Clinical Study Protocol

Drug Substance	Ticagrelor
Study Code	D5130C00076
Edition Number	1
Date	

An Open-label, Randomised, 3-Period, 3-Treatment, Crossover, Single-centre, Single-dose, Bioavailability Study with Alternative Methods of Administration of Crushed Ticagrelor Tablets, 90 mg, Compared to Whole Ticagrelor Tablets, 90 mg, in Healthy Volunteers

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

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

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

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

AstraZeneca

PROTOCOL SYNOPSIS

An Open-label, Randomised, 3-Period, 3-Treatment, Crossover, Single-centre, Single-dose, Bioavailability Study with Alternative Methods of Administration of Crushed Ticagrelor Tablets, 90 mg, Compared to Whole Ticagrelor Tablets, 90 mg, in Healthy Volunteers

Investigator

Study centre and number of subjects planned

This study will be conducted at 1 study centre. Up to 36 healthy volunteers will be randomised to ensure evaluable data from at least 30 volunteers.

Study period	Phase of development
Estimated date of first volunteer enrolled	Phase I
Estimated date of last volunteer completed	

Objectives

Primary objective

To evaluate the bioavailability of the crushed ticagrelor tablets when administered orally or through nasogastric tubes, compared to whole ticagrelor tablets given orally by assessment of the area under the plasma concentration-time curve and maximum plasma concentration for both ticagrelor and AR-C124910XX, the active metabolite of ticagrelor.

Secondary objective

To examine the safety and tolerability of ticagrelor when administrated as dispersed tablets orally, dispersed tablets via nasogastric tube and as whole tablet orally by assessment of adverse events, safety laboratory variables, physical examination, electrocardiogram and vital signs.

Study design

This study is a single-centre, open-label, randomised, 3-period, 3-treatment crossover study in which healthy volunteers will receive single doses of ticagrelor in three different ways (treatment A, B, and C). A total of 36 healthy volunteers (male and female) will be randomised in this study to ensure that at least 30 volunteers are evaluable. The dose will be administrated as:

- Treatment A = Ticagrelor 90 mg (whole) tablet administered as a single oral dose (without chewing)=
- Treatment B = Ticagrelor 90 mg tablet crushed and suspended in water (test product)
- Treatment C = Dispersed ticagrelor 90 mg tablet suspended in water and administered through a nasogastric tube into the stomach (test product)=

There will be 3 treatment periods of 4 days each, with each period separated by a washout period of at least 7 days between doses. During each treatment period, the volunteer will stay at the study centre from the evening before administration of the investigational product (Day -1) until 48 hours (Day 3) after administration of the investigational product on Day 1. The follow-up procedures will be performed 5 to 10 days after the last dose in treatment period 3.

Target subject population

Healthy male and female volunteers aged 18 to 50 years (inclusive) who have a body mass index between 18 and 30 kg/m^2 (inclusive) and weigh at least 50 kg (110 pounds) and no more than 100 kg (220 lbs).

Investigational product, dosage and mode of administration

- Treatment A = Ticagrelor 90 mg (whole) tablet administered as a single oral dose (without chewing)
- Treatment B = Ticagrelor 90 mg tablet crushed and suspended in water (test product)
- Treatment C = Dispersed ticagrelor 90 mg tablet suspended in water and administered through a nasogastric tube into the stomach (test product)

Duration of treatment

The study will consist of screening 28 days prior to administration of the first dose; 3 treatment periods of 4 days each, with each period separated by a washout period of at least 7 days between doses; and a follow-up 5 to 10 days after the last dose. The total duration from enrolment of volunteers in the study to follow-up will be approximately 60 days.

Outcome variables:

- Pharmacokinetics

  The following pharmacokinetic parameters will be calculated for ticagrelor and its metabolite AR-C124910XX in plasma:

  - Observed maximum plasma concentration (C_{max})
  - Time of maximum concentration (t_{max})
  - Area under plasma concentration-time curve from zero (pre-dose) to the last quantifiable concentration [$AUC_{(0-t)}$]
  - Area under plasma concentration-time curve from zero (pre-dose) to infinity (AUC)
  - Apparent terminal half-life ($t_{1/2}$)

  Additionally, metabolite to parent ratios (AR-C124910XX : ticagrelor) will be computed for C_{max}, $AUC_{(0-t)}$, and AUC.

- Safety

  Adverse events, laboratory variables, vital signs, physical examination, and electrocardiogram (ECG).

Statistical methods

All safety and pharmacokinetic data recorded during the study will be listed and summarised as appropriate. Continuous variables will be summarised using descriptive statistics (n, mean, standard deviation, minimum, median, maximum) by treatment groups and by time points where applicable. Categorical variables will be summarised in frequency tables (frequency and proportion) by treatment group. Graphical presentations will be used as appropriate.

Ticagrelor and AR-C124910XX PK parameters AUC and C_{max} will be analysed using a mixed-effects model. The results will be presented as geometric least-squares means (95% CIs) and the ratios of geometric least-squares means (90% CIs). The treatment comparisons will be test (Treatments B or C) versus reference (Treatment A).

The safety, tolerability, adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) for system organ class and preferred term. Adverse events will be summarised by Preferred Term and System Organ Class using MedDRA vocabulary by treatment and across all treatments. Medications will be classified according to the AstraZeneca Drug Dictionary. Tabulations and listings of data for vital signs, clinical laboratory tests, ECGs, and physical examination will be presented. For clinical laboratory

tests, listings of values for each volunteer will be presented with abnormal or out-of-range values flagged.

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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 (CSP).

Abbreviation or special term	Explanation
ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
AE	Adverse event (see definition in Section 6.3.1)
ALP	Alkaline phophatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$\%AUC_{ex}$	Percent of area extrapolated for area under the plasma concentration-time curve from zero to infinity
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from zero to the last quantifiable concentration
B	Blood
BLQ	Below limit of quantitation
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CI	Confidence intervals
C_{max}	Observed maximum plasma concentration
CPA	Clinical Pharmacology Alliance
CPTP	Cyclopentyltriazolopyrimidine
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV%	Co-efficient of variation
CYP	Cytochrome P450
DAE	Discontinuation of investigational product due to adverse event

Abbreviation or special term	Explanation
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GCV%	Geometric coefficient of variation
GMP	Good Manufacturing Practice
GRand	AstraZeneca global randomisation system
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IATA	International Air Transport Association
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IPA	Inhibition of platelet aggregation
λ_z	Apparent terminal rate constant
LC-MS	Liquid chromatography and mass spectrometry
LIMS	Laboratory Information Management System
LLOQ	Lower limit of quantification
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
min	Minimum
MTD	Maximum tolerated dose
NA	Not applicable
NB	Nota bene (Latin for note well)
ND	Not determined
NQ	Non-quantifiable
NSAIDs	Non-steroidal anti-inflammatory drugs
INR	International normalised ratio
NSTEMI	Non-ST segment elevation myocardial infarction

Abbreviation or special term	Explanation
$P2Y_{12}$	A G protein-coupled purinergic receptor found mainly on the surface of blood platelet cells and is an important regulator in blood clotting
PK	Pharmacokinetics
PLATO	A study of platelet inhibition and patient outcomes (AstraZeneca Study D51305262)
PT	Prothrombin time
QP	Qualified person
R&D	Research and Development
Rsq	Regression coefficient
S	Serum
SAE	Serious adverse event (see definition in Section 6.3.2).
SD	Standard deviation
SOC	System organ class
STEMI	ST segment elevation myocardial infarction
SUSARs	Suspected unexpected serious adverse reactions
$t_{1/2}$	Apparent terminal half-life
t_{max}	Time of maximum plasma concentration
TT	Thrombin time
U	Urine
UA	Unstable angina
ULN	Upper limit of normal

1. INTRODUCTION

1.1 Background

Atherosclerosis is a progressive disease of the large conduit arteries. It is a worldwide public health concern, primarily due to the death and disability caused through its clinical manifestations as coronary (eg, unstable angina [UA] and myocardial infarction [MI]) and cerebral (eg, stroke and transient ischemic attack) thrombotic events. The term "acute coronary syndromes" (ACS) encompasses a range of clinical conditions that includes UA, non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI). The process central to ACS is disruption or erosion of an atherosclerotic plaque, ultimately leading to the promotion of platelet aggregation and a thrombus.

