Clinical Study Protocol

AN OPEN-LABEL, RANDOMIZED, THREE-PERIOD, THREE-TREATMENT, CROSSOVER, SINGLE-CENTRE, SINGLE-DOSE STUDY TO ASSESS THE BIOEQUIVALENCE BETWEEN TICAGRELOR ORODISPERSIBLE TABLETS AND TICAGRELOR IMMEDIATE-RELEASE TABLETS IN HEALTHY JAPANESE SUBJECTS

PAREXEL STUDY NUMBER:	PXL221346
SPONSOR STUDY NUMBER:	D5139C00004
EudraCT No.:	2015-001045-91
TEST PRODUCT:	Ticagrelor OD tablet, 90 mg
REFERENCE PRODUCT:	Ticagrelor IR tablet, 90 mg
THERAPEUTIC INDICATION:	Thrombotic cardiovascular events in acute coronary syndrome
PHARMACOLOGICAL CLASS:	Oral antiplatelet agent
DEVELOPMENT PHASE:	Bioequivalence Study
SPONSOR:	AstraZeneca AB 151 85 Södertälje Sweden
STUDY CENTRE:	PAREXEL Early Phase Clinical Unit London United Kingdom
DATE OF PROTOCOL:	Final 1.0, 04 March 2015

This clinical study will be conducted according to the clinical study protocol and in compliance with Good Clinical Practice, with the Declaration of Helsinki (Version 1996) and with other applicable regulatory requirements.

PROTOCOL SYNOPSIS

Title of the study

AN OPEN-LABEL, RANDOMIZED, THREE-PERIOD, THREE-TREATMENT, CROSSOVER, SINGLE-CENTRE, SINGLE-DOSE STUDY TO ASSESS THE BIOEQUIVALENCE BETWEEN TICAGRELOR ORODISPERSIBLE TABLETS AND TICAGRELOR IMMEDIATE-RELEASE TABLETS IN HEALTHY JAPANESE SUBJECTS.

Principal Investigator

Dr. Annelize Koch

Study center

This study will be conducted at a single study center.

PAREXEL Early Phase Clinical Unit London,

United Kingdom

Study rationale and justification of study design

This study will be conducted to support the pharmaceutical development of the orodispersible tablet formulation of ticagrelor for the benefit of use by patients from Japanese origin. The purpose of the study is to assess the bioequivalence between ticagrelor orodispersible (OD) tablets when administered with water and without water, and ticagrelor immediate-release (IR) tablets in healthy Japanese subjects. A randomized, crossover design has been chosen to minimize the effects of between-subject variability and any period effects on the overall results. The study is open-label since the primary objective is to evaluate the bioequivalence between ticagrelor OD tablets and ticagrelor IR tablets in healthy Japanese subjects.

Number of subjects planned

Forty-two subjects will be randomized to ensure at least 30 evaluable subjects at the end of the last treatment period.

Study period

Estimated date of first subject enrolled: May 2015 (signing of informed consent)

Estimated date of last subject completed: August 2015

Study objectives

The objective of the study is to assess the bioequivalence between ticagrelor OD tablets and ticagrelor IR tablets in healthy Japanese subjects.

Primary objective:

- To evaluate bioequivalence of ticagrelor OD tablets when administered with water and without water, compared to ticagrelor IR tablets

Secondary objectives:

- To examine the pharmacokinetic (PK) profiles of ticagrelor OD tablets when administered with water and without water, compared to ticagrelor IR tablets
- To assess safety and tolerability of ticagrelor OD tablets when administered with water and without water, compared to ticagrelor IR tablets

Outcome variables

Pharmacokinetic parameters:

Where possible, the following PK parameters will be assessed for ticagrelor (parent) and its active metabolite AR-C124910XX on plasma concentrations.

- Primary PK parameters: C_{max}, $AUC_{(0-t)}$, AUC
- Secondary PK parameters: t_{max}, $t_{½,\lambda z}$, kel, MRT, metabolite to parent ratios (MRC_{max}, $MRAUC_{(0-t)}$, MRAUC)

Additional PK parameters may be determined where appropriate.

Safety and tolerability variables:

Safety and tolerability variables will include adverse events (AEs), vital signs (blood pressure [BP], pulse), 12-lead electrocardiograms (ECGs), physical examination and laboratory assessments (hematology, clinical chemistry and urinalysis).

Viral serology, follicle-stimulating hormone (FSH) (females only), coagulation and urine drugs of abuse, alcohol and cotinine will be assessed for eligibility. In addition to the above, pregnancy testing (females only) and use of concomitant medication will also be reported.

Study design

This study will be an open-label, randomized, three-period, three-treatment, crossover study in healthy Japanese subjects (males and females), performed at a single study center.

The study will comprise:

- A screening period of maximum 28 days;
- Three treatment periods during which subjects will be resident prior to the evening meal the night before dosing with ticagrelor (Day -1) until at least 48 hours after dosing; discharged on the morning of Day 3; and
- A final visit within 5 to 10 days after the last administration of ticagrelor.

There will be a minimum washout period of 7 days between each dose administration.

Subjects will receive single doses of ticagrelor in three different ways under fasted conditions.

Following an overnight fast of at least 10 hours, each subject will receive a single dose of each treatment on three occasions, respectively:

Treatment A	Test product	Ticagrelor OD tablets administered with 150 mL of water	1 x 90 mg
Treatment B	Test product	Ticagrelor OD tablets administered without water	1 x 90 mg
Treatment C	Reference product	Ticagrelor IR tablets administered with 150 mL of water	1 x 90 mg

End of study

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

Target study population

Healthy Japanese subjects, males and females (non-childbearing potential)

Inclusion criteria

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

1. Provision of signed and dated written informed consent prior to any study specific procedures.
2. Healthy male and female subjects aged 20 to 45 years with suitable veins for cannulation or repeated venepuncture.
3. Be Japanese.

   Japanese is defined as having both parents and four grandparents who are Japanese. This includes second and third generation Japanese whose parents or grandparents are living in a country other than Japan.
4. Females must have a negative pregnancy test at screening and on each admission to the clinical unit, must not be lactating, and must be of non-childbearing potential, confirmed at screening by fulfilling one of the following criteria:
   - Postmenopausal defined as amenorrhea for at least 12 months or more following cessation of all exogenous hormonal treatments and FSH levels in the postmenopausal range.

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

5. Have a body mass index (BMI) between 18.0 and 27.0 kg/m^2 inclusive and weigh at least 45 kg and no more than 85 kg inclusive.
6. Be able and willing to communicate with the investigator and comply with all study procedures, including reproductive restrictions.

Exclusion criteria

Persons who meet one or more of the exclusion criteria will not be considered eligible to participate in the study.

1. History of any clinically significant disease or disorder which, in the opinion of the investigator, may either put the potential subject at risk because of participation in the study, or influences the results or the potential subject'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 drugs.
3. Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks of the first administration of IMP.
4. Any clinically significant abnormalities in hematology, clinical chemistry, coagulation or urinalysis results, as judged by the investigator.
5. Any clinically significant abnormal findings in vital signs, as judged by the investigator.
6. Any clinically significant abnormalities on 12-lead ECG, as judged by the investigator.
7. Any positive result on screening for serum hepatitis B surface antigen (HBsAg), hepatitis C antibody, and human immunodeficiency virus (HIV) antibodies.
8. Known or suspected history of drug abuse, as judged by the investigator.
9. Has received a new chemical entity (defined as a compound which has not been approved for marketing) within 3 months of the first administration of IMP in this study. The period of exclusion begins 3 months after the final dose or 1 month after the last visit whichever is the longest.

   Note: Subjects consented and screened, but not randomized in this study or a previous Phase I study, are not excluded.
10. Plasma donation within 1 month of screening or any blood donation/loss more than 500 mL during the 3 months prior to screening.
11. 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.
12. Current smokers or those who have smoked or used nicotine products within the previous 3 months.
13. Positive screen for drugs of abuse or cotinine (cotinine level above 500 ng/mL) at screening or on each admission to the clinical unit or positive screen for alcohol on each admission to the clinical unit.
14. Use of drugs with enzyme-inducing properties such as St John's Wort within 3 weeks prior to the first administration of IMP.
15. Use of any prescribed or non-prescribed medication including antacids, analgesics (other than paracetamol/acetaminophen), herbal remedies, megadose vitamins (intake of 20 to 600 times the recommended daily dose) and minerals during 2 weeks prior to the first administration of IMP or longer than 5 half-lives if the medication has a long half-life.

    Note: Hormonal replacement therapy is not allowed for females.
16. Known or suspected history of alcohol or drug abuse or excessive intake of alcohol, as judged by the investigator.
17. Involvement of any AstraZeneca or clinical unit employee or their close relatives.
18. Judgment by the investigator that the potential subject should not participate in the study if they have any ongoing or recent (i.e., 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.
19. Consumption of poppy seeds within 7 days of first admission to the clinical unit.
20. History of hemophilia, 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 hemorrhage, hematemesis, melena, hemoptysis, severe epistaxis, severe thrombocytopenia, intracranial hemorrhage; or rectal bleeding within 1 year prior to screening; or history suggestive of peptic ulcer disease; or at the discretion of the investigator.
22. History of a clinically significant non-traumatic bleed or clinically significant bleeding risk, as judged by the investigator.
23. Use of aspirin, ibuprofen, non-steroidal anti-inflammatory drugs (NSAIDs), or any other drug known to increase the propensity for bleeding for 2 weeks before randomization.
24. Platelet count less than 150 x 10^9/L.
25. Vulnerable subjects, e.g., kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order.

Investigational medicinal product

Supplier:	AstraZeneca
Formulations:	*Test product:* Ticagrelor 90 mg OD tablets *Reference product:* Ticagrelor 90 mg IR tablets
Strength/Concentrations:	90 mg
Route of administration:	Oral
Regimen:	Single dose Treatment A: Ticagrelor OD tablets administered with 150 mL of water Treatment B: Ticagrelor OD tablets administered without water Treatment C: Ticagrelor IR tablets administered with 150 mL of water
Special handling requirements:	Not applicable
Availability of IMP:	The IMP will be provided to the study center by AstraZeneca.

Study duration

Each subject will be involved in the study for 7 to 8 weeks.

Pharmacokinetic sampling times and sample analysis

Blood samples for the determination of plasma concentrations of both ticagrelor and its active metabolite AR-C124910XX will be collected for each treatment period: 0 hours (pre-dose) and post-dose at 0.5 (30 minutes), 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours (14 samples per treatment period).

Samples will be collected, handled, labelled, stored and shipped as detailed in the Laboratory Manual. Plasma samples will be analyzed for ticagrelor and AR-C124910XX using a validated assay.

Pharmacokinetic data analysis

All PK computations will be performed using Phoenix® WinNonlin® 6.3, or higher.

