Clinical Pharmacology Study Protocol

Drug Substance	AZD6140
Study Code	D5130C00038
Date	

An open-label, single-centre, randomised, two-period, crossover study to determine the absolute bioavailability of AZD6140 in healthy male and female volunteers

Sponsor:

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

Amendment No.	Date of Amendment

Administrative Change No.	Date of Administrative Change

PROTOCOL SYNOPSIS

An Open-Label, Single-Centre, Randomised, Two-Period, Crossover Study to Determine the Absolute Bioavailability of AZD6140 in Healthy Male and Female Volunteers

Investigator

Study centre(s), type and number of volunteers planned

Approximately 12 healthy volunteers, male or female, age 18 to 45 years inclusive will be enrolled at a single centre.

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

Objectives

The primary objective of this study is:

- To determine the absolute bioavailability of AZD6140 following oral and intravenous administration.

The secondary objectives of this study are:

- To characterize the pharmacokinetics of AZD6140 following oral and intravenous administration of AZD6140.
- To characterize the pharmacokinetics of AR-C124910XX following oral and intravenous administration of AZD6140.
- To examine the safety and tolerability of AZD6140.

Study design

This study will be an open-label, randomised, two-period, crossover, single centre study conducted to determine the absolute bioavailability of AZD6140 following oral and intravenous administration.

It is estimated that up to 12 volunteers (males and females of non-child bearing potential) will be randomised into this study in order to ensure 10 healthy volunteers are evaluable for pharmacokinetic analysis.

Investigational product, dosage and mode of administration

Oral dose: 90 mg AZD6140 tablet, single dose oral administration.

IV dose: 15 mg AZD6140 - 150mL of AZD6140 solution for infusion, 0.1mg/mL as a 30-minute infusion with an infusion rate of 300mL/hr.

Duration of treatment

The duration of healthy volunteer participation will be approximately 53 days, including:

- **Screening period (visit 1):** within 28 days before Study Period 1, Day 1.
- **Study Period 1 (visit 2):** will consist of admission to the clinical research centre on Day –1, administration of study medication according to randomisation schedule at Day 1, and continued inpatient stay until after the 72 hour post-dose blood collection is performed and all safety assessments are complete.
- **Washout Period:** at least 7 days between discharge from Study Period 1 and dosing of Study Period 2.
- **Study Period 2 (visit 3):** will consist of admission to the clinical research centre on Day –1, administration of study medication according to randomisation schedule at Day 1, and continued inpatient stay until after the 72 hour post-dose blood collection is performed and all safety assessments are complete.
- **Follow-up visit (visit 4):** within 3-5 days of the last inpatient day of Study Period 2.

Variables

- Pharmacokinetic

Treatment A (Oral administration): Blood samples for the pharmacokinetic assessment of AZD6140 and its metabolite AR-C124910XX will be obtained starting on Day 1 of Study Period 1 and Study Period 2 at the following time points:

- Pre-dose, 15min, 30min, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, and 72 hours post-dose.

Treatment B (Intravenous administration): Blood samples for the pharmacokinetic assessment of AZD6140 and its metabolite AR-C124910XX will be obtained starting on Day 1 of Study Period 1 and Study Period 2 at the following time points:

- Pre-dose, 15min, 30min, 40min, 50min, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, and 72 hours post dose.

Pharmacokinetics will be assessed by: absolute bioavailability (F), single dose C_{max}, t_{max}, AUMC, AUC $_{(0-t)}$, AUC, and $t_{½}$ of AZD6140 and AR-C124910XX, metabolite to parent C_{max} and AUC ratios, CL (IV only), CL/F (oral), V_Z and V_{SS} (IV only), MAT (oral), and MRT of AZD6140 only.

- Pharmacodynamic

Not applicable.

- Safety

Safety and tolerability will be assessed by the incidence and severity of adverse events, vital signs, clinical laboratory parameters, physical examination, and electrocardiograms.

- Genetics

Genetic analysis of the genes that are involved in the absorption and disposition, and the response toAZD6140 including adverse effects may be performed.

An optional blood sample for this analysis will be collected only after the volunteer has given written informed consent, which includes consent for collection and analysis of genetic samples for this study. The genetic samples collected from this study may be pooled with those from other studies involving AZD6140.

- Statistical methods

The primary analysis will consist of the following methods:

The absolute bioavailability (F) of AZD6140 will be calculated by taking the dose-normalized AUC values for the two formulations of AZD6140 and logarithmically transforming these values. An ANOVA model will then be fit using these log-scale values. The effect of formulation will be the primary contrast [log (AUC (oral)/Dose (oral)-log (AUC (IV)/Dose (IV))]. The effect of formulation will be estimated using the 1smean and its 95% confidence interval. The 1smean and 95% confidence interval will then be exponentiated in order to estimate the absolute bioavailability. The lsmeans and 95% confidence intervals will be calculated and exponentiated for each treatment formulation