Ticagrelor (BRILINTA™, BRILIQUE™) is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in subjects with ACS. Ticagrelor has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI or stroke compared to clopidogrel. The difference between treatments was driven by cardiovascular deaths and MIs with no difference in stroke. In subjects treated with percutaneous coronary intervention, it also reduces the rate of stent thrombosis.

BRILINTA™ was approved on 20 July 2011 to reduce the rate of thrombotic cardiovascular events in patients with ACS (UA, NSTEMI, or STEMI).

1.2 Summary of relevant preclinical and clinical information

Adenosine diphosphate (ADP) is one of the primary mediators of platelet aggregation, and inhibition of ADP mediated platelet aggregation by clopidogrel in combination with acetylsalicylic acid (ASA) has been shown to provide improved efficacy over ASA therapy alone in ACS, with a favourable bleeding profile. However, clopidogrel has a slow onset of action, irreversibly binds to its receptor resulting in a slow offset of effect, and often has incomplete and variable inhibition of platelet aggregation (IPA) from patient to patient.

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. The goal of the ticagrelor phase III programme was to demonstrate substantial improvements in clinical efficacy (ie, clinical thrombotic event reduction) with an acceptable safety profile compared with currently available antiplatelet therapies (ie, ASA and clopidogrel). Most patients took concomitant ASA with ticagrelor. Inhibition of platelet aggregation mediated by ticagrelor increases with increasing plasma concentrations of ticagrelor and its active metabolite, AR-C124910XX, until almost complete inhibition is obtained. Ticagrelor has a more rapid onset, higher and less variable inter-patient IPA, and faster offset compared to clinical doses of clopidogrel.

The focus of the clinical pharmacology program for ticagrelor, has been to examine the exposure-response relationship, investigate safety, and characterise drug interactions. The

pharmacokinetics (PK) of ticagrelor, as well as the metabolism of the compound, has been characterised in healthy subjects and patients with coronary heart disease. The dose range of ticagrelor administered during these studies was 0.1 to 1260 mg, and 900 mg was established as the maximum tolerated dose (MTD) in healthy subjects.

1.3 Rationale for conducting this study

Alternative ways of administering a tablet are useful to help patients who, for different reasons, have difficulties with swallowing a whole tablet. Administration of dispersed tablets suspended in water is a common way of administering drugs to these patients. A useful method in patients whose condition prevents swallowing is administration of dispersed tablets through nasogastric tubes.

The purpose of this study is to evaluate the bioavailability of two alternative methods of administration of crushed ticagrelor tablets compared to whole ticagrelor tablets in healthy volunteers. The results of this study will define the alternative ways of administration of ticagrelor tablets.

1.4 Benefit/risk and ethical assessment

There are no direct benefits for the volunteers participating in this study. However, study related health assessments are provided at no cost.

As a consequence of the pharmacological properties of ticagrelor, there is an increased risk for bleeding. However, in this study as only a single dose is administered in each treatment period (within the therapeutic dose range) with adequate washout between the treatment periods, the risk for bleeding has been minimised. Moreover the inclusion and exclusion criteria have considered the contraindication and warning suggested by regulatory approved prescribing information.

Ticagrelor, like other inhibitors of platelet aggregation, increases the risk of bleeding. Reported events in previous Phase II and Phase III studies have included bleeding in areas considered to be clinically important such as the lung, brain, eye, and joints. In previous studies in healthy volunteers, adverse events (AEs) associated with bleeding were infrequent and were generally considered to be mild. In this study, necessary measures will be taken to minimise this risk of bleeding by excluding volunteers at high risk of bleeding such as volunteers with history of haemophilia, von Willebrand's disease, lupus anticoagulant, or other diseases/syndromes that can either alter or increase the propensity for bleeding. Also volunteers with a history of a clinically significant nontraumatic bleed or clinically significant bleeding risk, as judged by the Investigator, will be excluded.

The risk of ticagrelor exposure to volunteers in this study is expected to be equivalent to the safety profile in volunteers observed in previous Phase I studies where similar doses have been administered. The most common AEs, with an incidence of at least 2%, reported to date in the Phase I studies with at least 3 days of ticagrelor dosing include headache, somnolence, dizziness, epistaxis, nausea, abdominal pain, back pain, dyspnoea, ecchymosis, lethargy,

pharyngolaryngeal pain, blurred vision, postural dizziness, pollakiuria (frequent urination), and increased tendency for bruising.

Ticagrelor is well tolerated in single doses up to 900 mg and multiple doses up to 600 mg per day. The highest single dose studied was 1260 mg where adverse gastrointestinal effects limited tolerability and therefore established 900 mg as the maximum tolerated dose.

Dyspnoea was observed in patients with coronary artery disease (CAD) but rarely in healthy subjects. Ticagrelor does not appear to affect respiratory parameters in elderly subjects, patients with asthma or chronic obstructive pulmonary disease, and stable CAD patients.

When ticagrelor was administered orally to healthy subjects for 5 days under controlled conditions of diet, activity, and fluid intake, serum uric acid levels increased approximately by 10%, with no extreme individual elevations, and returned to baseline within 60 hours of discontinuing ticagrelor.

Ticagrelor (single 900 mg dose) had no cardiac ventricular repolarisation effect during the first 24 hours after administration compared with placebo as assessed by QT interval. In the PLATO study, more patients had ventricular pauses >3 seconds with ticagrelor than with clopidogrel, however, there were no adverse clinical consequences associated with this imbalance (including pacemaker insertions) in this population of patients.

For further relevant pre-clinical and clinical data see the current Investigator's Brochure.

In addition, this study requires application of a nasogastric tube and nose bleeding is not an uncommon effect with nasogastric tube insertion, therefore nasogastric tube will be applied by someone with experience. AstraZeneca will immediately notify the Investigator of important safety data that becomes available during the study.

2. STUDY OBJECTIVES

2.1 Primary objective

To evaluate the bioavailability of the crushed ticagrelor tablets when administered orally or through nasogastric tubes as aqueous solution, compared to whole ticagrelor tablets given orally by assessment of the area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}) for both ticagrelor and AR-C124910XX, the active metabolite of ticagrelor.

2.2 Secondary objectives

To examine the safety and tolerability of ticagrelor when administrated as dispersed tablets orally, dispersed tablets via nasogastric tube and as whole tablet orally by assessment of AEs, safety laboratory variables, physical examination, electrocardiogram (ECG) and vital signs.

3. STUDY PLAN AND PROCEDURES

This CSP has been subject to a peer review according to AstraZeneca Standard Operating Procedures.

3.1 Overall study design and flow chart

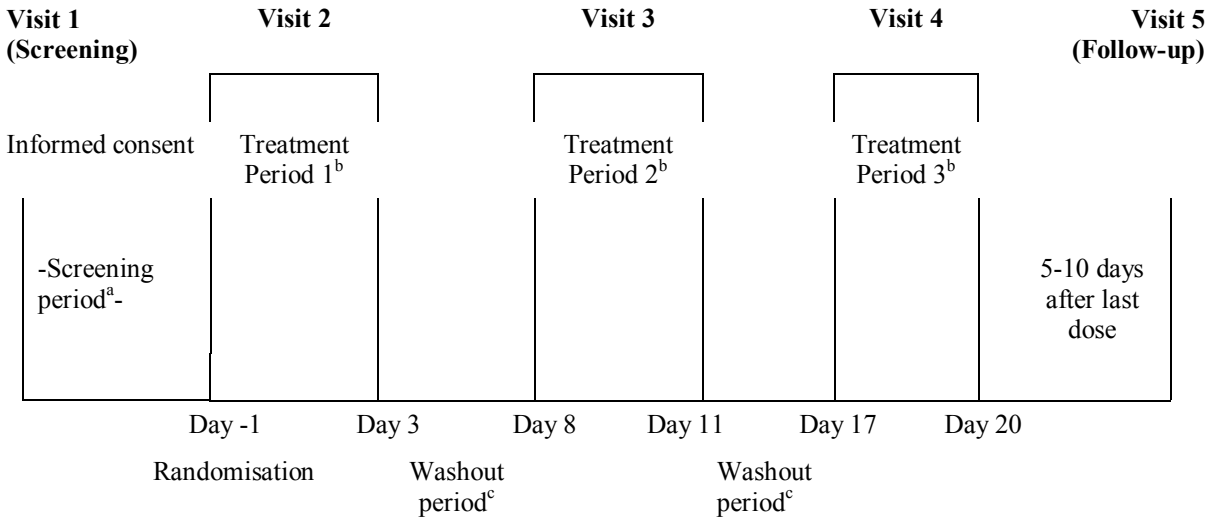
This study is a single-centre, open-label, randomised, 3-period, 3-treatment crossover study in which healthy volunteers will receive single doses of ticagrelor in three different ways (treatment A, B, and C). The dose will be administrated as

- Treatment A = Ticagrelor 90 mg (whole) tablet administered as a single oral dose
- Treatment B = Ticagrelor 90 mg tablet crushed and suspended in water (test product)
- Treatment C = Dispersed ticagrelor 90 mg tablet suspended in water and administered through a nasogastric tube into the stomach (test product)

Up to 36 healthy volunteers, males and females between the ages of 18 and 50 years (inclusive) will be randomised to ensure that at least 30 volunteers are evaluable at the end of the study.

