokinetic blood sampling for measurement of drug concentration of ticagrelor and its active metabolite, AR-C124910XX, will be assessed at the times outlined in Table 2. Samples for measurement of drug concentration of ticagrelor and its metabolite, AR-C124910XX, in plasma will be analysed by [redacted] on behalf of Clinical Pharmacology Sciences Group, Mölndal AstraZeneca using fully validated bioanalytical methods. The LLOQ for drug concentration will be 1 ng/mL and 2.5 ng/mL, respectively. Details of the methods used will be provided in the CSR. Samples will be destroyed after the CSR has been finalised.

Samples for PK determination of ticagrelor and its active metabolite, AR-C124910XX, will be analysed only for those patients receiving ticagrelor. The pharmacokinetic analyses will be performed by the Clinical Pharmacokinetics Group, AstraZeneca, Wilmington, DE.

6.6 Pharmacodynamics

6.6.1 Collection of pharmacodynamic markers

Pharmacodynamic measurements will include the VerifyNow™ $P2Y_{12}$ assay. Clinic staff performing these assays will remain independent of other study related activities to ensure the results remain blinded. 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. A 2mL discard sample should be collected before each PD sample. Should difficulty occur obtaining PK or PD blood samples, the PD blood sample takes priority.

For blood volume see Section 7.1.

6.6.2 VerifyNow™ $P2Y_{12}$ assay

6.6.2.1 Methods of assessment

A 2 mL blood discard sample will precede each VerifyNow™ sample.

A 2 mL blood sample will be collected in a Greiner Bio-One Vacuette tube. Gently invert the sample at least 5 times to ensure complete mixing. Blood must set a minimum of 10 minutes after collection before assay but no longer than 4 hours.

The VerifyNow™ System (Accumetrics, San Diego, CA) is a turbidimetric based optical detection system which 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.

6.6.2.2 Derivation or calculation of outcome variable

Light transmittance increases as activated platelets bind and aggregate fibrinogen-coated beads. The instrument measures this change in optical signal and reports results in $P2Y_{12}$ Reaction Units (PRU). The PRU data will be presented in the following ways. The absolute PRU at each timepoint and the % $P2Y_{12}$ inhibition from BASE (PRU vs BASE PRU at each timepoint.

An additional secondary analysis will be done on the percentage reduction from baseline (pre-treatment), which will be calculated as follows:

$$\%\ \text{Reduction from baseline} = \left(1 - \left[\frac{\text{PRU after study drug}}{\text{PRU at baseline}}\right]\right) \times 100\ \%$$

For blood volume see Section 7.1.

6.7 Pharmacogenetics

6.7.1 Collection of pharmacogenetic samples

The blood sample for genetic research will be obtained from the subjects at Visit 2 after randomisation. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an adverse event (AE), such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume see Section 7.1.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

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

Table 5 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	5	1	**5**
	Haematology	2	1	**2**
Pharmocokinetic		2	16	**32**
VerifyNow™ $P2Y_{12}$		2	32	**64**
Discard sample prior to PD sample		2	16	**32**
Pharmacogenetics		9	1	**9**
Pregnancy		5	1	**5**
Total				**149**

7.2 Handling, storage and destruction of biological samples

7.2.1 Pharmacokinetic and/or pharmacodynamic samples

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

7.2.2 Pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 25 years, from the date of the Last Subject's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

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

The samples and data for genetic analysis in this study will be single coded. The link between the subject enrolment/randomisation code and the DNA number will be maintained and stored

in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the subject has requested disposal/destruction of collected samples not yet analysed.

7.3 Labelling and shipment of biohazard samples

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

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

7.4 Chain of custody of biological samples

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

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

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

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

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

7.5 Withdrawal of informed consent for donated biological samples

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

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

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca

- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented

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

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

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

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Subject data protection

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

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

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

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

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

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

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

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

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

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

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

8.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject

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

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

- Determine the adequacy of the facilities

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

9.2 Training of study site personnel

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

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

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

9.3 Monitoring of the study

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

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

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

9.3.1 Source data

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

9.4 Study agreements

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

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

9.4.1 Archiving of study documents

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

9.5 Study timetable and end of study

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

The study is expected to start in 1Q2012 and to end by 1Q2013.

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 OR DELEGATE

Data management will be performed by [redacted].

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. The Medical Coding Team at ICON will perform all coding.

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 OR DELEGATE

11.1 Calculation or derivation of efficacy variable(s)

Not applicable.

11.2 Calculation or derivation of safety variable(s)

Not applicable.

11.2.1 Other significant adverse events (OAE)

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

11.3 Calculation or derivation of pharmacokinetic variables

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

Area under the plasma concentration-time curve from zero to 8 hours post-dose (AUC_{0-8}) may be calculated.