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
ACS	Acute Coronary Syndromes
AE	Adverse event
ADP	Adenosine diphosphate
ALT	Alanine aminotransferase
anti-HCV	Hepatitis C antibody
aPTT	Activated partial thromboplastin time
AR-C124910XX	Metabolite of AZD6140
Assessment	An observation made on a variable involving a subjective judgement
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration – time curve
$AUC_{(0-t)}$	Area under plasma concentration-time curse from time zero to time t
AUMC	Area under the first moment – time curve
β-HCG	β- Human chorionic gonadotropin
BMI	Body mass index
BP	Blood pressure
CGG	Clinical Genotyping Group
CI	Confidence interval
CL	Total body clearance
CL/F	Apparent oral clearance
C_{max}	Maximum plasma (peak) drug concentration after single dose administration
CPU	Clinical pharmacology unit
CRF	Case report form
CSR	Clinical study report
CV	Coefficients of variation
DCF	Data clarification form
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid

Abbreviation or special term	Explanation
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediamine tetra-acetic acid
F	Absolute bioavailability
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
λz	Elimination rate constant
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IPS	Investigational Product Supply
IV	Intravenous
kg	Kilogram
LLOQ	Lower limit of quantification
m	Meter
Measurement	An observation made on a variable using a measurement device
MedDRA	Medical dictionary for regulatory activities
MAT	Mean absorption time
MRT	Mean residence time
mg	Milligram
mL	Milliliter
NSAID	Non Steroidal Anti-Inflammatory Drugs
OAE	Other Significant Adverse Event (i.e., adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the volunteer from study treatment; see definition in Section 4.7).
OTC	Over-the-counter

Abbreviation or special term	Explanation
PCP	Phencyclidine
pCRF	Paper Case Report Form
PD	Pharmacodynamic
PGx	Pharmacogenetics
PK	Pharmacokinetic
Principal investigator	A person responsible for the conduct of a clinical study at a study site. Every study center has a principal investigator.
PT	Prothrombin time
RBCs	Red blood cells
SAE	Serious adverse event
THC	Tetrahydrocannabinol
$t_{1/2}$	Half-life of the terminal elimination phase
t_{max}	Time to reach peak or maximum concentration or maximum response following drug administration
ULN	Upper limit of normal
μmol	Micromole
V_{ss}	Volume of distribution at steady-state
V_z	Volume of distribution (apparent) during terminal (λ_Z) phase
WBCs	White blood cells
WHO	World Health Organisation

1. INTRODUCTION

1.1 Background

Adenosine diphosphate (ADP) is an important mediator of platelet activation and aggregation through its binding to at least 2 distinct subtypes of purinoceptor, designated $P2Y_1$ and $P2Y_{12}$, found on platelets. Two ADP receptor antagonists, thienopyridine pro-drugs, PLAVIX™ (clopidogrel) and TICLID™ (ticlopidine) have shown clear benefits for the reduction of clinical thrombotic events in patients with atherosclerosis due to their ability to block the $P2Y_{12}$ receptor. However, this blockade is irreversible and usually incomplete. Therefore, the search continues for agents that can further improve the clinical outcomes of these patients through improved efficacy and/or safety.

AZD6140 is a potent, reversible, selective $P2Y_{12}$-receptor antagonist (antiplatelet agent) being developed to reduce thromboembolic events in patients with atherosclerosis. It is orally active and does not require metabolic activation, different from clopidogrel, for which only the metabolites are active. Unlike clopidogrel and ticlopidine, which incompletely block the $P2Y_{12}$-receptor response in humans, pre-clinical studies indicate that AZD6140 can produce reversible and complete inhibition of ADP-induced platelet aggregation *ex vivo* following oral dosing. Additionally, AZD6140 has shown greater and more consistent inhibition of platelet aggregation compared to clopidogrel in both healthy volunteers and patients. It has also demonstrated a faster onset and offset of antiplatelet effect. These properties suggest that AZD6140 may be able to reduce the occurrence of thrombotic events compared to clopidogrel with an acceptable safety profile.

AZD6140 binds to plasma proteins (>99.7%), and is extensively metabolised by CYP3A4/5, with little parent drug excreted unchanged in the urine. AZD6140 has a number of drug–drug interactions of clinical relevance since it is a substrate, inhibitor, and activator of CYP3A4 /5 and a substrate and inhibitor of the P-glycoprotein transporter. Following an oral dose of ^{14}C-labelled AZD6140 in humans, approximately 27% was excreted in the urine and 57.8% in the faeces. The elimination half-life ($t_{½}$) of the parent compound is approximately 11 hours after single dose administration.

One of the primary metabolites, AR-C124910XX, is considered equipotent to the parent drug in the in vitro studies. The time course of the pharmacologically active metabolite approximately parallels AZD6140; the area under the plasma concentration curve (AUC) and maximum plasma drug concentration after single dose administration (C_{max}) of AR-C124910XX is typically 30 to 40% of the corresponding parameters for AZD6140.

Plavix™ (Clopidogrel bisulfate) is a registered trademark of Sanofi Aventis and distributed by Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, NY, NY.

TICLID™ (ticlopidine) is a registered trademark of Roche Pharmaceutical, Inc, Nutley, NJ.