There will be 3 treatment periods of 4 days each, with each period separated by a washout period of at least 7 days between doses. During each treatment period, the volunteer will stay at the study centre from the evening before administration of the investigational product (Day -1) until 48 hours (Day 3) after administration of the investigational product on Day 1. The follow-up procedures will be performed 5 to 10 days after the last dose in treatment period 3. A study flow chart is provided in Figure 1 and the study plan is presented in Table 1

Figure 1 Study flow chart



[a] Up to 28 days before first study day
[b] Administration of the investigational product according to randomisation; either Treatment A, Treatment B or Treatment C.
[c] at least 7 days
Treatment A: Ticagrelor 90 mg (whole) tablet administered as a single oral dose
Treatment B: Ticagrelor 90 mg tablet crushed and suspended in water
Treatment C: Dispersed ticagrelor 90 mg tablet suspended in water and administered through a nasogastric tube into the stomach

Table 1 Study plan

Assessment	Visit 1	Visit 2, 3, 4				Visit 5
	Screening visit Up to 28 days before first study day	**Day -1** Day before treatment	**Day 1** Treatment day	**Day 2** 24 hours after treatment	**Day 3** 48 hours after treatment	**Follow-up** (5 to 10 days after last dose)
Informed consent	X					
Demographics	X					
Inclusion and exclusion criteria	X	X[a]				
Medical and surgical history	X	X[b]				
Complete physical examination[d]	X					X
Brief physical examination		X[c]			X	
12-Lead electrocardiogram	X				X	X
Vital signs (blood pressure and pulse rate)	X	X[e]	X[e]	X[e]	X	X
Safety laboratory assessments	X	X[c,f]			X	X
PT and aPTT		X			X	
Assessment of FSH[g]	X					
Virology screen[h]	X					
Pregnancy test[i]	X	X[c]				X
Drugs of abuse screen	X	X[c]				
Urine alcohol test	X	X[c]				
Randomisation[j]			X			
Ticagrelor dose administration			X			
Ticagrelor pharmacokinetic sampling[k]			X	X	X	

Assessment	Visit 1	Visit 2, 3, 4				Visit 5
	Screening visit Up to 28 days before first study day	**Day -1** Day before treatment	**Day 1** Treatment day	**Day 2** 24 hours after treatment	**Day 3** 48 hours after treatment	**Follow-up** (5 to 10 days after last dose)
Recording of concomitant medication		X	X	X	X	X
Adverse event monitoring[l]	X	X	X	X	X	X
Confinement to study centre		X[m]	X[m]	X[m]	X[m]	
Insertion and removal of nasogastric tube			X[n]			

The study plan is applicable to all treatment periods.
FSH: Follicle-stimulating hormone; aPTT: Activated partial thromboplastin time; PT: Prothrombin time; TT: Thrombin time

[a] Inclusion and exclusion criteria will be checked within 24 hours prior to administration of the investigational product during treatment period 1 only.
[b] Updating of medical/surgical history to be done on Day -1 of treatment period 1 only.
[c] To be performed within 24 hours prior to administration of the investigational product in each treatment period.
[d] Complete physical examination at screening and follow-up. Height (centimetres) and weight kilograms) and BMI will be measured at screening only
[e] Vital signs will be recorded at screening, pre-dose, 1 hour, 3, 6, 12 and 24 hours post-dose, Day 3 for all treatment periods and follow-up visit
[f] Safety laboratory assessments should be analysed and checked before randomisation.
[g] In self declared post-menopausal female volunteers only
[h] Includes hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) screens.
[i] For female volunteers only; urine pregnancy test will be performed at screening, Day -1 (all treatment periods) and at follow-up.
[j] Will occur on Day 1 of treatment period 1.
[k] Pharmacokinetic blood sampling will be done at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours post-dose for determination of ticagrelor and AR-C124910XX concentrations in plasma.
[l] Serious adverse events (SAEs) will be collected from the time of obtaining informed consent through to the follow-up visit. All other AEs will be collected from the time of the first dose on Day 1 (treatment period 1) through to the follow-up visit.
[m] Discharge from the study centre will be after the PK sampling at 48 hours post-dose is obtained.
[n] According to randomised treatment.

3.2 Rationale for study design, doses and control groups

A randomised crossover design has been chosen to minimise the effects of between-volunteer variability and any period effects on the overall results. The study is open-label since the primary objective is to study the bioavailability of two alternative methods of administration of crushed ticagrelor tablets compared to whole ticagrelor tablets in healthy volunteers. This study is designed in accordance with the US Food and Drug Administration (FDA) Guidance for Bioavalability and Bioequivalence (Guidance for Industry 2003, EMEA Guidance for BA 2010).

Ticagrelor will be administered as single dose, 90 mg. This is the only dose strength that is commercially available and will provide sufficient plasma exposure for the PK analyses of ticagrelor and AR-C124910XX.

Ticagrelor is rapidly absorbed following oral dosing and the half-life is 5.9 to 8.4 hours for ticagrelor and 5.9 to 20 hours for AR-C124910XX. Pharmacokinetic sampling will be performed in each dosing period and the PK sampling for up to 48 hours after the morning dose is judged to be sufficient to fulfil the objectives of the study. A 7-day washout between treatment periods minimises the risk of carry-over in this study.

4. SUBJECT SELECTION CRITERIA

The Investigator should keep a record, the volunteer screening log, of volunteers who entered pre-study screening.

Each volunteer 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 volunteers should fulfil the following criteria:

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

2. Healthy male and female volunteers aged 18 to 50 years (inclusive) with suitable veins for cannulation or repeated venepuncture

3. Female volunteers must have a negative pregnancy test at screening and on admission to the study centre, must not be lactating and be using (confirmed by the Investigator) a highly effective form of birth control from the time of signing the informed consent and be willing to use a highly effective form of birth control during the study until last follow up visit to the study centre. Highly effective forms of birth control are listed in Appendix E. Females of non-childbearing potential are defined as:

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

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

4. Male volunteers should be willing to use barrier contraception ie, condoms, from the first dose of the investigational product until 3 months after the last dose of the investigational product

5. Have a body mass index between 18 and 30 kg/m^2 (inclusive) and weigh at least 50 kg (110 pounds [lbs]) and no more than 100 kg (220 lbs).

4.2 Exclusion criteria

Volunteers should not enter the study if any of the following exclusion criteria is fulfilled:

1. History of any clinically significant disease or disorder which, in the opinion of the Investigator, may either put the volunteer at risk because of participation in the study, or influence the results or the volunteer's ability to participate in the study

2. History or presence of gastrointestinal, hepatic or renal disease or any other condition known to interfere with absorption, distribution, metabolism or excretion of the investigational product

3. Any clinically significant illness, medical/surgical procedure or trauma within 4 weeks of the first administration of the investigational product

4. Any clinically significant abnormalities in clinical chemistry, haematology, urinalysis, results as judged by the Investigator

5. Any positive result on screening for serum hepatitis B surface antigen (HBsAg), antibodies against hepatitis C virus (HCV) and human immunodeficiency virus (HIV)

6. Abnormal vital signs, after 10 minutes supine rest, defined as any of the following:

   - Systolic blood pressure (BP) <90 mmHg or ≥ 140 mmHg

   - Diastolic BP <50 mmHg or ≥ 90 mmHg

   - Heart rate <40 or >85 beats per minute.

7. Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG that may interfere with the interpretation of QTc interval changes. This includes volunteers with any of the following:

   - Clinically significant PR (PQ) interval prolongation
   - Intermittent second or third degree atrioventricular block
   - Incomplete, full or intermittent bundle branch block (QRS <110 ms with normal QRS and T wave morphology is acceptable if there is no evidence of left ventricular hypertrophy)
   - Abnormal T wave morphology, particularly in the protocol defined primary lead.

8. Prolonged QTcF >450 ms or shortened QTcF <340 ms or family history of long QT syndrome

9. Known or suspected history of drug abuse as judged by the Investigator

10. Volunteers who smoke 10 or more cigarettes per day and/or unable to abstain from smoking during the residential stay in the study centre

11. History of alcohol abuse or excessive intake of alcohol as judged by the Investigator

12. Positive screen for drugs of abuse at screening or on admission to the study centre or positive screen for alcohol at screening and on admission to the study centre prior to the administration of the investigational product

13. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the Investigator or history of hypersensitivity to drugs with a similar chemical structure or class to ticagrelor or its metabolite AR-C124910XX

14. Excessive intake of caffeine-containing drinks eg, coffee, tea, caffeine-containing energy drinks and cola (more than 5 cups of coffee or equivalent per day)

15. Use of drugs with enzyme inducing properties (including particular attention to those that are known to inhibit or induce cytochrome P450 [CYP] 3A isoenzymes, such as St John's Wort) within 3 weeks prior to the first administration of the investigational product

16. Use of any prescribed or non-prescribed medication including antacids, analgesics other than paracetamol/acetaminophen during the two weeks prior to the first administration of the investigational product or longer if the medication has a long half-life. Use of systemic contraceptives as described in Appendix E, and occasional use of paracetamol/acetaminophen is allowed for minor pains and headache prior to first dose

17. Any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade or other products containing grapefruit or Seville oranges within 7 days of the first administration of the investigational product

18. Plasma donation within one month of screening or any blood donation/blood loss >500 mL during the 3 months prior to screening

19. Has received another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment within 90 days of the first administration of the investigational product in this study. The period of exclusion begins at the time of the last visit of the prior study. Note: Volunteers consented and screened, but not administered the investigational product in this study or a previous Phase I study, are not excluded

20. History of haemophilia, von Willebrand's disease, lupus anticoagulant or other diseases/syndromes that can either alter or increase the propensity for bleeding

21. A personal history of vascular abnormalities including aneurysms; a personal history of severe haemorrhage, haematemesis, melena, haemoptysis, severe epistaxis, severe thrombocytopenia, intracranial haemorrhage; or rectal bleeding within 3 months prior to the screening visit; or history suggestive of peptic ulcer disease

22. Having undergone any non-minor surgical procedure during the last 3 months

23. History of frequent and/or significant nose bleed or clinically significant non-traumatic bleed, bruise/haematoma or any other clinically significant bleeding risk, as judged by the Investigator

24. Previous randomisation to treatment in the present study

25. Involvement of any /third party contractor or AstraZeneca employee and their close relatives regardless of their role

26. Judgment by the Investigator that the volunteer should not participate in the study if they have any ongoing or recent (ie, during the screening period) minor medical complaints that may interfere with the interpretation of study data or are considered unlikely to comply with study procedures, restrictions and requirements.

27. Volunteers who cannot communicate reliably with the Investigator

Procedures for withdrawal of incorrectly enrolled volunteers see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

1. Fast from at least 10 hours before planned start of administration of the investigational product on Day 1. A moderate amount (not more than 200 mL) of water is allowed up to 1 hour prior to administration of the investigational product and may be resumed 2 hours after administration of the investigational product. A meal can be given 4 hours after administration of the investigational product

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

3. Abstain from consuming any of the following:

   - Alcohol from 72 hours before admission to the study centre, during the residential period and for 72 hours before the study follow-up visit

   - Energy drinks containing taurine or glucuronolactone eg, from 72 hours before admission, during the residential period and for 72 hours before the study follow-up visit

   - Caffeine-containing drinks during the residential period apart from any provided as part of a standardised meal. Excessive intake of caffeine should be avoided between discharge from the study centre and the study follow-up visit

   - Poppy seeds found in speciality bread from time of consent until after the final medical examination at the study follow-up

   - Grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade or other products containing grapefruit or Seville oranges from 7 days before admission until after the final medical examination at the study follow-up

4. Abstain from nicotine use and smoking during the residential stay in the study centre

5. Abstain from drugs of abuse from time of consent until after the final medical examination at the study follow-up

6. Abstain from taking any medication (prescribed or over the counter products), other than paracetamol/acetaminophen from two weeks prior to the first administration of the investigational product until after the final medical examination at the study follow-up. Note: Use of systemic contraceptives as described in Appendix E, and occasional use of paracetamol/acetaminophen is allowed for minor pains and headache during the study. However, this should not obviate necessary medical treatment. If any medication is necessary during the residential period, it should be

prescribed by the Investigator and the AstraZeneca Clinical Pharmacology Alliance (CPA) Physician should be informed

7. Volunteers should refrain from strenuous physical activity, which is not within the volunteer's normal daily routine, from 7 days prior to admission to the study centre until after the final medical examination at the study follow-up

8. Abstain from blood or plasma donation until 3 months after the final medical examination at the study follow-up

9. Male volunteers should use a condom to prevent pregnancy and drug exposure of a partner and refrain from donating sperm or fathering a child from the time of signing the informed consent until the last follow-up visit to the study centre

10. Female volunteers should be using (confirmed by the Investigator) a highly effective form of birth control from the time of signing the informed consent until the last follow-up visit to the study centre. Highly effective forms of birth control are listed in Appendix E

11. Refrain from the use of aspirin or any other drug known to increase the propensity for bleeding from 7 days prior to Day 1 of treatment period 1 through completion of the follow-up visit (Visit 5)

12. Refrain from the use of non-steroidal anti-inflammatory drugs (NSAIDs; including ibuprofen) from 3 days prior to Day 1 of treatment period 1 through completion of the follow-up (Visit 5)

13. Refrain from the use of prescribed medication (including particular attention to those that are known to inhibit or induce cytochrome P450 [CYP] 3A isoenzymes, such as St John's Wort) from 3 weeks prior to the first administration of the investigational product through completion of the follow-up visit

14. Refrain from scheduling or having surgery, including dental surgery, at anytime following the screening visit (Visit 1) and through completion of the follow-up visit (Visit 5).

5.2 Subject enrolment and randomisation and initiation of investigational product

The Investigator will:

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

2. Assign potential volunteer a unique enrolment number, beginning with eg, 'E0001001'

3. Determine volunteer eligibility. See Sections 4.1 and 4.2

4. Assign eligible volunteer unique randomisation code (volunteer number), beginning with 1001.

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

5.2.1 Procedures for randomisation

The randomisation scheme will be generated by using the AstraZeneca global randomisation system (GRand). Utilizing a Williams design, healthy volunteers will be randomised to 1 of 6 treatment sequences in a 1:1 ratio on Day 1 of the treatment period 1 (Visit 2).

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

5.3 Procedures for handling subjects incorrectly enrolled or randomised or initiated on investigational product

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

Where volunteers who do not meet the selection criteria are randomised in error or incorrectly started on treatment, or where volunteers subsequently fail to meet the study criteria post-initiation, a discussion should occur between the AstraZeneca CPA Physician and the Investigator regarding whether to continue or discontinue the volunteer from the investigational product.

For volunteers where there is deviation from the planned randomised sequence, they will be included and analysed according to the actual treatment sequence received.

The AstraZeneca CPA Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, further administration of the investigational product should be stopped.

5.4 Blinding and procedures for unblinding the study

This is an open-label study and therefore this section is not applicable.

5.5 Treatments

5.5.1 Identity of investigational product

The investigational product used in this study is presented in Table 2.

Table 2 Identity of investigational product

Investigational product	Dosage form and strength	Manufacturer
Ticagrelor	90 mg tablets	AstraZeneca

The investigational product is supplied to by AstraZeneca, Sweden as study qualified person (QP) released specific labelled bulk. The personnel will prepare the investigational product for each healthy volunteer according to the Handling Instructions provided by AstraZeneca and the randomisation scheme. will be the final QP releasing site.

5.5.2 Doses and treatment regimens

Investigational product, dosage and mode of administration

Each healthy volunteer will receive a single dose of ticagrelor in three different ways.

A. Ticagrelor 90 mg as a whole tablet. The ticagrelor tablet should be swallowed whole with 200 mL room temperature water and should not be split, chewed or crushed.