Pharmacokinetic parameters will be summarized for each treatment using descriptive statistics. Where possible, the following descriptive statistics will be presented: n, geometric mean, geometric coefficient of variation (CV), arithmetic mean, arithmetic SD, median, minimum and maximum. The correlation coefficient for determining kel will be estimated together with time-points used. The ratios of C_{max}, $AUC_{(0-t)}$ and AUC of Test product to those of Reference product in each individual and analyte will be calculated. For t_{max}, only n, median, minimum and maximum will be presented.

The ratios of C_{max}, $AUC_{(0-t)}$ and AUC of both ticagrelor and AR-C124910XX will be obtained using a two-sided 90% CI approach based on an analysis of variance (ANOVA) model including fixed effects for treatment, sequence, period and subject within sequence.

Primary PK parameters will be log-transformed prior to analysis. The estimated treatment differences and the 90% CIs on the log scale will be back-transformed to obtain the geometric mean ratios for each pair of treatments. The same ANOVA model will be applied to $t_{½\lambda z}$, kel and MRT using log-transformed values.

The least squares means (and 95% CIs) will be tabulated for each treatment and analyte.

For exploratory purposes, the ANOVA as outlined here will be repeated with a random effect of subject within sequence. Additionally, the 90% CI for the difference in t_{max} will be calculated.

Bioequivalence may be concluded if the 90% CI of the ratios for both C_{max} and $AUC_{(0-t)}$ for both analytes are contained completely within the limits of 0.80-1.25.

Determination of sample size

Based on the estimated within-subject CV for C_{max} and $AUC_{(0-t)}$ of ticagrelor and AR-C124910XX of less than or equal to 24%, 30 evaluable subjects are needed to achieve a power of 90% that a two-sided 90% CI for the ratio of C_{max} between two different ticagrelor treatments will totally be contained within the 0.8-1.25 limit.

Forty-two subjects will be randomized to a 6 sequence Williams square design for 3 periods and 3 treatments: ABC, BCA, CAB, ACB, BAC and CBA, in order to ensure at least 30 evaluable subjects at the end of the last treatment period.

1. TABLE OF CONTENTS

1.1. List of Tables

1.2. List of Figures

2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
ACS	Acute coronary syndrome
AE	Adverse event (see definition in Section 12.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under plasma concentration-time curve from zero to infinity
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from time zero to time of last quantifiable analyte concentration
$\%AUC_{extrap}$	Percentage of AUC obtained by extrapolation, calculated as $[(C_{last}/\lambda_z)/AUC * 100]$
BMI	Body mass index
BLQ	Below limit of quantification
BP	Blood pressure
bpm	Beats per minute
CAD	Coronary artery disease
CI	Confidence interval
C_{last}	Drug concentration at last observed time-point
ClinBase™	PAREXEL's electronic source data capturing and information management system
C_{max}	Maximum observed plasma concentration
CRF	Case report form
CRO	Contract Research Organization
CRP	C-reactive protein
CSR	Clinical study report
CV	Coefficient of variation
DBP	Diastolic blood pressure
DCF	Data clarification form
DES	Data Entry Site – where serious adverse event reports from AstraZeneca Clinical studies are entered onto the AstraZeneca Patient Safety database by Tata Consultancy Services
DMP	Data management plan

DVS	Data validation specification
ECG	Electrocardiogram
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase (transferase)
GMP	Good Manufacturing Practice
GRand	Global randomization system
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HCT	Hematocrit
HIV	Human immunodeficiency virus
IATA	International Airline Transportation Association
ICD	Informed Consent Document
ICH	International Conference on Harmonisation
ICH E3	ICH guideline for structure and content of clinical study reports
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INR	International Normalized Ratio
IR	Immediate-release
IRB	Institutional Review Board
kel	Elimination rate constant
λ_z	Terminal elimination rate constant
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LLOQ	Lower limit of quantification
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRAUC	Ratio of metabolite AUC to parent AUC, adjusted for differences in molecular weights
$MRAUC_{(0-t)}$	Ratio of metabolite $AUC_{(0-t)}$ to parent $AUC_{(0-t)}$, adjusted for differences in molecular weights
MRC_{max}	Ratio of metabolite C_{max} to parent C_{max}, adjusted for differences in molecular weights

MRT	Mean residence time
n	Number of subjects
NA	Not applicable
ND	Not determined
NR	No result
NSAID	Non-steroidal anti-inflammatory drug
OAE	Other significant adverse event
OD	Orodispersible
OTC	Over-the-counter
PCI	Percutaneous coronary intervention
PDF	Portable Document Format
PDS	Protocol deviation specification (document)
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetic(s)
PT	Preferred Term
QP	Qualified Person
RBC	Red blood cell
Rsq_adj	Regression coefficient adjusted for λ_z, N , Goodness of fit statistic for calculation of λ_z
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Half-life
$t_{½\lambda z}$	Half-life associated with terminal slope (λ_z) of a semi-logarithmic concentration-time curve
TCA	Tricyclic anti-depressants
TCS	Tata Consultancy Services – an AstraZeneca partner who conduct data entry onto Sapphire
TEAE	Treatment-emergent adverse event
t_{max}	Time to reach maximum observed concentration
US	United States (of America)
WAD	Windows Allowance Document

WBC	White blood cell

3. ETHICS

3.1. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (Version 1996) and are consistent with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and the AstraZeneca policy on Bioethics and Human Biological Samples.

3.2. Subject data protection

The Informed Consent Document (ICD) will incorporate wording that complies with relevant data protection and privacy legislation.

All clinical study findings and documents will be regarded as confidential. The investigator and members of his/her research team must not disclose such information without prior written approval from the sponsor.

The anonymity of participating subjects must be maintained. Subjects will be specified in ClinBase™ and other documents by their subject number, not by name. Documents that identify the subject (e.g., signed ICD) will be maintained in confidence by the investigator.

Study data will be stored in accordance with local and global data protection laws.

3.3. Ethics and regulatory review

The study will be submitted to the national regulatory authority for review and approval, by PAREXEL in accordance with local regulatory procedures.

The study will be submitted for ethical review and approval, by PAREXEL in accordance with local procedures.

AstraZeneca will provide the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and the national regulatory authority with safety updates and/or reports, according to local requirements, including suspected unexpected serious adverse reactions (SUSARs), where relevant.

3.4. Insurance

The sponsor has covered this clinical study by means of an insurance of the clinical study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's Site File.

3.5. Informed consent

The subjects shall be informed of the nature, significance, implications and risks of the research study; and informed consent will be freely given and evidenced in writing, dated and signed, by the subject as evidence to indicate his/her free informed consent, prior to the start of the study.

The nature of the informed consent will comply with the Declaration of Helsinki (Version 1996), the current requirements of GCP (CPMP/ICH/135/95) and local regulation whichever affords the greater subject protection.

3.6. Changes to the clinical study protocol and Informed Consent Document

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

If there are any substantial changes to the clinical study protocol, then these changes will be documented in a protocol amendment and where required in a new version of the clinical study protocol.

The amendment should be approved by the IEC/IRB and the national regulatory authority, before implementation. Local requirements should be followed for revised clinical study protocols.

If a protocol amendment requires a change to the ICD the IEC/IRB should approve the revised ICD before the revised document is used.

Administrative changes will be communicated to the IEC/IRB, in accordance with local requirements.

4. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden
Sponsor's Lead Physician:	AstraZeneca Pharmaceuticals
Sponsor's Biostatistician:	AstraZeneca R&D Mölndal
Principal Investigator (PI):	Dr. Annelize Koch PAREXEL Early Phase Clinical Unit London
Contract Research Organization (CRO):	PAREXEL Early Phase Clinical Unit London

Clinical Laboratory:	The Doctors Laboratory (TDL)
Analytical Laboratory: (PK sample analysis)	Covance Bioanalytical Services, LLC
	Contact:
Adverse Event Reporting:	AstraZeneca Patient Safety Data Entry Site

A list and contact details of investigators and other key study team members are provided in the Project Plan in the electronic Investigator's Site File. A list of all participating investigators will be provided in the clinical study report (CSR).

5. INTRODUCTION

5.1. Background information

Ticagrelor (Brilinta®) is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). Ticagrelor and its major metabolite reversibly interact with the platelet $P2Y_{12}$ ADP-receptor to prevent signal transduction and platelet activation.

Ticagrelor has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction, or stroke compared to clopidogrel. The difference between treatments was driven by cardiovascular death and myocardial infarction with no difference in stroke. In patients treated with percutaneous coronary intervention (PCI), it also reduces the rate of stent thrombosis [1].

Brilinta® is a trademark of the AstraZeneca group of companies [1].

5.2. Clinical pharmacokinetics

Ticagrelor and its active metabolite are approximately equipotent. Ticagrelor demonstrates dose proportional pharmacokinetics (PK), which are similar in patients and healthy volunteers [1].

Absorption:

Absorption of ticagrelor occurs with a median t_{max} of 1.5 hours (range 1.0-4.0). The formation of the major circulating metabolite AR-C124910XX (active) from ticagrelor occurs with a median t_{max} of 2.5 hours (range 1.5-5.0).

The mean absolute bioavailability of ticagrelor is about 36% (range 30-42%). Ingestion of a high-fat meal had no effect on ticagrelor C_{max}, but resulted in a 21%-increase in AUC. The C_{max} of its major metabolite was decreased by 22% with no change in AUC. Ticagrelor can be taken with or without food.

Distribution:

The steady state volume of distribution of ticagrelor is 88 L. Ticagrelor and the active metabolite are extensively bound to human plasma proteins (> 99%).

Metabolism:

CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. Ticagrelor and its major active metabolite are weak P-glycoprotein substrates and inhibitors. The systemic exposure to the active metabolite is approximately 30-40% of the exposure of ticagrelor.

Excretion:

The primary route of ticagrelor elimination is hepatic metabolism. When radiolabeled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (58% in feces, 26% in urine). Recoveries of ticagrelor and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the major metabolite of ticagrelor is most likely to be biliary secretion. The mean half-life is approximately 7 hours for ticagrelor and 9 hours for the active metabolite.

Special populations and effects of body weight and smoking:

The effects of age, gender, ethnicity, renal impairment and mild hepatic impairment on the PK of ticagrelor are modest and do not require dose adjustment. Ticagrelor has not been evaluated in a pediatric population [1].

No dose adjustment is necessary for ticagrelor based on body weight. Habitual smoking increased population mean clearance of ticagrelor by approximately 22% when compared to non-smokers. No dose adjustment is necessary for ticagrelor based on smoking status [1]. For reasons of homogeneity of the study population only non-smokers will be included in this study.

Drug interactions:

Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole and clarithromycin) substantially increase ticagrelor exposure. Moderate CYP3A inhibitors have lesser effects (e.g., diltiazem). CYP3A inducers (e.g., rifampin) substantially reduce ticagrelor blood levels. P-gp inhibitors (e.g., cyclosporine) increase ticagrelor exposure. Concomitant use of ticagrelor with strong CYP3A4 inhibitors and potent CYP3A4 inducers should be avoided [1].