Adverse events (AEs) reported with a frequency of at least 2% in Phase 1 studies with at least 3 days of AZD6140 dosing include: headache, somnolence, dizziness, epistaxis, nausea, abdominal pain, back pain, dyspnoea, ecchymosis, lethargy, pharyngolaryngeal pain, blurred vision, postural dizziness, pollakiuria (frequent urination), and increased tendency to bruise. Two serious adverse events (SAE) occurred during the Phase 1 program; an occurrence of chronic mediastinitis not considered by the investigator to be related to study drug, and an episode of sinus pause (high grade atrioventricular block and ventricular escape rhythm associated with syncope) in a volunteer who received a single 1260 mg dose of AZD6140. The volunteer recovered without sequelae, and the event was considered to be medically important and related to study drug.

Refer to the Investigator Brochure for further details on AZD6140 exposure, pharmacokinetic, and safety findings. These data support the further development of AZD6140 as an oral antiplatelet agent, which may be able to prevent more thrombotic events than clopidogrel by sustaining higher levels of $P2Y_{12}$ receptor blockade with an acceptable safety profile.

1.2 Rationale

The purpose of this study is to help complete the pharmacokinetic characterization of AZD6140. AZD6140 is extensively metabolized by CYP3A and other enzymes, and is a substrate of P-glycoprotein, an efflux transporter located in the gastrointestinal tract and the liver. The absolute bioavailability of orally administered AZD6140 (an estimate of the fraction of the dose that reaches the systemic circulation intact or escapes the "first pass effect") is not currently known. The minimal extent of absorption is at least 27% based on the urinary recovery of total radioactivity following oral administration of a ^{14}C-AZD6140 dose. Use of the intravenous dose in this study will allow the estimation of the absolute bioavailability (F) following oral dosing, the total body or systemic clearance (CL) and the volume of distribution (V_{ss}) of AZD6140.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to determine the absolute bioavailability of AZD6140 following oral and intravenous administration.

2.2 Secondary objective(s)

The secondary objectives of the study are:

- To characterize the pharmacokinetics of AZD6140 following oral and intravenous administration of AZD6140.
- To characterize the pharmacokinetics of AR-C124910XX following oral and intravenous administration of AZD6140.

- To examine the safety and tolerability of AZD6140.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design

This will be an open-label, randomised, two-period crossover study conducted at a single centre. Approximately 12 healthy volunteers, males and females between the ages of 18 and 45 (females must be of non-child bearing potential) will be randomised to ensure that at least 10 volunteers are evaluable.

There will be 2 study periods separated by at least a 7-day washout period. During each study period, the volunteer will stay at the clinic from the evening before dosing until approximately 72 hours after dosing of the investigational product for blood samples for determination of AZD6140 and its metabolite in plasma. Time points for blood samples are specified in Table 2.

A study flow chart is provided in Figure 1. Table 1and Table 2 show details of the study activities.

Volunteers who during the screening period (visit 1) of up to 28 days before admission to the study centre on Study Period 1, Day –1 (visit 2) satisfy all study eligibility criteria will be randomly assigned to receive two treatments in a crossover fashion, in one of two treatment sequences (AB, BA). Volunteers will return for a follow-up visit (visit 4) 3-5 days after discharge from Study Period 2.

Each treatment will consist of the following:

- **Treatment A:** a single 90 mg oral dose of AZD6140 administered following a 10 hour overnight fast.

- **Treatment B:** a single 15 mg AZD6140 intravenous infusion - 150mL of AZD6140 solution for infusion, 0.1mg/mL as a 30-minute infusion with an infusion rate 300mL/hr administered following a 10 hour overnight fast

The optional genetic sampling will be taken from volunteers who have signed a separate informed consent form for genetic analysis on Day 1 of Study Period 1.