B. Crushed ticagrelor 90 mg tablet suspended in water according to handling instructions, administered as a single oral dose with 200 mL water, including 75 mL used to rinse the container (3 rinses of 25 mL each) used for dose preparation.

C. A crushed ticagrelor 90mg tablet, suspended in water and administered through a nasogastric tube into the stomach. The total volume of water used for investigational product administration will be 200 mL including 75 mL of water to rinse the container (3 rinses of 25 mL each) used for preparation of dose and 25 mL of water used to flush the nasogastric tube.

For administration via nasogastric tube, the tablet should be crushed and mixed with water. The suspension should be drawn into a syringe and infused into the nasogastric tube.

The time point of the last drop of water consumed (orally) or injected through the nasogastric tube for investigational product administration will be considered as the timing for administration of the investigational product.

5.5.3 Labelling

The bulk bottles will be labelled by AstraZeneca Research and Development (R&D) Mölndal, Sweden according to Good Manufacturing Practice (GMP). Labels will fulfil GMP Annex 13 requirements for labelling and all local regulatory requirements. The dose containers will be

supplied and labelled by . The dose container labels will be supplied by AstraZeneca. The containers will be labelled with a 2 panel label. One part of the label will be permanently affixed to the container and the other part will be peel-off part for insertion in the healthy volunteer's electronic Case Report Form (eCRF).

5.5.4 Storage

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

The dispensing and retention of reserve samples of the investigational product will be performed with the FDA Code of Federal Regulations 21, Part 320 Bioavailability and Bioequivalence requirements (Guidance for Industry 2003).

5.6 Concomitant and post-study treatment(s)

No concomitant medication or therapy will be allowed except for systemic contraceptives as described in Appendix E and occasional use of paracetamol/acetaminophen is allowed for minor pains and headache during the study. No other prescription or over-the-counter drugs are allowed as specified in the exclusion criteria and restrictions. The volunteers must be instructed that no additional medication will be allowed without the prior consent of the Investigator.

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

5.7 Treatment compliance

The administration of the investigational product should be recorded in the appropriate sections of the eCRF.

5.7.1 Accountability

The investigational product provided for this study will be used only as directed in the CSP. The study personnel will account for all study drugs dispensed to and returned from the healthy volunteer.

Study site personnel will account for all study drugs received at the study centre, unused study drugs and for appropriate destruction. Destruction must not take place unless the responsible at AstraZeneca has approved it. Certificates of delivery and destruction must be signed.

5.8 Discontinuation of investigational product

Volunteers may be discontinued from investigational product and assessments in the following situations:

- Volunteer decision. The volunteer is at any time free to discontinue treatment, without prejudice to further treatment

- Adverse Events (including inter-current illness), laboratory variable, vital signs measurement, or ECG changes are seen during or after administration of the investigational product which would indicate that any further administration may have an impact on the safety of the volunteer, administration must be stopped or further study treatment must be discontinued, in particular for laboratory values of special interest

- Risk to volunteers as judged by the Investigator and/or AstraZeneca

- Severe non-compliance to study protocol as judged by the Investigator and/or AstraZeneca

- Volunteers who do not meet the selection criteria are randomised in error or incorrectly started on treatment, or where volunteers subsequently fail to meet the study criteria post-initiation (a discussion should occur between the AstraZeneca CPA Physician and the Investigator regarding whether to continue or discontinue the volunteer from the investigational product).

5.8.1 Procedures for discontinuation of a subject from investigational product

A volunteer that decides to discontinue the investigational product will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by the Investigator. Adverse events will be followed up (See Sections 6.3.3 and 6.3.4).

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

5.9 Withdrawal from study

Volunteers are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such volunteers will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by the Investigator. Adverse events will be followed up (See Sections 6.3.3 and 6.3.4).

At the discretion of AstraZeneca, volunteers that withdraw from the study may be replaced.

6. COLLECTION OF STUDY VARIABLES

Refer to Table 1 for the study assessments. When more than 1 assessment is required at a particular time point, PK samples should be prioritised.

6.1 Recording of data

The Investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

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

6.2 Data collection at enrolment and follow-up

6.2.1 Enrolment procedures

Each volunteer will undergo screening to confirm eligibility. This will consist of the following:

- Obtaining written informed consent before starting any study-specific procedures
- Review of the inclusion/exclusion criteria with the volunteer
- Recording of demographic data (date of birth, age and gender)
- A standard recording of relevant medical and surgical history
- A complete physical examination
- Height, weight, and calculation of BMI
- 12-Lead paper ECG
- Vital signs (BP and pulse rate)
- Blood sampling for routine clinical chemistry and haematology measurements, for FSH assessment (in self declared post-menopausal female volunteers) and a HBsAg, antibodies to HCV, and HIV screen
- Urine sampling for routine urinalysis
- Urine pregnancy test in female volunteers only
- Urine sampling for drugs of abuse and alcohol screening
- Adverse events and serious adverse events (SAEs) will be recorded (if any)
- Prior and concomitant medication recording (done on Day -1)
- After admission and before randomisation the investigator should reassess each volunteer to reconfirm eligibility.

6.2.2 Follow-up procedures

Volunteers will return to the study centre for follow-up 5 to 10 days after the last dose of the investigational product. The follow-up visit will include the following:

- A complete physical examination
- 12-Lead paper ECG
- Vital signs (BP and pulse rate)
- Blood sampling for routine clinical chemistry and haematology measurements
- Urine sampling for routine urinalysis
- Urine pregnancy test in female volunteers only
- Concomitant medication recording
- Adverse events and SAEs will be recorded.

6.3 Safety

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

6.3.1 Definition of adverse events

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

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

6.3.2 Definitions of serious adverse event

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

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

- 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 volunteer or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of an SAE, see Appendix B to the CSP.

6.3.3 Recording of adverse events

Time period for collection of adverse events

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

All SAEs will be recorded from the time of informed consent.

Follow-up of unresolved adverse events

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

Variables

The following variables will be collected for each AE;

- Adverse event (verbatim)
- The date and time when the AE started and stopped
- Intensity, rated according to the following scale:
  - Mild (awareness of sign or symptom, but easily tolerated)
  - Moderate (disturbing but still tolerable)
  - Severe (incapacitating, with inability to perform normal activities).
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to the investigational product
- Adverse event caused the volunteer'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
- Adverse event is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.3.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an 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 an SAE.

Causality collection

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

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

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

Adverse Events based on signs and symptoms

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

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the Clinical Study Report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs or ECG should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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

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

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

6.3.4 Reporting of serious adverse events

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

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

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

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. The Investigator 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 24 hours** of when he or she becomes aware of it.

The reference document for definition of expectedness/listedness is the investigator brochure for the ticagrelor.

6.3.5 Laboratory safety assessment

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

The safety laboratory variables are presented in Table 3.

Table 3 Safety laboratory assessments

Clinical chemistry	Haematology	Urinalysis
Serum (S)-albumin	Blood (B)-haemoglobin	Urine (U)-glucose
S-alkaline phosphatase	B-leucocyte	U-haemoglobin
S-aspartate aminotransfersase	B-absolute leucocyte differential count	U-protein
S-alanine aminotransferase	B-platelet count	U-pregnancy
S-FSH[a]		Urine drug and alcohol screen
S-calcium, total		
S-creatinine		
S-fasting glucose		
S-potassium		
S-sodium		
S-bilirubin, total		
Coagulation		
International normalised ratio (INR)		
Activated partial thrombin time (aPTT)		
Thrombin time (TT)		
Partial prothrombin time (PT)		

[a] self declared post-menopausal females volunteers only
FSH Follicle-stimulating hormone

Volunteers will also be screened for HBsAg, HCV antibody, HIV and drugs of abuse at the time points presented in Table 1. Drugs of abuse include: amphetamines, barbiturates, benzodiazepines, tricyclic antidepressants, cocaine, methadone, phencyclidine,

tetrahydrocannabinol, and opiates. The test will be performed at the study centre. If a volunteer tests positive for drugs of abuse, a retest will be performed and they may be excluded from entering the study, as judged by the Investigator. Urine alcohol screening will be performed at screening visit (Visit 1) and on Day -1 (day before administration of the investigational product for all the treatment periods). Urine pregnancy test will be performed on female volunteers at screening visit (Visit 1), Day -1 (day before administration of the investigational product for all the treatment periods) and at the follow-up visit (Visit 5).