In vitro metabolism studies demonstrate that ticagrelor and its major active metabolite are weak inhibitors of CYP3A4, potential activators of CYP3A5 and inhibitors of the P-gp transporter. Concomitant use of ticagrelor with substrate of the P-gp transporter with a narrow therapeutic index, such as digoxin, should be avoided. The *in vivo* effects of ticagrelor on the PK of several drugs are listed in the Summary of Product Characteristics [1].

5.3. Recommended dose

It is recommended to initiate ticagrelor treatment with a 180 mg (two 90 mg tablets) loading dose and continue treatment with 90 mg twice daily, to be administered with or without food [1]. In this study, the dose level to be investigated is 90 mg, administered as a single dose of each treatment on four occasions, respectively.

5.4. Adverse events, contraindications and warnings

Like other antiplatelet agents, ticagrelor increases the risk of bleeding. The most common adverse reactions reported include headache, somnolence, dizziness, epistaxis, nausea, abdominal pain, back pain, dyspnea, ecchymosis, lethargy, pharyngo-laryngeal pain, blurred vision, postural dizziness, pollakiuria (frequent urination), and increased tendency for bruising. Drug related dyspnea caused by ticagrelor is self-limiting [1].

Ticagrelor is contraindicated in conditions of history of intracranial hemorrhage, active pathological bleeding (e.g., peptic ulcer), severe hepatic impairment (i.e., increased risk of bleeding due to reduced synthesis of coagulation proteins) and hypersensitivity (e.g., angioedema) to ticagrelor or any component of the product [1].

5.5. Study rationale and justification of study design

This study will be conducted to support the pharmaceutical development of the orodispersible tablet formulation of ticagrelor for the benefit of use by patients from Japanese origin. The purpose of the study is to assess the bioequivalence between ticagrelor orodispersible (OD) tablets when administered with water and without water, and ticagrelor immediate-release (IR) tablets in healthy Japanese subjects. A randomized, crossover design has been chosen to minimize the effects of between-subject variability and any period effects on the overall results. The study is open-label since the primary objective is to evaluate the bioequivalence between ticagrelor OD tablets and ticagrelor IR tablets in healthy Japanese subjects.

For design of this study the following guidelines were considered:

- United States Department of Health and Human Services, Food and Drug Administration Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations. Center for Drug Evaluation and Research, March 2003 BP
- European Medicines Agency (EMA) Guideline on the Investigation of Bioequivalence CPMP/QWP/EWP/1401/98 Rev. 1, 2010
- Japanese Pharmaceutical and Food Safety Bureau Guideline for Bioequivalence Studies of Generic Products. February 29, 2012.

5.6. Risk-benefit assessment

There are no direct benefits for the subjects 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) and with adequate washout between the treatment periods, the risk for bleeding has been minimized. Moreover the inclusion and exclusion criteria have considered the contraindication and warnings suggested by regulatory approved prescribing information [1].

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 subjects, adverse events (AEs) associated with bleeding were infrequent and were generally considered to be mild. In this study, necessary measures will be taken to minimize this risk of bleeding by excluding subjects at high risk of bleeding such as persons with history of hemophilia, von Willebrand's disease, lupus anticoagulant, or other diseases/syndromes that can either alter or increase the propensity for bleeding. Also subjects with a history of a clinically significant non-traumatic bleed or clinically significant bleeding risk, as judged by the investigator, will be excluded (see Section 7.6.2).

The risk of ticagrelor exposure to subjects in this study is expected to be equivalent to the safety profile in subjects 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, dyspnea, ecchymosis, lethargy, pharyngo-laryngeal 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. Dyspnea 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 outliers, and returned to baseline within 60 hours of discontinuing ticagrelor. Ticagrelor (single 900 mg dose) had no cardiac ventricular

repolarization 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.

AstraZeneca will immediately notify the investigator of important safety data that becomes available during the study.

6. STUDY OBJECTIVES

The objective of the study is to assess the bioequivalence between ticagrelor OD tablets and ticagrelor IR tablets in healthy Japanese subjects.

6.1. Primary objective

- To evaluate bioequivalence of ticagrelor OD tablets when administered with water and without water, compared to ticagrelor IR tablets

6.2. Secondary objectives

- To examine the pharmacokinetic (PK) profiles of ticagrelor OD tablets when administered with water and without water, compared to ticagrelor IR tablets
- To assess safety and tolerability of ticagrelor OD tablets when administered with water and without water, compared to ticagrelor IR tablets

Refer to Section 11.9.1 and Section 9.3 for PK parameters and safety variables, respectively.

7. OVERALL DESIGN AND PLAN OF THE STUDY

7.1. Overall study design

This study will be an open-label, randomized, three-period, three-treatment, crossover study in healthy Japanese subjects (males and females), performed at a single study center.

The study will comprise:

- A screening period of maximum 28 days;
- Three treatment periods during which subjects will be resident prior to the evening meal the night before dosing with ticagrelor (Day -1) until at least 48 hours after dosing; discharged on the morning of Day 3; and
- A final visit within 5 to 10 days after the last administration of ticagrelor.

There will be a minimum washout period of 7 days between each dose administration.

7.1.1. End of study

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

7.1.2. Interim analyses

No interim analyses will be performed in this study.

7.1.3. Expected duration of study

Each subject will be involved in the study for 7 to 8 weeks.

7.2. Study flow chart and schedule of assessments

The flow of events is illustrated in Figure 1 for treatments A, B and C, depending on the subject's assigned randomization (refer to Section 11.4).

Forty-two subjects will be randomized to ensure at least 30 evaluable subjects at the end of the last treatment period. Subjects will receive single doses of ticagrelor in three different ways under fasted conditions.

Following an overnight fast of at least 10 hours, each subject will receive a single dose of each treatment on three occasions, respectively.

The schedule of assessments displaying assessments/tasks and time-points is presented in Table 1.

Figure 1 Study Flow Chart

	Visit 2 Treatment Period 1 Days 1, 2 and 3		Visit 3 Treatment Period 2 Days 1, 2 and 3		Visit 4 Treatment Period3 Days 1, 2 and 3
Sequence ABC	A	⇨	B	⇨	C
Sequence BCA	B	⇨	C	⇨	A
Sequence CAB	C	⇨	A	⇨	B
Sequence ACB	A	⇨	C	⇨	B
Sequence BAC	B	⇨	A	⇨	C
Sequence CBA	C	⇨	B	⇨	A

A = a single dose of 1 x 90 mg ticagrelor orodispersible (OD) tablet administered with 150 mL of water
B = a single dose of 1 x 90 mg ticagrelor OD tablet administered without water
C = a single dose of 1 x 90 mg ticagrelor immediate-release (IR) tablet administered with 150 mL of water

Table 1 Schedule of Assessments

Assessments/Tasks	Visit 1	Visit 2, 3 and 4		Visit 5
	Screening	Admission	Treatment Periods 1, 2 and 3	Follow-up/Early Termination
	From Day -28	Day -1	Days 1, 2 and 3	5 to 10 days after last administration of IMP
Signed informed consent	X			
Study residency[1]		X		
Ambulatory visits[2]	X			X
Randomization[3]			X	
Inclusion/exclusion criteria	X			
Eligibility check[4]		X		
Relevant medical and surgical history	X			
Demographic data	X			
Body weight, height, and BMI	X			
Viral serology screening[5]	X			
Serum FSH (females only)	X			
Coagulation	X			
Urine drugs of abuse, alcohol and cotinine testing	X	X		
Pregnancy testing (females only)[6]	X	X		X
Prior and concomitant medication[7]	◄——— X ———►			
Safety and tolerability				
Adverse event questioning[8]	◄——— X ———►			
Vital signs (blood pressure, pulse)[9]	X		X	X
12-Lead ECG[10]	X			X
Physical examination[11]	X			X

Assessments/Tasks	Visit 1	Visit 2, 3 and 4		Visit 5
	Screening	Admission	Treatment Periods 1, 2 and 3	Follow-up/Early Termination
	From Day -28	Day -1	Days 1, 2 and 3	5 to 10 days after last administration of IMP
Hematology and clinical chemistry; urinalysis (dipstick)[12]	X			X
Pharmacokinetics				
IMP administration[13]			X	
Pharmacokinetic sampling[14]			X	

BMI = body mass index; ECG = electrocardiogram; FSH = follicle-stimulating hormone; IMP = investigational medicinal product

1 Admission on Day -1 to each treatment period; discharged from the clinical unit 48 hours after dosing (morning of Day 3) to each treatment period.

2 Ambulatory visits: Screening and follow-up visit.

3 Randomization will be performed after confirmation of eligibility on Day 1 of the first treatment period.

4 In addition to the eligibility check, the recorded medical history will be updated if necessary before randomization.

5 Including Hepatitis B, Hepatitis C, and human immunodeficiency virus (HIV) screening.

6 Serum pregnancy test at screening; urine pregnancy tests thereafter (females only).

7 Prior and concomitant medication is defined in Section 11.8.1.

8 Serious adverse events (SAEs) will be recorded from the signing of informed consent and adverse events (AEs) will be recorded from randomization until the final follow-up visit.

9 Blood pressure and pulse measurements (supine position) will be collected at screening, during treatment periods at pre-dose and post-dose at 2, 4 and 24 hours, as well as at the follow-up visit. Subjects who discontinue the study will take part in a follow-up examination (early termination).

10 12-lead ECG will be performed at screening and the follow-up visit. Subjects who discontinue the study will take part in a follow-up examination (early termination).

11 Full physical examination will be performed at screening and at the follow-up visit.

12 Hematology, clinical chemistry and urinalysis will be performed at screening and at the follow-up visit. Subjects who discontinue the study will take part in a follow-up examination (early termination).

13 IMP administration: On Day 1 after an overnight fast of at least 10 hours. Details of IMP administration is described in Section 8.1.

14 Blood samples for the determination of plasma concentrations of both ticagrelor and AR-C124910XX will be collected at 0 hours (pre-dose) and post-dose at 0.5 (30 minutes), 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours (14 samples per treatment period).

7.3. Order of assessments

It is important that PK sampling occurs as close as possible to scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the time-point.

The sequence at a particular time-point is:

1. Vital signs (blood pressure [BP] and pulse)
2. Pharmacokinetic blood sampling (will be drawn at the specified time-point)

7.4. Dose rationale

In clinical use, it is recommended to initiate ticagrelor treatment with 180 mg (two 90 mg tablets) loading dose and to continue ticagrelor treatment with 90 mg twice daily [1]. Thus, the dose of 90 mg should provide sufficient plasma exposure for the PK analysis of ticagrelor and its active metabolite AR-C124910XX. Ticagrelor 90 mg is the only dose strength commercially available as oral IR tablets (not available in Japan).