11.4 Calculation or derivation of pharmacodynamic variable(s)

$P2Y_{12}$ reaction units (PRU) will be measured by VerifyNow™ $P2Y_{12}$ assay. The PRU data will be presented in the following ways. The absolute PRU at each timepoint and the % $P2Y_{12}$ inhibition from BASE (PRU vs BASE PRU) at each timepoint. For analysis, the variable will be percent inhibition of the $P2Y_{12}$ receptor from baseline. It will be calculated as percent change from baseline (pre-treatment) PRU versus each timepoint post treatment.

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

Only data from patients in the PK/PD analysis set will be summarized and formally analysed. Graphical methods will be employed to explore possibilities for PK/PD modelling if appropriate a sigmoid E_{max} model may be used.

11.4.2 Population analysis of pharmacokinetic/pharmacodynamic variables

Not applicable.

11.5 Calculation or derivation of pharmacogenetic variables

The results will be provided in a separate report.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

12.1 Description of analysis sets

12.1.1 Pharmacodynamic analysis set

The pharmacodynamics analysis set will include all patients for whom PD data was available with no major protocol deviations thought to significantly affect the pharmacodynamics of ticagrelor or clopidogrel.

12.1.2 Safety analysis set

All subjects who received at least one dose of study medication will be included in the safety population. Throughout the safety results sections, erroneously treated subjects (eg, those randomised to treatment A but actually given treatment B) will be accounted for in the actual treatment group.

12.2 Methods of statistical analyses

All data from patients included in the pharmacodynamics (PD) analysis set will be summarized using descriptive statistics by sequence, treatment, period and time relative to dose. The primary analysis of the difference between ticagrelor and clopidogrel in PRUs at 2 hours will be analyzed using a mixed effect model with terms for period (I/II, treatment (A/B), pre-dose PRU, and a random effect for patient within sequence. Treatment level means will be estimated using least squares means and 2-sided 95% confidence intervals. Tests will be evaluated with a 2-sided alpha level of 0.05. Distribution assumptions underlying the analysis will be assessed by residual plots. If the assumptions are violated, a Wilcoxon signed rank test will be used.

Secondary analyses of PRUs at other time points will be analyzed with similar mixed effects models. Analyses will be done at 0.5, 8 hours after the loading dose. Separate analyses will be done for pre-dose, 2, 8 hours after last morning dose, and 12 hours after last evening dose for ticagrelor or 24 hours after last dose of clopidogrel. There will be secondary analyses of percentage change from baseline in PRUs and of percentage inhibition of platelet aggregation.

Safety will be evaluated using the safety analysis set. Adverse events will be reported as proportions of subjects with adverse events. Adverse events that lead to discontinuation will be summarized. Clinical labs and vital signs will be reported using descriptive statistics by treatment and protocol time point.

12.2.1 Outcome variables

12.2.1.1 Pharmacodynamic outcome variables

– **Primary outcome variables:**

- Inhibition of the $P2Y_{12}$ receptor at 2 hours after loading dose with ticagrelor compared with clopidogrel as measured by PRU from Verify Now™ in Hispanic patients.

– **Secondary outcome variables:**

-Inhibition of the $P2Y_{12}$ receptor at 0.5 and 8 hours after loading dose with ticagrelor compared with clopidogrel as measured by PRU from Verify Now™ in Hispanic patients.

-Inhibition of the $P2Y_{12}$ receptor at 2 hours, 8 hours and end of dosing interval after 7 days of administration with ticagrelor compared with clopidogrel as measured by PRU from Verify Now™ in Hispanic patients.

- Percent reduction in platelet $P2Y_{12}$ receptor activity measured by VerifyNow™ on $P2Y_{12}$ reaction units (PRU) measured by VerifyNow™ $P2Y_{12}$ assay, represented as percentage change from baseline (pre-treatment)

$$\%\ \text{Reduction from baseline} = \left(1 - \left[\frac{\text{PRU after study drug}}{\text{PRU at baseline}}\right]\right) \times 100\%$$

- Percentage inhibition of platelet aggregation as measured by Verify Now™ measured as change from BASE (on-treatment)

12.2.1.2 Safety outcome variables

- Adverse events, physical examination and vital signs

12.2.2 Interim analyses

An interim analysis will not be performed.

12.3 Determination of sample size

The primary outcome of this study is $P2Y_{12}$ receptor inhibition at 2 hours, as measured by PRUs using Verify Now™, comparing that measure after ticagrelor with that after clopidogrel. Calculations using 90% power, detection of a difference of 100 PRUs, a 2-sided alpha=0.05, and a correlation of 0.5 between paired observations yields a required sample size of 12 completed subjects. This assumes a standard deviation of 93 PRUs, which represents the largest variability for ticagrelor or clopidogrel observed in study D5130C00048 at time-points within the first 24 hours. This also assumes a correlation of 0.5 between paired observations.