Figure 1 Study flow chart

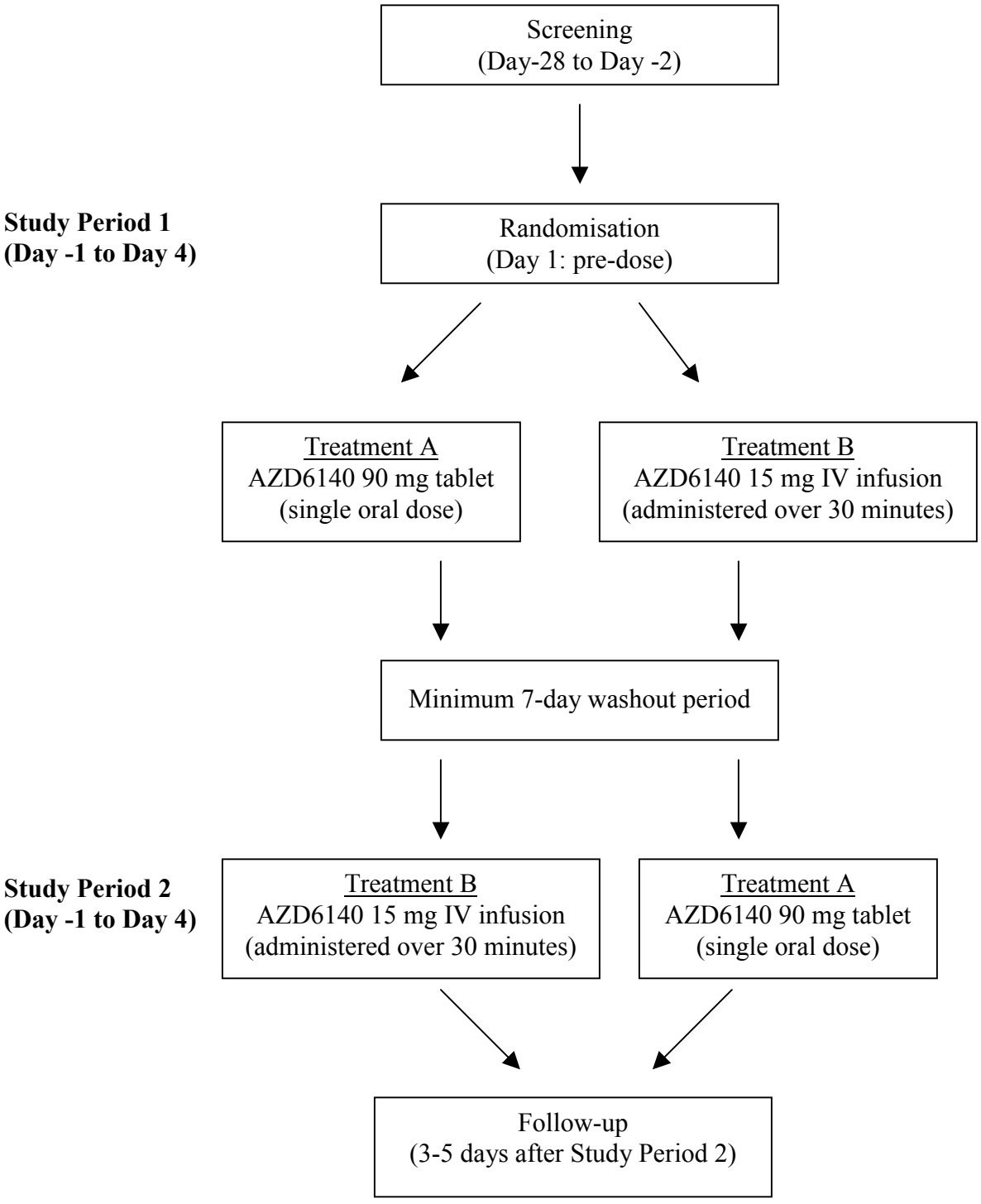

Table 1 Study plan

	Screening Visit 1	Study Period 1 Visit 2					WASHOUT (At least 7 days)	Study Period 2 Visit 3					Follow-up Visit 4 (3-5 days after Study Period 2)
Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**		**-1**	**1**	**2**	**3**	**4**	**7 to 9**
Assessment													
Informed Consent	X												
Demographics	X												
Inclusion/Exclusion Criteria	X	X						X					
Medical/Surgical History	X												
Complete Physical Exam[a]	X												X
Brief Physical Exam[b]		X		X				X		X			
12 Lead ECG	X	X						X					X
Vital Signs[c]	X	X	X					X	X				X
Safety Labs[d]	X	X		X				X		X			X
Virology Screen[e]	X												
Pregnancy Test[f]	X	X						X					X
Urine alcohol/drugs of abuse screen[g]	X	X						X					
Randomisation			X										
AZD6140 PK Samples[h]			X	X	X	X			X	X	X	X	
AZD6140 Dose			X						X				
Concomitant Medication	X==========												==========X
AE Monitoring[i]	X==========												==========X
Genetic Informed Consent	X												
Genetic Blood Sample[j]			X										

	Screening Visit 1	Study Period 1 Visit 2					WASHOUT (At least 7 days)	Study Period 2 Visit 3					Follow-up Visit 4 (3-5 days after Study Period 2)
Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**		**-1**	**1**	**2**	**3**	**4**	**7 to 9**
Assessment													
Confinement to Unit		X	X	X	X	X		X	X	X	X	X	

[a] Includes height and weight; performed at screening only.
[b] Brief physical exam pre-dose and 24 hours after dosing.
[c] Vital signs include blood pressure and pulse and will be collected in the morning of Day 1 (pre-dose) and 2and 4 hrs post IV dose.
[d] Laboratory testing includes clinical chemistry, haematology and urinalysis parameters as specified in Section 4.4.1 and will be collected at screening, follow-up, Day –1 and at 24 hrs post dose.
[e] Includes Hepatitis B, Hepatitis C, and HIV screens.
[f] For female volunteers only; serum pregnancy test performed at screening, at Day –1 (Study Periods 1 and 2) and follow-up.
[g] Urine alcohol and drugs of abuse screen to be performed at screening and on Day –1 (Study Periods 1 and 2).
[h] Refer to Table 2 for sampling schedule. For IV dose, blood must be taken from arm contralateral to arm with infusion line.
[I] SAEs will be collected from the time of obtaining informed consent through the Follow-up Visit. All other AEs will be collected from the time of the first dose on Day 1 (Study Period 1) through the Follow-up Visit.
[j] Performed pre-dose on Day 1 (Study Period 1).