7.5. Restrictions during the study

The following restrictions apply for the specified times during the study period:

1. On Day 1 of each treatment period, subjects will be fasted for at least 10 hours prior to dosing and until 4 hours after dosing. No fluids will be allowed apart from water which can be given until 1 hour prior to dosing and then from 2 hours after dosing (excluding water used in conjunction with IMP administration; see Section 8.6).
2. Subjects should not lie fully supine (unless specified for certain assessments) for 4 hours after dosing.
3. Subjects should not engage in any strenuous activity from 72 hours prior to dosing on Day 1 of the first treatment period until after their follow-up visit.
4. Prior to each treatment period subjects should abstain from alcohol for 72 hours prior to admission until after their last PK sample was collected. Between treatment periods subjects should consume no more than 2 units of alcohol per day and completely abstain from 72 hours prior to their next admission. Subjects should also abstain from alcohol for 72 hours before their follow-up visit.

   One unit is equal to approximately ½ pint (200 mL) of beer, one small glass (100 mL) of wine, or one measure (25 mL) of spirits.
5. Prior to each treatment period subjects should abstain from caffeine-containing foods and beverages for 24 hours prior to dosing until discharge from the clinical unit. At other times, subjects should limit their caffeine intake to equivalent of 3 cups of coffee per day (1 cup = 360 mL soda, 180 mL coffee, or 240 mL tea) for the duration of the study.
6. Subjects should abstain from grapefruit or grapefruit juice, Seville oranges (also called bitter orange [a hybrid between a mandarin and pomelo], including marmalade), and quinine (e.g., tonic water) from 7 days prior to admission on Day -1 of the first treatment period until after their follow-up visit.

7. During in-house stay subjects will receive a standard diet (Japanese meals), which excludes all alcohol and grapefruit-containing products. No additional food or beverages must be consumed whilst in the clinical unit.

8. During the subjects' outpatient periods, subjects should abstain from consuming high energy drinks (e.g., Red Bull), and food containing poppy seeds (e.g., specialty breads and muffins) and any over the counter (OTC) medication or herbal preparations until after their final follow-up visit has been completed.

9. Subjects will be required to abstain from blood or plasma donation until 3 months after their follow-up visit.

10. Medication restrictions

    - Abstain from use of aspirin, ibuprofen, non-steroidal anti-inflammatory drugs (NSAIDs) or any other drug known to increase the propensity for bleeding until the follow-up visit.
    - Also refer to Section 8.7.

11. Reproductive restrictions

    - Female subjects

      Women of childbearing potential are not allowed to participate in this study.

      Women of non-childbearing potential are defined in Section 7.6.1.

    - Male subjects

    It is important that women of childbearing potential who are the partners of male subjects do not become pregnant during the study and for a total period of 3 months after the subjects have taken the last dose of IMP.

    As a precaution, all male subjects should avoid fathering a child by either true abstinence or the use of two effective means of contraception with their partner from the time of IMP administration until 3 months after the last dose of IMP.

    Two or more of the following methods are acceptable and must include at least one barrier method:

    – Surgical sterilization (i.e., bilateral tubal ligation for females; vasectomy for male partners)
    – Placement of an intrauterine device or intrauterine system
    – Hormonal contraception (implantable, patch, oral)

– Barrier methods: Condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository

Male subjects who have been sterilized are required to use one barrier method of contraception (condom).

- Sperm donation

  Male subjects should not donate sperm for the duration of the study and for at least 3 months after the last day of IMP administration.

- Pregnancy

  Subjects will be instructed that if their partner becomes pregnant during the study this should be reported to the investigator. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject's partner is subsequently found to be pregnant after the volunteer is included in the study, then consent will be sought from the partner and if granted any pregnancy will be followed and the status of mother and/or child will be reported to the sponsor after delivery.

  A pregnancy notification form and follow-up will be completed.

7.6. Selection of study population

The investigator should keep a subject screening log of all potential subjects who consented and were subjected to screening procedures.

Subjects who fail to meet the inclusion criteria or meet any exclusion criterion should not, under any circumstances, be randomized into the study. There can be no exceptions to this rule.

This study will be conducted in male and female subjects. The study may not necessarily be balanced regarding gender. The study was not formally powered to detect differences between genders for the primary endpoint. It is not planned to perform sub-analyses on gender.

7.6.1. Inclusion criteria

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

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

2. Healthy male and female subjects aged 20 to 45 years with suitable veins for cannulation or repeated venepuncture.

3. Be Japanese.

   Japanese is defined as having both parents and four grandparents who are Japanese. This includes second and third generation Japanese whose parents or grandparents are living in a country other than Japan.

4. Females must have a negative pregnancy test at screening and on each admission to the clinical unit, must not be lactating, and must be of non-childbearing potential, confirmed at screening by fulfilling one of the following criteria:

   - Postmenopausal defined as amenorrhea for at least 12 months or more following cessation of all exogenous hormonal treatments and FSH levels in the postmenopausal range.
   - Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.

5. Have a body mass index (BMI) between 18.0 and 27.0 kg/m^2 inclusive and weigh at least 45 kg and no more than 85 kg inclusive.

6. Be able and willing to communicate with the investigator and comply with all study procedures, including reproductive restrictions.

7.6.2. Exclusion criteria

Persons who meet one or more of the exclusion criteria will not be considered eligible to participate in the study.

1. History of any clinically significant disease or disorder which, in the opinion of the investigator, may either put the potential subject at risk because of participation in the study, or influences the results or the potential subject'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 drugs.

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

4. Any clinically significant abnormalities in hematology, clinical chemistry, coagulation or urinalysis results, as judged by the investigator.

5. Any clinically significant abnormal findings in vital signs, as judged by the investigator.

6. Any clinically significant abnormalities on 12-lead ECG, as judged by the investigator.

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

8. Known or suspected history of drug abuse, as judged by the investigator.

9. Has received a new chemical entity (defined as a compound which has not been approved for marketing) within 3 months of the first administration of IMP in this study. The period of exclusion begins 3 months after the final dose or 1 month after the last visit whichever is the longest.

   Note: Subjects consented and screened, but not randomized in this study or a previous Phase I study, are not excluded.

10. Plasma donation within 1 month of screening or any blood donation/loss more than 500 mL during the 3 months prior to screening.

11. 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.

12. Current smokers or those who have smoked or used nicotine products within the previous 3 months.

13. Positive screen for drugs of abuse or cotinine (cotinine level above 500 ng/mL) at screening or on each admission to the clinical unit or positive screen for alcohol on each admission to the clinical unit.

14. Use of drugs with enzyme-inducing properties such as St John's Wort within 3 weeks prior to the first administration of IMP.

15. Use of any prescribed or non-prescribed medication including antacids, analgesics (other than paracetamol/acetaminophen), herbal remedies, megadose vitamins (intake of 20 to 600 times the recommended daily dose) and minerals during 2 weeks prior to the first administration of IMP or longer than 5 half-lives if the medication has a long half-life.

    Note: Hormonal replacement therapy is not allowed for females.

16. Known or suspected history of alcohol or drug abuse or excessive intake of alcohol, as judged by the investigator.

17. Involvement of any AstraZeneca or clinical unit employee or their close relatives.

18. Judgment by the investigator that the potential subject should not participate in the study if they have any ongoing or recent (i.e., 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.

19. Consumption of poppy seeds within 7 days of first admission to the clinical unit.

20. History of hemophilia, 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 hemorrhage, hematemesis, melena, hemoptysis, severe epistaxis, severe thrombocytopenia, intracranial hemorrhage; or rectal bleeding within 1 year prior to screening; or history suggestive of peptic ulcer disease; or at the discretion of the investigator.

22. History of a clinically significant non-traumatic bleed or clinically significant bleeding risk, as judged by the investigator.

23. Use of aspirin, ibuprofen, NSAIDs, or any other drug known to increase the propensity for bleeding for 2 weeks before randomization.

24. Platelet count less than 150 x 10^9/L.

25. Vulnerable subjects, e.g., kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order.

7.6.3. Discontinuation of investigational medicinal product, individual stopping criteria and withdrawal from the study

Subjects may be discontinued from the IMP in the following situations:

- Healthy subject decision. The healthy subject is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse event
- Severe noncompliance to study protocol
- Any significant and clinically relevant changes in the safety parameters (e.g., ECG, blood pressure, pulse, laboratory assessments and AEs) making the continuation of IMP administration unjustified.

- Study-specific withdrawal criteria: If a subject reports symptoms, which are considered unacceptable by the subject or the investigator, he/she will be withdrawn from the study. In particular:
  - Any moderate or severe bleeding event
  - Any other severe or serious adverse event (SAE) that is judged as possibly related to the IMPs by the investigator
  - Any case of Potential Hy's Law (PHL) according to Appendix 15.3

  The appropriate AE form in the case report form (CRF) is to be completed.

7.6.4. Replacement of subjects

Subjects who are withdrawn from the study due to AEs or changes in safety parameters will not be replaced unless a specific sample size is to be met for statistical purposes and if the sponsor's responsible physician and the Principal Investigator (PI) agree it is safe to do so. Subjects who withdraw or are withdrawn from the study for other reasons may be replaced following discussion with the sponsor.

Where a subject, who does not meet the selection criteria, is randomized in error and this is identified before IMP administration, the subject should be withdrawn from the study. If a subject is withdrawn prior to IMP administration, the subject will be replaced.

If a subject, who does not meet the selection criteria, has been dosed before the error is identified, the subject should be advised to continue safety assessments to ensure their safety. The PI will inform the AstraZeneca Lead Physician of the error and a joint decision will be made as to whether the subject should be replaced.

7.6.5. Premature termination of the study and stopping criteria

The study may be terminated prematurely if:

- The PI and the sponsor assess that the number and/or severity of AEs justify discontinuation of the study. For instance when there is at least 1 case of fatal SAE or 2 cases of other SAEs, in both situations considered related by the investigator and the sponsor.
- The sponsor considers the applied doses of the study drug to be no longer relevant.
- The sponsor decides to discontinue the study.
- Data not known before become available and raise concern about the safety of IMP so that continuation would pose potential risks to the subjects.

Premature termination of the study must be mutually agreed upon by the PI and the sponsor and must be documented. However, study results will be reported according to the requirements outlined in this clinical study protocol as far as applicable.

7.6.6. Total blood volume

The approximate total amount of blood to be collected from each subject in this study, excluding repeat samples, is summarized in Table 2.

Table 2 Total Blood Volume

Assessment	Sample volume	Number of samples				Total volume
		Screening	Admission	Treatment period	Follow-up	
Hematology	2.7 mL	1	0	0	1	5.4 mL
Clinical chemistry†	7.5 mL	1	0	0	1	15.0 mL
Coagulation	3.0 mL	1	0	0	0	3.0 mL
Pharmacokinetics*	3.0 mL	0	0	3 x 14	0	126.0 mL
Total						**149.4 mL**

† At screening, viral serology, pregnancy testing (females only) and serum FSH (females only) will be performed on the sample collected for clinical chemistry assessments.

* More details on pharmacokinetic (PK) sampling will be provided in the Laboratory Manual.

Repeat blood samples may be collected for safety reasons. The maximum volume to be drawn from each subject must not exceed 500 mL.