Laboratory values outside the reference limit suspected to be of any clinical significance will be repeated. Volunteers in who suspected clinical significance is confirmed will either not be included or if already enrolled will be followed until normalisation or for as long as the Investigator considers necessary. Additional laboratory variables may be performed for safety reasons if judged appropriate by the Investigator.

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

For blood volume see Section 7.1.

6.3.6 Physical examination

A complete physical examination will be performed at the screening visit (Visit 1) and at the follow-up visit (Visit 5), and will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

A brief physical examination will be performed on Day -1 (day before administration of the investigational product for all the treatment periods) and before discharge from the study centre for all the treatment periods and will include an assessment of the following: general appearance, lungs, cardiovascular, and neurological evaluations. Results will be recorded as an overall normal or abnormal with a listing of abnormalities.

Height will be measured in centimetres and weight in kilograms. Measurements should be taken without shoes and the same scale used for all measurements. Body mass index will be calculated from the height and weight.

6.3.7 ECG

A 12-lead paper ECG for safety review by the Investigator will be performed after 10 minutes in the supine position and the outcome of the overall evaluation is to be recorded as normal/abnormal in the eCRF, with any abnormalities specified. The print-out of the ECG is to be signed, dated, and filed in the Investigator's Study File. The ECG measurements will be performed at the screening visit (Visit 1), Day 3 and at the follow-up visit (Visit 5).

Additional ECGs may be taken at the discretion of the Investigator or his/her delegate at other times for safety reasons. These will be reviewed and evaluated by the Investigator and stored with the source documents. At each time point the Investigator's assessment of the ECG (normal or abnormal) will be recorded.

6.3.8 Vital signs

6.3.8.1 Pulse rate and blood pressure

Supine systolic and diastolic BP and pulse rate will be measured using non-invasive equipment after the volunteer has been resting for 5 minutes. Vital signs will be measured on Day -1 (day before administration of the investigational product for all the treatment periods), pre-dose, 1 hour, 3, 6, 12 and 24 hours after administration of the investigational product, before discharge from the study centre for all the treatment periods, and at the follow-up visit (Visit 5).

6.4 Pharmacokinetics

6.4.1 Collection of samples

Blood samples (4 mL) for determination of ticagrelor and its metabolite (AR-C124910XX) in plasma will be collected at times presented in the study plan table (Table 1). The date and time of collection of each sample will be recorded on the eCRF.

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

For blood volume see Section 7.1.

6.4.2 Determination of drug concentration

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

Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites. Any results from such analyses may be reported separately from the CSR.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each volunteer in this study is presented in Table 4.

Table 4 Volume of blood to be drawn from each volunteer

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	5	8	40
	Haematology	2	8	16
	HBsAg, HCV and HIV serology	3.5	1	3.5
	Endocrinology (FSH)[a]	3.5	1	3.5
	aPTT and PT	1.8	6	10.8
Pharmacokinetics	Ticagrelor and AR-C124910XX	4	42 (14 x 3)	168
Blood loss for catheter flush		0.5	30	15
Total				256.8

HBsAg: hepatitis B antigen;
HCV: hepatitis C virus;
HIV: human immunodeficiency virus.
APTT: activated partial thromboplastin time;
PT: prothrombin time

The number of samples taken, as well as the volume required for each analysis, maybe changed during the study (ie, if additional samples are drawn for repeated safety assessments). However, the maximum volume to be drawn from each volunteer will not exceed 350 mL ie, the same volume as would be drawn during a regular blood donation.

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here.

Pharmacokinetic samples (the second portion after the first shipment) will be retained to further investigate potential metabolite(s) and it's PK as per AstraZeneca's request. Instruction details of the retaining samples will be provided in the Laboratory Manual.

7.2.1 Safety samples

Blood samples for safety assessments will be disposed of after analysis.

7.2.2 Pharmacokinetic samples

The primary PK samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

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

7.3 Labelling and shipment of biohazard samples

The 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 volunteer 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 Investigator keeps full traceability of collected biological samples from the volunteers 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 centre 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 volunteer 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 donated biological samples is an integral part of the study, then the volunteer is withdrawn from further study participation.

The Investigator:

- Ensures volunteers' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that volunteer, if stored at the study centre, 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 centre
- Ensures that the volunteer and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the 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 centre.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Subject data protection

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

8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the volunteers. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study centre 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 volunteer into the study.

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

AstraZeneca should approve any modifications to the ICF 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 volunteer into the study, the final study protocol, including the final version of the ICF, 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 the Investigator with safety updates/reports according to local requirements, including SUSARs, where relevant.

8.4 Informed consent

The Investigator at the study centre will:

- Ensure each volunteer is given full and adequate oral and written information (in English or any other preferable language) about the nature, purpose, possible risk and benefit of the study
- Ensure each volunteer is notified that they are free to discontinue from the study at any time
- Ensure that each volunteer is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each volunteer provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the volunteer
- Ensure that any incentives for volunteers who participate in the study as well as any provisions for volunteers harmed as a consequence of study participation are described in the ICF 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 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 CSP).

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 the Investigator. For distribution to Ethics Committee see Section 8.3.

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

If local regulations require, any administrative change will be communicated to or approved by the 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, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT

will manage the study on behalf of AstraZeneca.

9.1 Pre-study activities

Before the first volunteer is entered into the study, it is necessary for to:

- Determine the adequacy of the facilities
- Determine availability of appropriate volunteers for the study
- Discuss with the Investigator (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 volunteer is entered into the study, a representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilised.

The 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 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, a monitor will have regular contacts with the study centre, including visits to:

- Provide information and support to the Investigator
- Confirm that facilities remain acceptable
- Confirm that the study centre personnel are adhering to the CSP, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that the investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the volunteer's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating volunteers. This will require direct access to all original records for each volunteer (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the volunteer's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the volunteer.

The monitor will be available between visits if the Investigator or other staff at the centre needs information and advice about the study conduct.

9.3.1 Source data

The Clinical Study Agreement provides the location of the source data.

9.4 Study agreements

The Investigator at the study 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 CSP and the Clinical Study Agreement, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of volunteers and in all other respects, not relating to study conduct or treatment of volunteers, the terms of the Clinical Study Agreement shall prevail.

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

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement.

9.5 Study timetable and end of study

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

The study is expected to start and end in 3rd Quarter 2013.

The study may be terminated at the study centre 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

Data management will be performed by

The Data Management Plan will describe the methods used to collect, check, validate and process clinical data in detail. It will also clarify the roles and responsibilities for the different functions and personnel involved in the data management process. Furthermore the Data Management Plan will describe the data flow and timelines within the study.

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

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.

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, and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

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

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of safety variable(s)

All AEs will be collected for each volunteer from the time when informed consent is obtained until the follow-up visit.

11.2 Calculation or derivation of pharmacokinetic variables

The PK analysis of ticagrelor and its metabolite AR-C124910XX will be the responsibility of the Pharmacokineticist at . Standard Operating Procedures and Work Instructions will be used as the default methodology if not otherwise specified. Actual sampling times will be used for the computation of PK parameters.

Pharmacokinetic parameters will be derived using standard non-compartmental methods with WinNonlin® Professional Version 5.2, or higher. All PK computations will be performed using WinNonlin® Professional Version 5.2 (or higher) or SAS® Version 9.2 or higher.

Volunteers who withdraw from the study following administration of the investigational product, but prior to study completion, will be included in the PK analysis provided they have evaluable concentrations over the planned collection period. Volunteers with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for meaningful analysis.

If data permits, the following plasma PK parameters will be calculated for ticagrelor and its metabolite AR-C124910XX for each treatment:

- Observed maximum plasma concentration (C_{max})
- Time of maximum concentration (t_{max})
- Area under plasma concentration-time curve from zero (pre-dose) to the last quantifiable concentration [$AUC_{(0-t)}$]
- Area under plasma concentration-time curve from zero (pre-dose) to infinity (AUC)
- Apparent terminal half-life ($t_{1/2}$)

Additionally, the following will also be computed:

AR-C124910XX: ticagrelor ratios for $C_{max,}$ $AUC_{(0-t)}$, and AUC.