Table 2 Pharmacokinetic Sampling Schedule (Study Periods 1 and 2)

	AZD6140/AR-C124910XX Plasma Sampling	
Study Day	**Treatment A (Oral administration)**	**Treatment B (Intravenous administration)**
1	Pre-dose, 15min, 30min, 1hr, 1.5hr, 2hr, 2.5hr, 3hr, 4hr, 5hr, 6hr, 8hr, 10hr, 12hr, 16hr, and 20 hours post-dose	Pre-dose, 15min, 30min[a], 40min, 50min, 1hr, 1.25hr, 1.5hr, 1.75hr, 2hr, 2.5hr, 3hr, 4hr, 5hr, 6hr, 8hr, 10hr, 12hr, 16hr, and 20 hours post-dose
2	24 hours post dose	24 hours post-dose
3	36 and 48 hours post-dose	36 and 48 hours post dose
4	72 hours post-dose	72 hours post-dose

[a] Pharmacokinetic sample to be taken just prior to the end of the 30-minute infusion.

3.2 Rationale and risk/benefit assessment

3.2.1 Rationale for study design, doses and control groups

The 90 mg oral dose selected was chosen because it is the planned oral treatment dose for patients.

The 15mg intravenous dose was selected based on estimates predicted C_{max} and AUC using an estimate of absolute oral bioavailability in marmosets (Report SC103087-1). The predicted C_{max} and AUC are well within the range of exposure observed in both human and preclinical species.

Healthy volunteers are an appropriate study population to minimize the effect of concomitant medications and disease on PK parameters.

IV dosing is required to estimate the bioavailability of AZD6140 following oral dosing.

AZD6140 oral dosing under fasting conditions is required to reduce variability in AZD6140 absorption and PK parameters.

The randomised crossover design minimizes the number of volunteers required for the study by allowing intra-volunteer comparisons of PK parameters.

A retrospective analysis of the polymorphisms of genes that may be correlated with the disposition and response to AZD6140 may improve understanding of any variability in response to AZD6140. Genetic sampling is optional for all healthy volunteers enrolled. The genetic data from this study may be pooled with genetic results from other studies on AZD6140 to generate hypotheses to be tested in future studies.

3.2.2 Risk/benefit and ethical assessment

This study will not provide any direct medical benefits to the volunteer who participates. The benefit derived from this study will allow further understanding of the pharmacokinetic properties of AZD6140, which may be of benefit to further development of the drug and patients with ACS who may potentially receive AZD6140 in the future. Volunteers will be monitored under supervision in a clinical pharmacology unit (CPU), where management of any adverse events can take place.

The pre-clinical work in rats and marmosets indicates that AZD6140 exposure via the IV route in humans should be in the range or lower than that observed in animal studies following oral dosing, both on a C_{max} and AUC basis. The exposures in preclinical species have been determined in single dose studies as well as in studies up to 6 months in duration in rats and 12 months in duration in marmosets. The toxicities seen at the higher doses used in those studies support the safety of single 15 mg IV dosing in humans. There were no safety signals of concern in those species following IV administration of AZD6140, including perivenous irritation and flocculation.

The Investigator's Brochure for AZD6140 contains the information supporting the overall risk/benefit assessment of the test product and is available as a reference. It contains a summary of all relevant pharmaceutical, non-clinical and clinical findings with AZD6140.

Risks observed after administration of AZD6140 to healthy volunteers in Phase 1 studies are outlined below.

Phase 1 experience: The most common adverse events with an incidence of at least 2% reported to date in the Phase 1 studies with at least 3 days of AZD6140 dosing include: headache, somnolence, dizziness, epistaxis, nausea, abdominal pain, back pain, dyspnea, ecchymosis, lethargy, pharyngolaryngeal pain, blurred vision, postural dizziness, pollakiuria (frequent urination), and increased tendency to bruise. Other adverse events reported less frequently include: elevations in liver enzymes, tachycardia, orthostatic hypotension, rash, and gingival bleeding as possible adverse events associated with AZD6140 administration.

3.3 Selection of study population

3.3.1 Study selection record

Investigator(s) must keep a record of volunteers who were considered for enrolment but never enrolled, e.g., volunteer screening log, according to local procedures. This information is necessary to establish that the volunteer population was selected without bias.

3.3.2 Inclusion criteria

For inclusion in the study volunteers must fulfil all of the following criteria:

1. Provide written informed consent and agree to comply with all requirements of the study.

2. Healthy female volunteers of non-childbearing potential and male volunteers, ages 18 to 45 inclusive. Women must meet one of the following conditions:

   – have been surgically sterilised (hysterectomy or tubal ligation) at least 12 months prior to screening.