8. TREATMENTS

8.1. Identity of the investigational medicinal product

Supplier:	AstraZeneca
Formulations:	*Test product:* Ticagrelor 90 mg OD tablets *Reference product:* Ticagrelor 90 mg IR tablets
Strength/Concentrations:	90 mg
Route of administration:	Oral
Regimen:	Single dose
Special handling requirements:	Not applicable
Availability of IMP:	The IMP will be provided to the study center by AstraZeneca.

AstraZeneca will provide detailed preparation, storage and handling instructions for each product and treatment. Details of the batch numbers will be included in the Trial Master File and the final CSR, as applicable.

8.2. Supply of investigational medicinal product

The IMP will be manufactured in accordance with Good Manufacturing Practice (GMP) and will be supplied by AstraZeneca.

The IMP will be provided in bulk labelled with a study specific label and re-packaged into subject-specific containers by PAREXEL, as applicable.

An agreement between PAREXEL and AstraZeneca will be in place to cover all pharmacy related activities, detailing roles and responsibilities prior to receipt of the IMP at the clinical unit.

A release document signed by a legally authorized Qualified Person (QP) at PAREXEL will be placed in the appropriate section of the Trial Master File to document labelling.

Dispensing and retention of reserve BE samples of IMP will be performed in accordance with the FDA Code of Federal Regulations 21, Part 320 Bioavailability and Bioequivalence requirements. To avoid misuse, reserve samples should be labeled as such.

8.3. Storage and handling procedures

The IMP will be stored in a secure facility under appropriate storage conditions. Details of storage conditions will be provided on the label of the IMP.

AstraZeneca will be permitted upon request to audit the supplies, storage, dispensing procedures and records.

8.4. Labelling

Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements and medical device directive for labelling.

8.5. Drug accountability, dispensing and destruction

The IMP provided for this clinical study will be used only as directed in the clinical study protocol. In accordance with GCP, the clinical unit will account for all supplies of the IMP. Details of receipt, storage, assembly/dispensing and return will be recorded.

All used and unused supplies of the IMP will be destroyed by PAREXEL at the end of the study. The certificate of delivery and destruction must be signed, in accordance with instruction by AstraZeneca. Destruction must not take place unless the responsible person at AstraZeneca has approved it.

8.6. Doses and treatment regimen

Subjects will receive single doses of ticagrelor in three different ways under fasted conditions.

Following an overnight fast of at least 10 hours, each subject will receive a single dose of each treatment on three occasions, respectively:

Treatment A	Test product	Ticagrelor OD tablets administered with water Place the OD tablet, with dry hands on the tongue where it will disintegrate and be swallowed subsequently with 150 mL non-carbonated water at room temperature	1 x 90 mg
Treatment B	Test product	Ticagrelor OD tablets administered without water Place the OD tablet, with dry hands on the tongue where it will disintegrate and be swallowed subsequently with saliva	1 x 90 mg
Treatment C	Reference product	Ticagrelor IR tablets administered orally with 150 mL of water	1 x 90 mg

No fluids will be allowed apart from water which can be given until 1 hour prior to administration of the IMP and then from 2 hours after administration of the IMP. A meal can be given 4 hours after administration of the IMP.

Other restrictions, including posture control are described in Section 7.5. Data of subjects may be excluded from the PK analysis set as described in Section 11.3.2.

8.7. Concomitant medication

Apart from paracetamol/acetaminophen, no concomitant medication or therapy will be allowed, including herbal remedies, vitamin supplements and OTC products, without the consent of the investigator. For females, hormonal replacement therapy is not allowed.

Medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the investigator during the residential period. When any medication is required, it should be prescribed by the investigator. Following consultation with AstraZeneca Lead Physician, the investigator must determine whether or not the subject should continue in the study.

8.8. Treatment compliance

Dosing will take place at the PAREXEL Early Phase Clinical Unit. After IMP administration, a check of the subject's mouth and hands will be performed. The exact day and time of IMP administration, as well as the volume of water accompanying the administration will be recorded in ClinBase.

8.9. Randomization

8.9.1. Subject enrolment and randomization

The PI will ensure:

- Signed informed consent is obtained from each potential subject before any study specific procedures are performed.
- Each potential subject is assigned a unique enrolment number at screening upon signing the ICD.
- The eligibility of each subject is in accordance with the inclusion and exclusion criteria.
- Each eligible subject is assigned a unique randomization code (subject number).

Randomization will be performed after confirmation of eligibility on admission to Treatment period 1 (on Day -1). Randomization codes will be assigned strictly sequentially as subjects become eligible for randomization, starting from e.g., 101 (no leading zeroes). When using unique enrolment number, the specific format must be followed (i.e., reduced enrolment number, e.g., "1001" in ClinBase and on labels, full enrolment number, e.g., "E0001001" for

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

8.9.2. Procedures for randomization

Upon completion of the randomization request form, the randomization will be produced by AstraZeneca using the global randomization system (GRand).

The number of subject identifiers generated for the study will account for the number of randomized subjects per the sample size calculation (N = 42 (see Section 11.4) as well as providing sufficient randomization numbers for replacements. For this study, a total of 84 subject identifiers will be randomly assigned to six treatment sequences: ABC, BCA, CAB, ACB, BAC, CBA.

Subjects will be assigned a randomization number for dosing in consecutive order per the randomization list.

Once a randomization number has been allocated to one subject, it may not be assigned to another subject. If subjects withdraw prematurely from the study and are replaced under the direction of the sponsor, then a new randomization number will be assigned. The replacement subjects will be assigned to the same treatment sequence as the discontinued subject using the next available randomization number that corresponds to the specific sequence.

8.10. Blinding

This is an open-label study.

9. MEASUREMENTS AND METHODS OF ASSESSMENT

9.1. Appropriateness of measurements

Standard measures to assess PK, safety and tolerability apply during the study. For the single doses of ticagrelor planned to be given during this study, no safety issues are expected.

9.2. Pharmacokinetics

9.2.1. Sample collection and handling

Blood samples for the determination of plasma concentrations of both ticagrelor and its active metabolite AR-C124910XX will be collected for each treatment period: 0 hours (pre-dose) and post-dose at 0.5 (30 minutes), 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours (14 samples per treatment period).

Samples will be collected, handled, labelled, stored and shipped as detailed in the Laboratory Manual. Plasma samples will be analyzed for ticagrelor and AR-C124910XX using a validated assay.

9.2.2. Labelling and shipment of biohazard samples

Samples will be 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) (for International Airline Transportation Association [IATA] guidance, see Appendix 15.2 of this clinical study protocol).

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

9.2.3. Chain of custody of biological samples

A full chain of custody will be maintained for all samples throughout their life cycle.

The PI will ensure full traceability of collected biological samples from the subjects while in storage at the clinical unit until shipment and will keep documentation of receipt of arrival.

The sample receiver will keep full traceability of samples while in storage and during use, until used, disposed of, or until further shipment or disposal (where appropriate) and will keep documentation of receipt of arrival.

Samples retained for further use will be registered in the AstraZeneca bio-bank system during the entire life cycle.

9.2.4. Pharmacokinetic drug assays

Blood samples for determination of ticagrelor and AR-C124910XX concentrations in plasma will be analyzed by Covance on behalf of Clinical Bioanalysis Alliance, AstraZeneca Research and Development, using a validated assay. Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites.

Full details of the analytical method and analyses performed used will be described in a separate Bioanalytical Report.

9.2.5. Sample storage and destruction

Pharmacokinetic samples will be disposed of after finalization of the Bioanalytical Report or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, 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 be reported separately in a Bioanalytical Report, not in the CSR.

9.2.6. Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed if not already analyzed and the action documented. As collection of donated biological samples is an integral part of the study, consent withdrawal implies that the subject is withdrawn from further study participation.

AstraZeneca ensures the laboratory holding the samples is informed about the withdrawn consent immediately and that samples are disposed of or destroyed, the action documented and the signed document returned to the clinical unit.

9.3. Safety and eligibility measurements

Safety and tolerability variables will include AEs, vital signs (blood pressure [BP], pulse), 12-lead electrocardiograms (ECGs), physical examination and laboratory assessments (hematology, clinical chemistry and urinalysis).

Viral serology, follicle-stimulating hormone (FSH) (females only), coagulation and urine drugs of abuse, alcohol and cotinine will be assessed for eligibility. In addition to the above, pregnancy testing (females only) and use of concomitant medication will also be reported.

For timing of assessments refer to the Schedule of Assessments in Table 1.

9.3.1. Adverse Events

Refer to Section 12.

9.3.2. Vital Signs

The following variables will be collected after the subject has rested in the supine position for at least 5 minutes:

- Systolic BP (SBP) (mmHg)
- Diastolic BP (DBP) (mmHg)
- Pulse (beats per minute [bpm])

The measurement of vital signs will be carried out according to the relevant PAREXEL standard operating procedures (SOPs).

9.3.3. Resting 12-lead electrocardiograms

A 12-lead ECG will be obtained after the subject rested in the supine position for at least 10 minutes.

The investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided as to whether or not the abnormality is clinically significant and the reason for the abnormality will be recorded. The overall evaluation (normal/abnormal) will be reported in ClinBase.

The investigator may add extra 12-lead resting ECG safety assessments if there are any abnormal findings or if the investigator considers it is required for any other safety reason. These assessments should be entered as an unscheduled assessment.

All ECG readings will be digitally stored as source documents.

9.3.4. Physical examination

Full

The complete physical examinations will include an assessment of the general appearance, respiratory, cardiovascular, abdomen, skin, head, and neck (including ears, eyes, nose, mouth and throat), lymph nodes, thyroid, musculoskeletal and neurological systems.

Abbreviated (Brief)

The abbreviated physical examinations will include an assessment of the general appearance, skin, abdomen, musculoskeletal, cardiovascular and respiratory systems.

9.3.5. Laboratory assessments

9.3.5.1. Hematology

White blood cell (WBC) count
Red blood cell (RBC) count
Hemoglobin (Hb)
Hematocrit (HCT)
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Neutrophil absolute count
Lymphocyte absolute count
Monocyte absolute count
Eosinophil absolute count
Basophil absolute count
Platelet count
Reticulocyte absolute count

9.3.5.2. Serum clinical chemistry

Sodium
Potassium
Urea
Creatinine
Albumin
Calcium
Phosphate
Glucose (fasting)
C-reactive protein (CRP)
Alkaline phosphatase (ALP)
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Gamma-glutamyl transpeptidase (GGT)
Total bilirubin
Unconjugated bilirubin
Conjugated bilirubin
FSH (postmenopausal women only)

9.3.5.3. Coagulation

International Normalized Ratio (INR)
Prothrombin time
Activated Partial Thromboplastin Time (aPTT)

9.3.5.4. Urinalysis

Glucose
Protein
Blood
Microscopy (if positive for blood or protein)

9.3.5.5. Viral serology

HIV I and II
HBsAg
Hepatitis C Virus antibody

9.3.5.6. Urine drugs of abuse, alcohol and cotinine

Amphetamine / Ecstasy
Alcohol
Cannabinoids
Cocaine
Opiates
Cotinine (screening only)
Tricyclic anti-depressants (TCA)
Benzodiazepines
Methadone metabolites
Barbiturates
Phencyclidine
Urine creatinine

9.3.5.7. Pregnancy testing

Beta human chorionic gonadotropin will be measured in serum and urine samples as per schedule of assessments (female subjects only).