Based on a need to enrol a cohort of sufficient size for clinical credibility and to evaluate $P2Y_{12}$ receptor inhibition at secondary timepoints and to collect potential adverse events, we plan to obtain 28 subjects completing the study; this yields >99% power to demonstrate the anticipated effect.

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

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 Major bleeding events

Major bleeding events should be managed according to accepted standard of care.

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

13.2 Minor bleeding events

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

13.3 Medical emergencies and AstraZeneca contacts

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

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

Name	Role in the study	Address & telephone number
[redacted]	Medical Advisor responsible for protocol implementation	[redacted]

13.4 Overdose

- 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 **within one day**, ie, immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

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

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

13.5 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

Women recruited into the study must be either post-menopausal or surgically sterile.

If a patient becomes pregnant, the patient should be discontinued from the study treatment and attend an End Of Treatment visit and be followed until study closure.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication.

However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to AstraZeneca on the "Pregnancy Outcomes Report" form.

13.5.1 Maternal exposure

Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur, the investigational product should be discontinued immediately and the pregnancy reported to AstraZeneca.

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

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

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

The same timelines apply when outcome information is available.

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Clinical Study Protocol
Appendix A

Drug Substance	Ticagrelor
Study Code	D5130L00012
Edition Number	1
[redacted]	[redacted]
Protocol Dated	[redacted]

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Randomized, Open-Label, Multiple Dose, Crossover, Multiple Center Study of the Antiplatelet Effects of Ticagrelor versus Clopidogrel in Hispanic Patients with Stable Coronary Artery Disease

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

[redacted]

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

ASTRAZENECA SIGNATURE(S)

A Randomized, Open-Label, Multiple Dose, Crossover, Multiple Center Study of the Antiplatelet Effects of Ticagrelor versus Clopidogrel in Hispanic Patients with Stable Coronary Artery Disease

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AstraZeneca Research and Development site representative

[redacted]

ASTRAZENECA SIGNATURE(S)

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[redacted]

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SIGNATURE OF PRINCIPAL INVESTIGATOR

A Randomized, Open-Label, Multiple Dose, Crossover, Multiple Center Study of the Antiplatelet Effects of Ticagrelor versus Clopidogrel in Hispanic Patients with Stable Coronary Artery Disease

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations and I ensure that all relevant site staff follows the instructions given in the latest version of the Laboratory Manual for Investigators

Centre No.: 001

Signature: [redacted]

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

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

AstraZeneca

Clinical Study Protocol Appendix D

Drug Substance	Ticagrelor
Study Code	D5130L00012
Appendix Edition Number	1
Appendix [redacted]	[redacted]

Appendix D
Pharmacogenetics Research

TABLE OF CONTENTS PAGE

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
LIMS	Laboratory information management system
PGx	Pharmacogenetics

1. BACKGROUND AND RATIONALE

AstraZeneca intends to perform genetic research in the ticagrelor clinical development programme to explore how genetic variations may affect the clinical parameters associated with ticagrelor. Likewise, the clinical programme may explore how genetic variations affect the clinical parameters of clopidogrel.

The benefits of being able to explore associations between genes and clinical outcomes within the clinical programme are potentially many and include: identifying markers of any observed pharmacokinetic variability of ticagrelor or clopidogrel, identifying markers of response to AZD6140 and/or clopidogrel, where the term response is used broadly to include efficacy, safety and tolerability, aiding in the understanding mechanisms of action of any safety signals that may become apparent during the study. Future research may suggest other genes or gene categories as candidates for influencing the response to ticagrelor/clopidogrel; thus, this genetic research may involve study of additional un-named genes or gene categories, as they relate to clinical response and/or drug action.

2. GENETIC RESEARCH OBJECTIVES

To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to ticagrelor and clopidogrel.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic research population

3.1.1 Study selection record

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

3.1.2 Inclusion criteria

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

- Provide informed consent for the genetic sampling and analyses.

3.1.3 Exclusion criteria

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

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

3.1.4 Discontinuation of subjects from this genetic research

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

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

3.2 Collection of samples for genetic research

The blood sample for genetic research will be obtained from the subjects at Visit 2 after randomisation. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2 it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

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

3.3 Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 25 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

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

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

with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

4. ETHICAL AND REGULATORY REQUIREMENTS

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

4.1 Informed consent

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue from the genetic aspect of the study at any time.

4.2 Subject data protection

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

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

5. DATA MANAGEMENT

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze the samples.

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

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

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

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

7. LIST OF REFERENCES (NOT APPLICABLE)