   – are postmenopausal having had no regular menstrual bleeding for at least one (1) year prior to inclusion. Post- menopausal status will be confirmed by a plasma FSH level of > 40 IU/L at screening;

3. Weigh at least 50 kg and have a Body Mass Index (BMI) between 20 to 30 kg/m^2 inclusive;

4. Have a normal physical examination, vital signs, ECG and laboratory values (unless investigator considers a lab abnormality not to be clinically significant);

5. Are able to communicate with the investigator, and to understand and comply with all study requirements.

For inclusion in the genetic component of the study, Volunteers must fulfil the following criterion:

- Provide informed consent for genetic research.

If a volunteer declines to participate in the genetic component of the study, there will be no penalty or loss of benefit to the volunteer. The volunteer will not be excluded from other aspects of the study described in this Clinical Study Protocol, so long as they consent.

3.3.3 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. History of hypersensitivity or adverse reaction to dicalcium phosphate and lactose excipients.

2. Use of a prescription medication for acute or chronic medical conditions within 4 weeks prior to Day 1 of Study Period 1 through completion of Study Period 2;

3. Use of aspirin or any other drug known to increase the propensity for bleeding within 7 days prior to Day 1 of Study Period 1 through completion of Study Period 2 ;

4. Use of NSAIDs (including ibuprofen) within 3 days prior to Day 1 of Study Period 1 through completion of Study Period 2 ;

5. Use of over-the counter preparations including herbal remedies such as *Cordyceps sinensis*, dan shen, feverfew, *Ganoderma lucidum*, ephedra, echinacea, St. John's Wort, and garlic, [aged extract taken on an ongoing basis], ginseng, ginkgo, and vitamin preparations within 7 days prior to Day 1 of Study Period 1 through completion of Study Period 2;

6. History or presence of neurological, haematological, psychiatric, gastrointestinal, hepatic, or renal disease, or other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs;

7. History of post-surgical bleeding or excessive bleeding after dental extraction;

8. History of any first degree atrioventricular block (PR interval >0.2 sec), second or third degree heart block;

9. Screening Period (visit 1) or Day –1 of Study Period 1 ECG with any clinically significant abnormalities or QTc > 480ms;

10. Any previous recent episodes of unexplained syncope;

11. History of vascular abnormalities including aneurysms; a personal history of severe haemorrhage, hematemesis, melena, haemoptysis, severe epistaxis, or intracranial haemorrhage; rectal bleeding within 3 months prior to Screening Period (visit 1);

12. History suggestive of peptic ulcer disease or bleeding diatheses;

13. History of anxiety disorder;

14. Platelet count <150,000/mm^3 at screening;

15. History of alcohol or substance abuse within the past year;

16. Surgery or significant trauma within 3 months prior to Day 1 of Study Period 1;

17. Positive test results for HIV, (human immunodeficiency virus) HBsAg, (hepatitis B surface antigen) or hepatitis C antibody (anti-HCV);

18. Positive urine drug screen;

19. Receipt of an investigational drug or participation in another clinical study within 60 days prior to Day 1 of Study Period 1;

20. Previous participation in an AZD6140 study;

21. Blood donation within 90 days prior to Day 1 of Study Period 1;

22. Clinical judgment, by the investigator, that the volunteer should not participate in the study;

23. A suspected/manifested infection according to WHO risk categories 2, 3 and 4 (Refer to Appendix C);

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

3.3.4 Restrictions

Volunteers have the following restrictions:

1. Refrain from consumption of alcoholic beverages from 7 days prior to Day 1 of Study Period 1 and through the completion of the follow-up visit (visit 4).

2. Refrain from the consumption of caffeine-containing products from 48 hours prior to Day 1 of Visit 2 through in-patient discharge on Day 4 and from

48 hours prior to returning to Day –1 of Visit 3 through in-patient discharge on Day 4.

3. Refrain from consumption of Seville oranges and grapefruit-containing products from 7 days prior to Day 1 of Study Period 1 through the completion of the follow-up visit (visit 4);

4. Refrain from strenuous exercise from 48 hours prior to Day 1 of Study Period 1 through the completion of the follow-up visit (visit 4). Volunteer will have reduced physical activity for 72 hours in the unit under constant monitoring;

5. Refrain from the use of over-the-counter preparations including herbal remedies such as *Cordyceps sinensis*, dan shen, feverfew, *Ganoderma lucidum*, ephedra, echinacea, St. John's Wort, and garlic, [aged extract taken on an ongoing basis], ginseng, ginkgo, and vitamin preparations from 7 days prior to Day 1 of Study Period 1 through completion of the follow-up visit (visit 4);

6. Refrain from the use of aspirin or any other drug known to increase the propensity for bleeding from 7 days prior to Day 1of Study Period 1 through completion of the follow-up visit (visit 4);

7. Refrain from the use of NSAIDs (including ibuprofen) from 3 days prior to Day 1 of Study Period 1 through completion of the follow-up visit (visit 4);

8. Refrain from scheduling or having surgery, including dental surgery, at anytime following the Screening Period (visit 1), and through completion of the follow-up visit (visit 4);

9. Refrain from the use of tobacco or other nicotine-containing products from Screening Period (visit 1) and throughout the follow-up visit (visit 4).