9.3.6. Concomitant medication

Refer to Section 8.7.

10. DATA QUALITY ASSURANCE AND DATA MANAGEMENT

10.1. Quality control and source data verification

Source data verification will be conducted with due regard to subject confidentiality.

The clinical unit will allow the study monitor and sponsor representative direct access to all study documents, medical files, and source documents to enable verification of the study data, whilst maintaining the anonymity of the subject and confidentiality of the data.

Internal quality control will be performed at all stages of the study by the clinical unit.

10.2. Audit/Inspections

The clinical unit facilities and all study data/documentation may be audited/inspected by independent auditor/inspector/any representatives of regulatory authorities. The investigator must allow the applicable persons access to all relevant facilities and data/documents. The investigator must be available to discuss any findings/issues.

If an audit was performed, the audit certificate will be included in the CSR.

10.3. Study monitoring

The conduct of the study will be monitored by an independent PAREXEL monitor or a subcontracted monitor to ensure compliance with applicable regulatory requirements and GCP. The summary of the documentation of the monitoring visits will form part of the study documentation and will be archived as such.

10.4. Data collection

PAREXEL's ClinBase™ system is an electronic source data capturing and information management system. The system combines all aspects of source data capturing with process control and clinical study management. All clinical and laboratory data, except those which are paper-based, will be collected in ClinBase. Only paper-based data will be subject to data entry. For electronic source data, no data entry will be performed.

The responsible study monitor will check data at the monitoring visits to the clinical unit. The investigator will ensure that the data collected are accurate, complete and legible. Data will be monitored within ClinBase by the study monitor before being exported. Any changes made during monitoring will be documented with a full audit trail within ClinBase.

10.4.1. Case report forms and source documents

All data obtained using paper collection methods during the clinical study will be recorded in ClinBase. All source documents from which ClinBase entries are derived should be placed in the subject's personal records.

The original ClinBase entries for each subject will be checked against source documents by the study monitor. Instances of missing or uninterpretable data will be discussed with the investigator for resolution.

10.4.2. Access to source documents

During the course of the clinical study, a study monitor will make clinical unit visits to review protocol compliance, compare ClinBase entries and individual subject's personal records, assess IMP accountability and ensure that the clinical study is being conducted according to pertinent regulatory requirements. ClinBase entries will be verified against source documents. The review of medical records will be handled confidentially to ensure subject anonymity.

Checking of the ClinBase entries for completeness and clarity and verifying with source documents, will be required to monitor the clinical study for compliance with GCP and other regulations. Moreover, regulatory authorities of certain countries, IECs/IRBs may wish to carry out source data inspections on-site, and the sponsor's clinical quality assurance group may wish to carry out audits. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and subject confidentiality. The investigator assures the sponsor of the necessary support at all times.

10.5. Data management

PAREXEL will utilize standardized and validated procedures and systems to collect, process and file the clinical data of this study. Any system used will be compliant with FDA 21 CFR Part 11 requirements.

A data management plan (DMP) will be prepared to describe the processes and data-flow within the clinical study. Timelines, versions for the computer systems and the coding will be defined in the DMP, and if applicable, sponsor specific requests will also be documented within. The DMP will be finalized before first dose where possible but before database lock.

A data validation specification (DVS) will be created to outline the validation checks to be performed during the study. The DVS must be finalized before data validation.

After the data has been monitored by the responsible study monitor all data received will be reviewed, logged and filed.

The raw data intended for further processing will be checked by standard routines or according to the DVS and queries will be generated and sent to the investigator for review and resolution. Corrections resulting from these queries will be confirmed on the data clarification forms (DCFs). This process will be repeated until no further discrepancies are found. The data will then be declared as clean. Applicable documentation will be stored in the study files.

Only trained study staff will have access to the clinical database and every change in data will have a full audit trail.

11. STATISTICAL METHODS

11.1. Overview

The statistical methodology below describes the statistical analysis as it is foreseen when the study is being planned.

If circumstances should arise during the study rendering the analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be performed. A separate statistical analysis plan (SAP) will not be written for the study. Any deviations from the statistical methodology defined in this protocol, reasons for such deviations and all alternative/additional statistical analyses that may be performed will be described in the CSR. Such changes to analyses may be written into an abbreviated SAP, if appropriate. The verification and review of all statistical modelling assumptions will be documented appropriately.

11.2. General statistical methodology

All original and derived parameters as well as demographic and disposition data will be listed and described using summary statistics. All safety data (scheduled and unscheduled) will be presented in the data listings.

Demographic and baseline data will be summarized by treatment sequence and overall. Pharmacokinetic data will be summarized by treatment. Safety and tolerability data will be summarized by treatment, if applicable.

Frequency counts (number of subjects [n] and percentages) will be made for each qualitative variable. Descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum) will be calculated for each quantitative variable (unless otherwise stated). Descriptive statistics will only be presented if $n \geq 3$.

The following rules will apply to any repeated safety assessments occurring within each treatment period:

- If the repeated measurement of a specific parameter occurs prior to IMP administration (Day 1), then the last obtained value prior to dosing will be used in the descriptive statistics and in the calculation of changes from baseline;
- If the repeated measurement of a specific parameter occurs after IMP administration (Day 1), then the first (non-missing) value after dosing will be used in descriptive statistics and in the calculation of changes from baseline.

The planned sequence for measurement of multiple assessments at the same time-point is described in Section 7.3.

For safety assessments performed at screening and the follow-up, the following rules will apply for any repeated assessments:

- If the repeated assessment occurs at screening the last available value will be used in the summary statistics;
- If the repeated assessment occurs at the follow-up visit the first non-missing assessment will be used in the summary statistics.

All statistical analyses and production of tables, figures and listings will be performed using SAS® version 9.2 or later.

11.2.1. Missing data

Missing dates and times in the AE data will be handled as described in Section 11.10.1. Concentrations that are below limit of quantification (BLQ) in the PK data will be handled as described in Section 11.9.2.

There will be no imputations of other missing data. All subjects will be included into the safety analyses as far as the data permit.

11.3. Study populations

11.3.1. Safety analysis set

The safety analysis set will include all subjects who received at least one dose of ticagrelor and for whom any safety post-dose data are available.

Unless otherwise stated the safety analysis set will be used for the presentation of all demographic and disposition data, as well as all safety analyses. Exposure to IMP will also be presented using the safety analysis set.

11.3.2. Pharmacokinetic analysis set

The PK analysis set will consist of all subjects in the safety analysis set for whom at least one of the primary PK parameters, for a given analyte, can be calculated for at least two treatment periods (where one of the treatment periods needs to be the period in which the subject received the Reference product [Treatment C]), and who have no major protocol deviations thought to impact on the analysis of the PK data.

Subjects may be excluded from the PK analysis set as a result of the following:

- Data from subjects who experienced vomiting during the course of the study may be deleted from statistical analysis if vomiting occurred at or before median t_{max}

  Clinical PK of ticagrelor are described in Section 5.2.

- Data from subjects for whom the pre-dose concentration is > 5% of C_{max} for ticagrelor in a specific treatment period

A subject may be excluded from the analysis only for the specific treatment period in which the AE occurred.

The exclusion of any subjects or time-points from the calculation of the PK parameters will be documented by the PK Scientist including the reason(s) for exclusion.

The available concentration data and PK parameter data for any subjects excluded from the PK analysis set will be listed only. Concentration data for subjects excluded from the PK analysis set will be presented in the individual figures of concentration versus time plots.

11.4. Determination of sample size

Based on the estimated within-subject coefficient of variation (CV) for C_{max} and $AUC_{(0-t)}$ of ticagrelor and AR-C124910XX of less than or equal to 24%, 30 evaluable subjects are needed to achieve a power of 90% that a two-sided 90% confidence interval (CI) for the ratio of C_{max} between two different ticagrelor treatments will totally be contained within the 0.8-1.25 limit.

Forty-two subjects will be randomized to a 6 sequence Williams square design for 3 periods and 3 treatments: ABC, BCA, CAB, ACB, BAC and CBA, in order to ensure at least 30 evaluable subjects at the end of the last treatment period.

11.5. Protocol Deviations

Protocol deviations are considered any deviation from the clinical study protocol relating to a subject, and include the following:

- Inclusion/exclusion criteria deviations
- Dosing deviations (e.g., incorrect treatment received, subject was not fasted as per the protocol requirements prior to and after dosing)
- Time window deviations for safety and/or PK assessments
- Subjects receiving prohibited concomitant medications
- Other procedural and study conduct deviations recorded by the clinical unit on a protocol deviation log

The criteria for the assessment and reporting of protocol deviations will be stipulated in a separate study-specific protocol deviation specification (PDS) document. This will include a Windows Allowance Document (WAD) which stipulates tolerance windows for safety and PK assessments. Measurements performed within these tolerance windows will not be considered as protocol deviations and will not be reported.

All protocol deviations will be discussed at the data review meeting prior to database hard lock in order to define the analysis sets for the study.

Important protocol deviations will be listed by subject.

Protocol deviations will be handled in accordance with PAREXEL SOPs.

For handling of protocol amendments, see Section 3.6.

11.6. Subject disposition

Subjects and/or data excluded from the PK analysis set will be listed including the reason for exclusion. Subject disposition will be summarized and will include the following information: number of subjects randomized and dosed, number and percentage of subjects completing the study and the number and percentage of subjects who were withdrawn (including reasons for withdrawal). Disposition data will be presented based on all subjects randomized.

Subject discontinuations will be listed including the date of study exit, duration of treatment and reason for discontinuation. A listing of informed consent response will also be presented.

11.7. Demographic and baseline data

Demographic variables (age, gender, race, ethnicity, height, weight and BMI) will be listed by subject. Demographic characteristics (age, gender, race and ethnicity) and subject characteristics (height, weight and BMI) will be summarized separately by treatment sequence and for all subjects in the safety analysis set. The denominator for percentages will be the number of subjects in the safety analysis set for each treatment sequence or for all subjects as applicable.

Medical history data will be listed by subject including visit, description of the disease/procedure, Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC), MedDRA preferred term (PT), start date, and stop date (or ongoing if applicable).

A summary of the number and percentage of subjects who had relevant medical histories will be presented by treatment sequence and for all subjects for the medical history PT.

11.8. Prior and concomitant medication and drug administration

11.8.1. Prior and concomitant medication

Prior medications are those that started and stopped prior to the first dose of IMP; all medications taken after first dosing are considered as concomitant (including medications that started prior to dosing and continued after).

Prior and concomitant medication will be listed by subject and will include the following information: reported name, PT, the route of administration, dose, frequency, start date/time, duration and indication. Prior and concomitant medication will be coded according to the sponsor's drug dictionary.