The following PK diagnostic parameters will be calculated for both analytes, as appropriate, and will be listed, but not summarised:

- The time interval ($t_{1/2}$, interval) of the log-linear regression to determine $t_{1/2}$
- Number of data points ($t_{1/2}$, N) included in the log-linear regression analysis to determine $t_{1/2}$ (a minimum of 3 points will be used)
- Regression coefficient (Rsq), a goodness-of-fit statistic for calculation of λ_z. If Rsq is less than 0.800, then $t_{1/2}$ and related parameters will not be reported
- Percent AUC that is extrapolated (%AUC_{ex}). If %AUC_{ex} is greater than 20% then AUC will not be reported.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 General principles

The analysis of data will be based on different subsets according to the purpose of analysis, ie, for safety and PK. The decision regarding validity of data for each of the analysis sets will be based on a blind review of data.

The as-treated principle will be applied to all evaluations; ie, volunteers who received another treatment than the one assigned in the randomisation list will be analysed as belonging to the actual treatment group and not that assigned by randomisation.

12.1.2 All Subjects

All volunteers who received an enrolment number and at least 1 dose of the investigational product.

12.1.3 Safety analysis set

All volunteers who received at least 1 dose of the investigational product and for whom any post-dose data are available will be included in the safety analysis set. Volunteers will be analysed according to the treatment they actually received. The safety analysis set will be used as the primary analysis set for the reporting of safety data.

12.1.4 Pharmacokinetic analysis set

The PK analysis set will be a subset of the safety analysis set and will include only volunteers who receive at least 1 dose of the investigational product and have at least 1 post-dose plasma concentration measurement at a scheduled time point without important protocol deviations/violations or events thought to significantly affect the PK (eg, volunteer vomited at or before 2 times median t_{max}; wrong dose administered; prohibited concomitant medication; etc).

12.2 Methods of statistical analyses

12.2.1 General principles

The statistical analyses will be performed using SAS®, Version 9.2 or higher.
Standard Operating Procedures and Work Instructions will be used as the default methodology if not otherwise specified. Graphics will be prepared using SAS® Version 9.2 and Sigmaplot® 9.0.

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

No adjustment for multiplicity will be made.

A volunteer who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of discontinuation.

All data will be included in the data listings. Any data excluded from the summaries and statistical analyses will be flagged accordingly

Data will be presented by treatment for the purpose of summarising the safety results. A volunteer who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of discontinuation.

Tabulations and listings of data for vital signs, clinical laboratory tests, ECGs, and physical examination findings will be presented. All continuous safety data will be summarised across all treatments for the absolute value at each scheduled assessment and for the corresponding change from baseline.

Demographic data and baseline data

Demographic data, baseline characteristics, and disposition of volunteers will be summarised for 'All subjects' (Section 12.1.1). Demographic and baseline characteristic data recorded at the screening visit will be listed. Demographic data will include date of birth, age, and gender. Baseline characteristics will be summarised across all volunteers. Volunteer characteristics and baseline data will include smoking status and history and physical examination findings.

Continuous variables will be summarised using descriptive statistics (n, mean, standard deviation [SD], minimum [min], median and maximum [max]) by treatment group. Categorical variables (eg, gender) will be summarised in frequency tables (frequency and proportion of volunteers in analysis set).

In general, descriptive statistics will follow the rounding convention in Global Standard Operating Procedures.

Subject identification and disposition

A listing of the enrolment code and the volunteer randomisation number will be produced. This list will also indicate whether the volunteers' data are included in the safety analysis sets. Listings will also be produced which detail why enrolled volunteers who received ticagrelor and AR-C124910XX, the active metabolite of ticagrelor were not randomised and why randomised volunteers withdrew prematurely from the study.

12.2.2 Safety and tolerability

The following safety clinical assessments will be done: AEs, vital signs, physical exams, clinical chemistry and haematology, and ECGs. All safety data (scheduled and unscheduled) will be presented in the data listings.

All safety data (scheduled and unscheduled) will be presented in the data listings. Continuous variables will be summarised using descriptive statistics (n, mean, SD, min, median, max) by treatment at each scheduled time and for the corresponding change from baseline where applicable. Categorical variables will be summarised in frequency tables (frequency and proportion) by treatment group and by scheduled time where applicable. Safety variables (eg, clinical laboratory values and vital signs) will be reported to the same precision as the source data. Derived variables will be reported using similar precision to those from which they were derived (eg, QTc derived from QT interval).

Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive. All AEs, ECG outliers, and clinical laboratory outliers that occur following the first administration of the investigational product will be included in the tabulations of AEs and outlier events, including episodes that occur at unscheduled evaluations.

All available data from volunteers in the safety analysis set will be included in the safety analyses. No adjustment or imputation will be utilised for missing values or for volunteers who withdraw prior to completing the study, neither will analyses be restricted to volunteers with complete data.

All AEs will be collected for each volunteer from the time when informed consent is obtained until the follow-up visit. Adverse events that occur before dosing will be reported separately. Adverse events will be summarised by Preferred Term and System Organ Class using Medical Dictionary for Regulatory Activities (MedDRA) vocabulary (Version 12.0 or higher) by treatment and across all treatments, as appropriate. Furthermore, listings of SAEs and AEs

that lead to withdrawal will be presented and the number of volunteers who have any AEs, SAEs, AEs that lead to withdrawal, and AEs with severe intensity will be summarised.

For clinical laboratory tests, listings of values for each volunteer will be presented with abnormal or out-of-range values flagged. Clinical laboratory data will be reported in Système International units in the CSR.

Adverse Events

All AEs will be collected for each volunteer from the time when informed consent is obtained until the follow-up visit. Adverse events that occur before administration of the investigational product will be reported separately.

Adverse events will be summarised by Preferred Term and System Organ Class (SOC) using MedDRA vocabulary (Version 12.0 or higher) by treatment and across all treatments. Furthermore, listings of SAEs and AEs that lead to withdrawal will be made and the number of volunteers who have any AEs, SAEs, AEs that lead to withdrawal, and AEs with severe intensity will be summarised.

All AEs occurring at any time during the study will be listed. All summary tables of AE data will include all AEs starting or worsening after administration of the investigational product. Overall summaries of AEs will be provided at both the volunteer level and the event level, detailing the number of AEs, SAEs, discontinuations due to AEs and other significant AEs by treatment. Adverse events will be summarised by treatment by SOC and preferred term assigned to the event using the MedDRA vocabulary. In volunteer level summaries, a volunteer will only be counted once in each SOC or preferred term. Adverse events will also be summarised by treatment by maximum intensity and by investigator's causality assessment. In addition, separate listings for all SAEs, OAEs, deaths and discontinuations due to AEs will be presented.

Any AEs determined to be of interest or occurring frequently may be summarised separately using the same methodology as described above.

Laboratory data

Safety laboratory data consists of clinical chemistry, haematology and urinalysis. These data will be summarised by treatment group. For clinical laboratory tests, listings of values for each volunteer will be presented with abnormal or out-of-range values flagged. Clinical laboratory data will be reported in Système International units in the CSR.

Absolute values will be compared to the project extended reference range and classified as low (below range), normal (within range or on limits of range) and high (above range). All values classified as high or low will be flagged on the listings. The qualitative urinalysis data will be summarised at each time point by treatment group.

Local laboratory reference ranges will be used for the primary interpretation of laboratory data by physicians. The project reference ranges will be based on the AstraZeneca reference ranges where they exist; otherwise project reference ranges agreed by the Patient Safety Physician and the study physician will be used. Both the project and the local laboratory ranges will be listed.

Numerical laboratory data will be summarised using standard summary statistics for each treatment group at each visit. Discrete laboratory data will be summarised showing the number of volunteers at each level of measurement at each visit by treatment group. Summaries of the number of volunteers falling outside the reference ranges at each time point will also be provided by treatment group. Separate listings of only those values falling outside these reference ranges will also be produced.

Physical Examination

Each measurement will be categorised as normal/abnormal. Summaries of the number of volunteers falling in each category at each time point will also be provided by treatment group. Height, weight and BMI will be summarised at each time point by treatment group using standard summary statistics.

Vital signs

Vital signs data consists of pulse rate, systolic BP and diastolic BP. These data will be summarised by treatment group at each time point.

Absolute values will be compared to the AstraZeneca project extended reference range and classified as low (below range), normal (within range or on limits of range) and high (above range). All values classified as high or low will be flagged on the listings.

Pulse rate, systolic BP, diastolic BP will be summarised at each time point by treatment group using standard summary statistics. Summaries of the number of volunteers falling outside the reference ranges at each time point will also be provided by treatment group.