3.3.5 Discontinuation of volunteers from treatment or assessment

3.3.5.1 Criteria for discontinuation

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

1. Voluntary discontinuation by the volunteer, who is at any time free to discontinue his/her participation in the study without prejudice to further treatment.

2. Safety reasons as judged by the investigator and/or AstraZeneca.

3. Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca.

4. Incorrect enrolment i.e., the volunteer does not to meet the required inclusion/exclusion criteria for the study.

5. Volunteer lost to follow-up.

Specific reasons for discontinuing a volunteer from the genetic research when genetics is a secondary objective of the study are:

- Withdrawal of consent for genetic research. A volunteer may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study described in this protocol. Voluntary discontinuation by the volunteer will not prejudice further treatment.

3.3.5.2 Procedures for discontinuation

Volunteers who discontinue should always be asked about the reason(s) for their discontinuation and the presence of any adverse events. If possible, they should be seen and assessed by an investigator(s). Adverse events should be followed up.

If a volunteer is being withdrawn due to a suspected infection in WHO risk categories 2, 3, and 4 as defined in Appendix C, no biological samples from this volunteer are allowed to be sent to the laboratory. Samples will be destroyed according to normal routines at the study site.

If a volunteer is withdrawn or drops out, he/she will be replaced at the discretion of the sponsor.

3.3.5.3 Procedures for handling incorrect enrolled volunteers

Volunteers not meeting the inclusion/exclusion criteria for this study must, under no circumstances, not be enrolled into this study; there can be no exceptions to this rule. Where volunteers not meeting the study criteria are enrolled in error, incorrectly randomised, or where volunteers subsequently fail to meet the criteria for the study, the volunteer should return for the procedures and assessments scheduled for the follow-up visit if study drug has been administered.

3.3.5.4 Procedures for discontinuation from genetic aspects of the study

Volunteers who discontinue from the study should always be asked specifically whether they are withdrawing or continuing their consent for this linked genetic research. It must be established whether the volunteer:

- Agrees to the genetic sample and any DNA extracted from the sample being kept for genetic analyses in the future.

- Withdraws consent for the sample to be kept for genetic analysis in the future and wishes the sample to be destroyed. Destruction of the sample (or the DNA extracted from the sample) will only be possible so long as the particular sample

is traceable. In the event that genetic research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

The principal investigator is responsible for providing written notification to AstraZeneca of any volunteer who has withdrawn consent for the use of the sample taken for genetic research. AstraZeneca will provide written confirmation to the investigator of the actions taken with the sample, which must be filed in the investigator study file.

3.4 Treatment(s)

3.4.1 Investigational product(s)

3.4.1.1 Identity of investigational product

Table 3 Identity of investigational product

Investigational product	Dosage form and strength	Manufacturer	Formulation number	Batch number
AZD6140	Yellow, oval, biconvex, film coated 90 mg tablets	AstraZeneca	FDN 334	*
AZD6140	15 mg intravenous infusion	AstraZeneca	FDN 308	*

* The batch number will be recorded in the study master file and identified in the Clinical Study Report.

3.4.1.2 Labelling

AZD6140 tablets will be packaged as open-label, bulk supply, 60 tablets per bottle and labelled with a single panel.

AZD6140 IV solution will be packaged, open-label, in 50 mL vials, labelled with a single panel. Each volunteer will require a total of 4 vials for the 150 mL infusion. One of the vials will be used for priming the infusion lines and pump.

The supplies will be labelled including the following information in accordance with Good Manufacturing Practice (GMP) and local regulatory requirements:

- Name of sponsor and address
- Pharmaceutical dosage form
- Route of administration
- Number of dosage units
- Study code

- USA caution statement
- Keep out of the reach of children

The investigational products will be supplied as bulk supply. Study site dispensary staff will dispense the investigational product. Individual dosing containers will be labelled with the study number, volunteer number and study day.

3.4.1.3 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions for the tablets are specified on the investigational product label and investigator brochure.

AZD6140 IV solution should be stored at 4-8 degrees C. Excursion data ensures stability out of this range for greater than 24 hours. This will allow for loss of temperature control during shipping and infusion at room temperature.

3.4.1.4 Accountability

The investigator (or delegate) is responsible for maintaining drug accountability records for study drugs. Drug accountability for this study will be carried out in accordance with standard procedures at the study centre.

The medication provided for this study is for use only as directed in the protocol. Study site personnel or the AstraZeneca monitor will return all unused drugs to a vendor delegated by AstraZeneca. The study site personnel will account for all drugs dispensed and returned. Certificates of delivery and return must be signed.

3.4.2 Doses and treatment regimens

Each healthy volunteer will receive all of the following treatment regimens according to the randomised dose sequence.

Each volunteer will receive one of the following 2 treatments in the morning of Day 1 of each treatment period. The treatment periods will be separated by at least 7 days.

Each volunteer will receive:

- **Treatment A**: single 90 mg oral dose of AZD6140. (The tablet is not to be divided, chewed or crushed).
- **Treatment B:** 15 mg AZD6140 intravenous infusion - 150mL of AZD6140 solution for infusion, 0.1mg/mL as a 30-minute infusion with an infusion rate 300mL/hr.