11.8.2. Drug administration

Drug administration dates and times will be listed for each subject and treatment period.

11.9. Pharmacokinetic analysis

11.9.1. Pharmacokinetic parameters

Where possible, the PK parameters will be assessed for ticagrelor (parent) and its active metabolite AR-C124910XX on plasma concentrations.

Primary PK parameters

C_{max}	Maximum observed plasma concentration
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from time zero to time of last quantifiable analyte concentration
AUC	Area under plasma concentration-time curve from zero to infinity

Secondary PK parameters

t_{max}	Time to reach maximum observed concentration
$t_{½\lambda z}$	Half-life associated with terminal slope (λ_z) of a semi-logarithmic concentration-time curve
kel	Elimination rate constant
MRT	Mean residence time
MRC_{max}	Ratio of metabolite C_{max} to parent $C_{max,}$ adjusted for differences in molecular weights
$MRAUC_{(0-t)}$	Ratio of metabolite $AUC_{(0-t)}$ to parent $AUC_{(0-t),}$ adjusted for differences in molecular weights

MRAUC	Ratio of metabolite AUC to parent AUC, adjusted for differences in molecular weights

The following diagnostic parameters will be listed, but not summarized:

λ_z upper and lower	The time interval (h) of the log-linear regression to determine $t_{½}$
λ_z, N	Number of data points included in the log-linear regression analysis
Rsq_adj	Regression coefficient adjusted for λ_z, N , Goodness of fit statistic for calculation of λ_z
$\%AUC_{extrap}$	Percentage of AUC obtained by extrapolation, calculated as $[(C_{last}/\lambda_z)/AUC * 100]$ where λ_z refers to the terminal elimination rate constant and C_{last} to the drug concentration at last observed time-point

Additional PK parameters may be determined where appropriate.

11.9.2. Derivation of pharmacokinetic parameters

The PK analyses of the plasma concentration data for ticagrelor and its active metabolite, AR-C124910XX, will be performed by Covance, on behalf of Clinical Pharmacokinetic Alliance, AstraZeneca Research and Development.

PK parameters will be derived using non-compartmental methods with Phoenix® WinNonlin® Version 6.3, or higher and/or SAS® Version 9.2, or higher. All descriptive and inferential statistical computations will be performed using SAS® Version 9.2, or higher.

PK analysis will, where possible, be carried out using actual times recorded in the raw data. If actual times are missing, nominal times may be used.

Plasma concentrations BLQ from the time of pre-dose sampling (t=0) up to the time of the first quantifiable concentration will be set to a value of zero. After this time-point, BLQ plasma concentrations will be set to missing for all concentration profiles. Where two or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.

Terminal elimination half-life, estimated as $(\ln 2)/\lambda_z$, where λ_z refers to the terminal elimination rate constant, estimated by log-linear least squares regression of the terminal part of the concentration-time curve. For the determination of λ_z, the start of the terminal elimination phase for each subject will be defined by visual inspection and will be the first point at which there is no systematic deviation from the log linear decline in plasma concentrations. A minimum of 3 data points will be used in calculating λ_z, and the duration of time over which λ_z is estimated will be at least twice the subsequently estimated terminal half-life. Where an elimination half-life is estimated over less than two half-lives, it will be flagged, commented upon in the study report and interpreted with caution. AUC is estimated by $AUC_{(0\text{-}t)} + C_{last}/\lambda_z$ where C_{last} is the drug concentration at last observed time-point.

AUC values where the percentage extrapolation is less than 20% will be reported. The AUC values where the percentage extrapolation is greater than 20% will be flagged in the data listings.

AUCs will be calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing.

The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.

11.9.3. Presentation of pharmacokinetic data

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. Plasma concentrations and PK parameters will be summarized by treatment using appropriate descriptive statistics. Where possible, the following descriptive statistics will be presented: n, geometric mean, geometric CV, arithmetic mean, arithmetic SD, median, minimum and maximum. The correlation coefficient for determining kel will be estimated together with time-points used. For t_{max}, only n, median, minimum and maximum will be presented.

The ratios of C_{max}, $AUC_{(0\text{-}t)}$ and AUC of Test product to those of Reference product in each individual and analyte will be calculated.

The geometric mean is calculated as the exponential of the arithmetic mean calculated using log-transformed data.

The geometric CV% is calculated as $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where s is the SD of the log transformed data.

Individual PK parameters will be presented to three significant figures, with the exception of t_{max} which will be presented to two decimal places. Values >1000 in either the concentration data or PK parameter data will be presented to the nearest integer. For concentration and PK parameters summary data, the arithmetic mean, geometric mean, SD, median, minimum and maximum values will be reported to three significant figures and CV% to one decimal place.

Plasma concentrations that are BLQ or if there are missing values (e.g., no result [NR]) will be handled as follows:

- Where there is NR, these will be set to missing.
- At a time-point where less than or equal to 50% of the values are BLQ, all BLQ values will be set to the LLOQ, and all descriptive statistics will be calculated.
- At a time-point where more than half (but not all) of the values are BLQ, the arithmetic and geometric 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 standard deviation and CV% and BLQ will be written in fields for arithmetic mean, geometric mean, minimum, median, and maximum.
- The number of BLQ values (n below LLOQ) will be reported for each time-point.

Data from subjects excluded from the PK analysis set will be included in the data listings, but not in the descriptive statistics or in the inferential statistics.

Individual plasma concentrations versus actual time will be plotted in linear and semi logarithmic scale with all treatments overlaid on the same plot and separate plots for each subject and analyte. Plots will be based on the safety analysis set.

Combined individual plasma concentration versus actual times will be plotted in linear and semi logarithmic scale. Plots will be grouped by treatment separately for each analyte, based on the PK analysis set.

Arithmetic mean plasma concentration (±SD) versus nominal sampling time will be plotted in linear and semi logarithmic (no SD presented) scale with all treatments overlaid on the same figure and separate plots for each analyte.

For mean plots, BLQ values will be handled as described for the summary tabulations; for individual plots BLQ values will be set to missing. All mean plots will be based on the PK analysis set.

11.9.4. Statistical analysis

The statistical analysis will be conducted separately for the following:

- Treatment A versus Treatment C
- Treatment B versus Treatment C

Only the data for the comparison under investigation will be included in the statistical analysis i.e., when comparing Treatment A and Treatment C, the data for Treatment B will be removed from the dataset.

Subjects must have the primary PK parameter (C_{max}, $AUC_{(0-t)}$ or AUC) available for both treatments for the given analyte under consideration (for either ticagrelor or AR-C124910XX) in order to be included in a specific analysis; a subject may therefore be included in one or two comparisons for a given analyte and parameter.

The ratios of C_{max}, $AUC_{(0-t)}$ and AUC of both ticagrelor and AR-C124910XX will be obtained using a two-sided 90% CI approach based on an analysis of variance (ANOVA) model including fixed effects for treatment, sequence, period and subject within sequence. For exploratory purposes, the ANOVA as outlined here will be repeated with a random effect of subject within sequence. Additionally, the 90% CI for the difference in t_{max} will be calculated.

Bioequivalence may be concluded if the 90% CI of the ratios for both C_{max} and $AUC_{(0-t)}$ for both analytes are contained completely within the limits of 0.80-1.25.

Primary PK parameters will be log-transformed prior to analysis. The estimated treatment differences and the 90% CIs on the log scale will be back-transformed to obtain the geometric mean ratios for each pair of treatments. The least squares means (and 95% CIs for each), geometric mean ratios and 90% CIs will be tabulated for each treatment and analyte (ticagrelor and AR-C124910XX). The same ANOVA model will be applied to $t_{½\lambda z}$, kel and MRT using log-transformed values [2].

In the analyses no adjustments will be made for multiple comparisons.

11.10. Analysis of safety data

The analysis of the safety variables will be based on the safety analysis set.

11.10.1. Adverse events

All AEs will be coded using MedDRA, and will be listed for each subject. A treatment-emergent adverse event (TEAE) is defined as an AE with onset (start date/time)

after the first dose of IMP in Treatment period 1. Adverse events will be assigned to a treatment based on the start date/time of the AE:

- Screening: AEs with start date/time prior to dosing in Treatment period 1.
- Treatment period 1: AEs with start date/time at the time of or after dosing in Treatment period 1 until the time of dosing in Treatment period 2.
- Treatment period 2: AEs with start date/time at the time of or after dosing in Treatment period 2 until the time of dosing in Treatment period 3.
- Treatment period 3: AEs with start date/time at the time of or after dosing in Treatment period 3 until the follow-up visit.

In the statistical output, AEs with missing start dates/times will be handled as follows:

- If the start date is completely missing the date will be imputed as the first day of dosing (Treatment period 1) unless a known end date shows otherwise in which case the screening date will be used
- If the start day is missing the day will be imputed as the first day on which a dose was given in that month unless a known end date shows otherwise, in which case the date will be imputed as 01. If the month is not a dosing month the date will be imputed as 01.
- If the start day and month is missing the date will be imputed as the first day of dosing in the known year unless a known end date shows otherwise in which case the screening date will be used. If the year is not a year of dosing then the date will be imputed as 01Jan
- Missing times will be imputed as 00:00 h or with the time of dosing for events starting on a dosing day

Adverse events will be summarized by treatment and overall, including tabulations by causality and severity (mild, moderate and severe). All tabulations will be presented by SOC and PT. Furthermore, listings of SAEs and AEs that led to discontinuation will be made and the number of subjects who had any AEs, SAEs, AEs that led to discontinuation, and AEs with outcome of death will be summarized. The AEs that occur before (first) dosing will be excluded from the summary tables.

The following information will be included in the listings: verbatim term, MedDRA SOC, PT and lowest level term, start date/time, end date/time, time from last dose, causality, action taken, whether the AE was classified as serious and the outcome.

All tabulations will include the number and percentage of subjects.

11.10.2. Vital signs and 12-lead electrocardiograms

The results of the vital signs measurements will be listed by subject and time-point including the date/time of the assessment, flags for measurements that are outside the reference range (L or H, if applicable), changes from baseline and repeat/unscheduled measurements. The baseline for these measurements will be the pre-dose measurements on Day 1 in each treatment period. Descriptive statistics will be presented by treatment and time-point for both observed values and changes from baseline. Screening and follow-up will be summarized separately, over all subjects and by time-point (screening or follow-up).

12-Lead ECG results will be listed for each subject.

11.10.3. Laboratory assessments

Hematology, clinical chemistry and coagulation values will be listed (including changes from baseline and repeat/unscheduled measurements, where applicable) and summarized overall by time-point (screening and follow-up, as applicable), where applicable, for all subjects in the safety analysis set. The baseline for the hematology and clinical chemistry tests will be the Screening values. Shift tables will also be presented.

Any laboratory parameters that are given as '<xx' or '>xx' in the database will be imputed with the absolute value of the number without the sign (e.g., <2.2 will be imputed as 2.2) for the descriptive statistics.