Medical and surgical history

Medical and surgical histories will be summarised by MedDRA preferred term within MedDRA system organ class. All data will be listed by volunteer.

Concomitant medication

Concomitant medications will be classified according to the AstraZeneca Drug Dictionary. All concomitant medications reported from Visit 2 (Day -1) and recorded during the study will be listed and summarised if appropriate.

Incomplete and missing data

Data arising from volunteers who do not complete the study will be recorded in the database and presented in listings. Data will also be included in summary tables up until the point of withdrawal.

No imputation will be performed for missing values. However for missing baseline values, the previous non-missing alternative baseline values (screening visit) will be used as appropriate. In the absence of screening visit values, baseline will be considered as missing and no imputation will be performed.

If the start date/time of an AE is missing and it cannot be determined if the AE started pre or post the last administered dose of the investigational product, it will be assumed, for the purposes of presentation, that the AE started post investigational product administration.

12.2.3 Pharmacokinetics

The PK and safety summaries, individual figures and data listings, as well as the statistical analysis of PK variables will be the responsibility of the study biostatistician at . (using SAS® Version 9.2 or higher and, where appropriate, additional validated software).

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. Plasma concentrations and PK parameters for ticagrelor and its metabolite will be summarised using appropriate descriptive statistics (ie, n, mean, standard deviation [SD], geometric mean, geometric coefficient of variation [CV%], minimum, median, maximum) by analyte and treatment. The geometric mean is calculated as the exponential of the mean calculated from data on a log scale. The CV% is calculated as $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where s is the SD of the data on a log scale. Mean, SD, geometric mean, and CV% will not be calculated for t_{max}.

For descriptive statistics, plasma concentrations that are below the LLOQ will be handled as follows:

- At a time point where less than or equal to 50% of the values are below the LLOQ (BLQ), all BLQ values will be set to LLOQ, and all descriptive statistics will be calculated
- At a time point where more than half of the values are BLQ, the mean, SD, geometric mean and CV% will be set to Not Determined (ND). The maximum value will be reported from the individual data, and the minimum and median will be set to BLQ
- If all values are BLQ at a time point, no descriptive statistics will be calculated for that time point. Not Applicable (NA) will be written in the field for SD and CV% and BLQ will be written in fields for mean, geometric mean, minimum, median, and maximum

- The number of BLQ values (n below LLOQ) will be reported for each time point

Graphical presentations will include mean (±SD) plasma concentration-time curves by treatment and individual volunteer plasma concentration-time curves over the PK sampling times. The PK parameters C_{max}, AUC, and $AUC_{(0-t)}$ will be presented graphically by scatter plots comparing individual and mean PK parameters between treatments.

Ticagrelor and AR-C124910XX PK parameters AUC and C_{max} will be analysed using a mixed-effects model with fixed effects for sequence, period, and treatment with volunteer nested within sequence as a random effect. AUC and C_{max} will be natural log transformed prior to analyses. The results will be back transformed and presented as geometric least-squares means (95% CIs) and the ratios of geometric least-squares means (90% CIs). The treatment comparisons will be test (Treatments B or C) versus reference (Treatment A). The PK parameters AUC and C_{max} for ticagrelor will be the primary PK variables. However, if there are more than 20% of the volunteers whose AUC values are not available for either treatment for the given comparison, $AUC_{(0-t)}$ will also be analysed statistically and presented in the same way as AUC.

12.3 Determination of sample size

Based on a previous study (AZD6140 Study D5130C00040), where 18 healthy volunteers received a single 90 mg dose of the ticagrelor formulation, the intra-subject CV for AUC and C_{max} of ticagrelor and AR-C124910XX were estimated to be less than or equal to 24%. Assuming similar variability for the AUC and C_{max} of both the crushed formulations and a log-normal distribution of the data, a total of 30 healthy volunteers would ensure that the 90% confidence interval for the ratios of interest, for both AUC and C_{max}, are contained within the limits of 0.8 to 1.25. Thirty-six healthy volunteers would be enrolled to allow for dropouts.

These calculations were based on inverting two one-sided tests, each at an alpha level of 0.05 and with 90% power, and assuming a true ratio of 1.0 for both tests.

The sample size of 30 subjects would also be sufficient to ensure that if the observed geometric mean ratio is in the interval (0.88, 1.13), the 90% confidence interval for the ratio of interest would still be contained within the limits of 0.8 to 1.25. No adjustments will be made for pre-planned multiple comparisons.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

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

In the case of a medical emergency the Investigator may contact the CPA Physician. If the CPA Physician is not available, contact the CPA Program Director at AstraZeneca Research and Development.

Name	Role in the study	Address & telephone number
	AstraZeneca Clinical Pharmacology Alliance Physician	
	AstraZeneca Clinical Pharmacology Alliance Programme Director	
Serious adverse event reporting	24-hour emergency cover at central R&D site	
	Investigator	
	Clinical Project Manager	

13.2 Overdose

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

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

If an overdose on an AstraZeneca investigational product occurs in the course of the study, then the Investigator or other site personnel will 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 6.3.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the volunteer was discontinued from the study.

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.3.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

13.3.2 Paternal exposure

Male volunteers should refrain from fathering a child or donating sperm during the study and 3 months following the last dose.

Pregnancy of a volunteer's partner will not be considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be monitored and documented, if possible.

The outcome of any conception occurring from the date of the first dose until 3 months after the last dose should be followed up and documented.

14. LIST OF REFERENCES

Guidance for Industry 2003
Guidance for Industry-Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations. U.S. Department of Health and Human Services 2003.

EMEA Guidance for BA 2010
Guideline on the Investigation of Bioequivalence. The European Agency for Evaluation of Medicinal Products 2010

Clinical Study Protocol Appendix A

Drug Substance	Ticagrelor
Study Code	D5130C00076
Edition Number	1
Date	
Protocol Dated	

Appendix A
Signatures

Clinical Study Protocol Appendix B

Drug Substance	Ticagrelor
Study Code	D5130C00076
Edition Number	
Date	

Appendix B
Additional Safety Information

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

Life threatening

'Life-threatening' means that the volunteer 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 volunteer'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 volunteer 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 jeopardise the volunteer 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:

- Angiooedema 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 volunteer actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

Clinical Study Protocol Appendix C

Drug Substance	Ticagrelor
Study Code	D5130C00076
Edition Number	1
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Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

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

AstraZeneca

Clinical Study Protocol Appendix D	
Drug Substance	Ticagrelor
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Appendix D
Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

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1. INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a volunteer meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the ticagrelor.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN) **and** total bilirubin (TBL) ≥ 2xULN at any point during the study irrespective of an increase in alkaline phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT ≥ 3x ULN **and** TBL ≥ 2xULN, where no other reason, other than ticagrelor, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any volunteer who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the volunteer meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory electronic case report form (eCRF)

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the volunteer does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the volunteer has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the volunteer does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study volunteers' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the volunteer until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the three Liver eCRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria were met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by ticagrelor. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there **is** an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the eCRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the ticagrelor:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to

determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Clinical Study Protocol Appendix E

Drug Substance	Ticagrelor
Study Code	D5130C00076
Edition Number	1
Date	

Appendix E
Highly Effective Forms of Birth Control

1. HIGHLY EFFECTIVE FORMS OF BIRTH CONTROL

1. Total sexual abstinence (for the total duration of the trial including the follow-up period)
2. Vasectomised sexual partner (with participant assurance that partner received post-vasectomy confirmation of azoospermia)
3. Tubal occlusion
4. Intra-uterine device (IUD, provided that coils are copper-banded)
5. Levonorgestrel Intrauterine System (eg, Mirena)
6. Medroxyprogesterone injections (Depo-Provera)
7. Etonogestrel implants (Implanon, Norplan)
8. Normal and low-dose combined oral pills
9. Norelgestromin/ethinylestradiol transdermal system
10. Intravaginal device (eg, ethinylestradiol and etonogestrel)
11. Cerazette (desogestrel).

In addition to the use of a highly-effective form of birth control, women of childbearing potential are instructed to use a barrier method of contraception during sexual intercourse (female or male condom).

The following methods are considered **NOT** to be highly effective and are therefore not acceptable contraceptive methods in ticagrelor trials

1. Triphasic combined oral contraceptives
2. All progesterone only pills, except Cerazette
3. All barrier methods, if intended to be used alone
4. Non-copper containing IUDs
5. Fertility awareness methods
6. Coitus interruptus.