The listings will include the following information: test name, date of measurement, reference range, result and flags for any measurements that are outside the reference range (e.g., AZ, program, or laboratory ranges). Clinical laboratory data will be reported in the units provided by the clinical laboratory for the SRC meeting (if applicable), and in System International units in the CSR.

Additional listings will be presented for the following:

- Urinalysis (macroscopic and microscopic, if applicable)
- Pregnancy testing (including FSH)

11.10.4. Physical examination

The results of the physical examination will be listed by body system for each subject.

12. ADVERSE EVENTS

12.1. Definitions

12.1.1. 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 (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, ECG).

In clinical studies an AE can include an undesirable medical condition occurring at any time after the subject/patient has signed informed consent, including run-in or washout periods, even if no specific treatment has been administered.

The term AE is used generally to include any AE whether serious or non-serious.

12.1.2. Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or 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 jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of an SAE, see Appendix 15.1 of this clinical study protocol.

12.1.3. Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs or AEs leading to withdrawal. Based on the

expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered as other significant adverse events (OAEs) and reported as such in the CSR. A similar review of other data from vital signs, laboratory assessments and other safety assessments will be performed for identification of OAEs.

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

12.2. Recording of adverse events

12.2.1. Time period for collection of adverse events

SAEs will be collected from the signing of informed consent and AEs from randomization until the final follow-up visit.

12.2.2. Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in ClinBase.

AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

12.2.3. Variables

The following variables will be collected for each AE:

- AE diagnosis/description
- The date and time when the AE started and stopped
- Intensity
- Whether the AE is serious or not
- Investigator causality rating against the IMP (yes or no)
- AE caused subject's withdrawal from study (yes or no)
- Outcome

Additional variables (e.g., action taken with study drug) will be collected for all SAEs including treatment given for the event.

The following intensity ratings will be used:

1. mild (awareness of sign or symptom, but easily tolerated)

2. moderate (discomfort sufficient to cause interference with normal activities)

3. severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 12.1.2.

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.

12.2.4. Causality collection

The investigator will assess causal relationship between IMP 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 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 15.1 of this clinical study protocol.

12.2.5. Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: *"Have you had any health problems since you were last asked?"*, or revealed by observation will be collected and recorded in ClinBase.

When collecting AEs the recording of diagnoses is preferred (when possible) to recording a list of symptoms and signs. However, if a diagnosis is known and there are other symptoms or signs that are not generally part of the diagnosis, the diagnosis and each symptom or sign will be recorded separately.

12.2.6. Adverse events based on examinations and tests

The results from protocol mandated safety assessments will be summarized in the CSR.

Deterioration as compared to baseline in protocol mandated safety assessments should therefore only be reported as AEs if they fulfill any of the SAE criteria.

If deterioration in a vital sign or laboratory value is associated with clinical symptoms and signs, the symptom or sign will be reported as an AE and the associated vital sign or laboratory result will be considered as additional information.

Wherever possible the reporting investigator should use the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value).

In the absence of clinical symptoms or signs, 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.

12.3. Reporting of serious adverse events

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

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

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety Data Entry Site **within 1 calendar day** of initial receipt for fatal and life-threatening events and **within 5 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 will be undertaken immediately.

Investigators or other clinical unit personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

In addition to recording of SAEs in ClinBase, the AstraZeneca Serious Adverse Event Report – Clinical Study form for reporting an SAE to the Data Entry Site (DES) will also be used.

All information provided for the SAE sent into the DES will be in English.

The following CRF modules will be completed for each SAE report:

- Demography
- Dosing
- AE (including start and stop date/time for the AE, the investigator's causality assessment to study drug, action taken with study drug, severity and outcome)

- SAE (including serious criteria, causality assessment to study procedure any investigations, the symptoms and course of the event and any treatments given)
- Medical History
- Concomitant Medications
- LIVERRF (risk factors), LIVERSS (signs and symptoms) and LIVERDI (additional diagnostic with results) for all SAEs with a reported term of 'Potential Hy's Law' or 'Hy's Law' will be provided in a narrative form by the PI
- Any additional supporting information e.g., laboratory test results, vital signs, ECG assessments

The 'AstraZeneca first aware date' for all SAEs reported is the date that any member of the Provider or AstraZeneca first become aware of the SAE and for regulatory reporting purposes this is the 'clock start date'.

Each SAE (as Portable Document Format [PDF]) should be sent to the DES Tata Consultancy Services (TCS) preferably via secure e-mail using the mailbox e-mail address:

The e-mail should contain the following information in the e-mail header:

Subject Title: New SAE; <study code>, <SAE text>, <Country>, <Center No>, <Enrolment code>, <Randomization code>

The message in the e-mail itself should contain the following:

A NEW serious adverse event has been reported for the following subject:
Study Code:
Country: <country>
Center No: <study site number>
Enrolment Code: <SUBJECT>
Randomization Code: <SUBJECT>
SAE Description:
Seriousness Criteria:
Study Drug Causality/Additional Med Causality/other Med Causality/Study Procedure Causality
Date SAE met criteria for serious:
AZ (= PAREXEL investigator) first aware date:

13. LEGAL AND ADMINISTRATIVE ASPECTS

13.1. Archiving of study documents

All source documents generated in connection with the study will be retained in the limited access file storage area, respecting the privacy and confidentiality of all records that could identify the subjects. Direct access is allowed only for authorized people for monitoring and auditing purposes. Source documents will be handled, stored and archived according to in house procedures.

Investigator specific essential documents will be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents could be retained for a longer period however, if required by the regulatory requirements or by an agreement with AstraZeneca. It is the responsibility of AstraZeneca to inform the investigator as to when these documents no longer need to be retained.

Study documentation will be archived by the contract research organization (CRO) for 15 years.

13.2. Publication of study results

If a publication (e.g., in a scientific journal) based on the results of this study is envisaged, approval from AstraZeneca will be obtained and a draft manuscript will be submitted to AstraZeneca for scrutiny and comment. The choice of conduit will be mutually agreed on by the PI and AstraZeneca.

13.3. Clinical study report

An integrated CSR will be prepared in accordance with the standards of the ICH guideline for structure and content of clinical study reports (ICH E3). Copies of the CSR will be provided to the IEC/IRB and the national regulatory authority in accordance with regulatory requirements and PAREXEL SOPs. In the event of premature termination of the study or other conditions specified in ICH E3, an abbreviated CSR may be prepared.

14. REFERENCE LIST

1. Brilinta® (ticagrelor) tablets. Prescribing information (Summary of Product Characteristics). AstraZeneca, December 2013.

2. Niazi S.K. Handbook of Bioequivalence Testing, Second edition. Boca Raton, Florida, USA:CRC Press, 2015.

3. FDA Guidance for Industry 'Drug-induced liver injury: Premarketing clinical evaluation'. July 2009. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

15. APPENDICES

15.1. Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT

Life-threatening

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

Hospitalization

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

Important medical event or medical intervention

Medical and scientific judgment 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, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

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

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment.
- Hepatotoxicity caused by paracetamol/acetaminophen overdose requiring treatment with N-acetyl cysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.

- Blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization.
- 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 investigational medicinal product (IMP).

- **Time Course / Exposure to suspect drug**

  Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- **Consistency with known drug profile**

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

- **Dechallenge experience**

  Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- **No alternative cause**

  The AE cannot be reasonably explained by other etiology 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?

  Note: 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 recognized 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.

15.2. International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies bio hazardous 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

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 for example, Ebola and Lassa Fever viruses. Category A pathogens:

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

CATEGORY B

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are for example, hepatitis A, B, C, D, and E viruses, and 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

Category B pathogens:

- Are to be packed in accordance with UN3373 and IATA Instruction 650.

EXEMPT

Exempt refers to 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. 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.

15.3. Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

1. INTRODUCTION

During the course of the study the investigator will remain vigilant for increases in liver clinical chemistry. The investigator is responsible for determining whether a subject/patient 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. The HL criteria are met if there is no alternative explanation for the elevations in liver clinical chemistry other than Drug Induced Liver Injury (DILI) caused by the investigational medicinal product (IMP).

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) ≥ 2x ULN 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 ≥ 2x ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., 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 subject/patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3x ULN
- AST ≥ 3x ULN

- TBL ≥ 2x ULN

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

- Notify the AstraZeneca representative
- Determine whether the subject/patient 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 case report form (CRF)

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the subject/patient does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the subject/patient 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 subject/patient 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 subjects'/patients' follow-up and the continuous review of data.

Subsequent to this contact the investigator will:

- Monitor the subject/patient until liver clinical chemistry variables 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 CRF 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 clinical chemistry 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 the IMP. 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 an SAE:

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

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

- 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 [3].

16. SIGNATURES

16.1. Declaration of Sponsor or Responsible Medical Expert (Lead Physician)

Protocol Title: AN OPEN-LABEL, RANDOMIZED, THREE-PERIOD, THREE-TREATMENT, CROSSOVER, SINGLE-CENTRE, SINGLE-DOSE STUDY TO ASSESS THE BIOEQUIVALENCE BETWEEN TICAGRELOR ORODISPERSIBLE TABLETS AND TICAGRELOR IMMEDIATE-RELEASE TABLETS IN HEALTHY JAPANESE SUBJECTS.

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice applicable to this clinical study.

Sponsor Signatory/Responsible Medical Expert

	9-MARCH-2015
Signature	**Date of signature**

Lead Physician
AstraZeneca Pharmaceuticals

16.2. Declaration of Sponsor or Responsible Medical Expert (Biostatistician)

Protocol Title: AN OPEN-LABEL, RANDOMIZED, THREE-PERIOD, THREE-TREATMENT, CROSSOVER, SINGLE-CENTRE, SINGLE-DOSE STUDY TO ASSESS THE BIOEQUIVALENCE BETWEEN TICAGRELOR ORODISPERSIBLE TABLETS AND TICAGRELOR IMMEDIATE-RELEASE TABLETS IN HEALTHY JAPANESE SUBJECTS.

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice applicable to this clinical study.

Sponsor Signatory/Responsible Medical Expert

	9 March 2015
Signature	**Date of signature**

Global Biostatistician
AstraZeneca R&D Mölndal

16.3. Declaration of the Principal Investigator

Protocol Title: AN OPEN-LABEL, RANDOMIZED, THREE-PERIOD, THREE-TREATMENT, CROSSOVER, SINGLE-CENTRE, SINGLE-DOSE STUDY TO ASSESS THE BIOEQUIVALENCE BETWEEN TICAGRELOR ORODISPERSIBLE TABLETS AND TICAGRELOR IMMEDIATE-RELEASE TABLETS IN HEALTHY JAPANESE SUBJECTS.

This clinical study protocol was subjected to critical review and has been released by the sponsor. The information it contains is consistent with current risk and benefit evaluation of the investigational medicinal product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice applicable to this clinical study. This clinical study involves research.

Principal/Coordinating Investigator

	04 Mar 2015
Signature	**Date of signature**

Dr. Annelize Koch
Principal Investigator
PAREXEL Early Phase Clinical Unit