The volunteers will receive the study medication following an overnight (10 hour) fast and will continue to fast for 4 hours post dose.

Water permitted ad libitum (freely) up until two hours prior to and not again until two hours after dosing. Meals will be provided on a fixed schedule.

Oral Dose

The oral dose will be administered with 240mL of room temperature water while the volunteer is sitting in an upright or in a semi-recumbent position. Volunteers must remain either sitting or semi-recumbent for at least 2 hours after dose intake.

IV Dose

The IV dose will be a single dose of 15 mg AZD6140 given as AZD6140 solution for infusion at a concentration of 0.1mg/mL. 150 mL solution will be infused as a 30-minute infusion at an infusion rate of 300 mL/hour. The solution will be dispensed from the supplied vials into an empty IV infusion bag.

Each supplied vial will have a volume of 50ml. A sufficient volume of additional AZD6140 solution will be added to the infusion bag in order to match to required volume to prime the IV tubings. Additional vials of AZD6140 solution will be supplied for use in priming.

The solution will be allowed to reach room temperature and be visibly checked for clarity and any precipitates prior to starting the infusion. The intravenous catheter should be flushed with saline before beginning the infusion. The drug will be administered using a calibrated infusion pump (IVAC 7100 Gold series pump). The pump and IV tubing will be primed with AZD6140 solution before infusion.

The first volunteer to receive the IV treatment will be given the infusion and observed for at least 30 minutes after the infusion has ended. If no adverse clinical reactions are observed after the first infusion completes, the remainder of volunteers may be dosed per unit routine.

3.4.3 Method of assigning volunteers to treatment groups

Written informed consent will be obtained before enrolment and the volunteers identified with an enrolment number starting with E0001001. Volunteers fulfilling the eligibility criteria will be assigned volunteer numbers starting with 101 prior to dosing.

Volunteers will be assigned volunteer numbers strictly sequentially as volunteers are eligible for dosing. If a volunteer discontinues from the study the volunteer number will not be re-used and the volunteer will not be allowed to re-enter the study. If a volunteer discontinues from the study that volunteer may be replaced at the discretion of the sponsor.

QDS will generate the treatment randomisation code using its internal SAS v. 8.2-based randomisation application. QDS will complete the necessary AstraZeneca Global Randomisation (GRand) request form and transfer the form and treatment randomisation to AstraZeneca for importation into the GRand system. QDS will retain the original treatment

randomisation code. QDS will generate additional randomisation treatment assignments for replacement volunteers if necessary and follow the process as previously described.

All study drug will be dosed open label. Before study drug administration on Day 1 of Period 1, healthy volunteers who are eligible to continue the study will be randomised to one of two treatment sequences (AB or BA), in a balanced fashion, strictly sequentially. If the healthy volunteer should be incorrectly randomised, randomisation should continue with no attempt to correct the error. If a healthy volunteer discontinues from the study, the randomisation number will not be re-used, and the healthy volunteer will not be allowed to re-enter the study. Volunteers who discontinue prematurely will not be replaced unless it appears that sufficient volunteers will not complete the study. The randomisation of replacement volunteers will be at the discretion of the sponsor.

3.4.4 Concomitant medication

All volunteers should refrain from taking any of the following medications:

- Prescribed medication from 4 weeks prior to the 1st dose of study drug until completion of the assessments and procedures scheduled during the follow-up visit (visit 4) including particular attention to those that are known to inhibit or induce CYP3A isoenzymes.

- Over the counter (OTC) preparations that include herbal remedies and vitamin preparations from 7 days prior to the 1st dose of study drug and through completion of the assessments and procedures scheduled during the follow-up visit (visit 4) including particular attention to those that are known to inhibit or induce CYP3A isoenzymes.

- Aspirin or any other drug known to increase the propensity for bleeding are specifically prohibited within 7 days prior to Day 1 of Study Period 1 and through completion of the assessments and procedures scheduled during the follow-up visit (visit 4).

- NSAIDS (including ibuprofen) within 3 days prior to Day 1 of Study Period 1 and through completion of the assessments and procedures scheduled during the follow-up visit (visit 4).

Any medication, which is considered necessary for the volunteer 's safety and well-being, may be given at the discretion of the investigator(s). The administration of all medication (including investigational products) must be recorded in the appropriate sections of the paper case report form (pCRF).

3.4.5 Treatment compliance

Compliance will be assured by supervised administration of the investigational product by the investigator and/or his or her designee.

4. MEASUREMENT OF STUDY VARIABLES

The following study measurements will be obtained. The timing of these measurements is detailed in the study plan (Table 1 and Table 2). The following 'priority order' will be in effect when more than one assessment is required at a particular time point:

- Pharmacokinetic blood sampling will take priority over all study procedures except for study drug administration. Pre-dose samples should be obtained shortly (within 15 minutes) prior to dose administration.
- Safety assessments (e.g., vital signs, 12-lead ECGs, safety laboratory tests and adverse event questioning) may be performed within 15 minutes prior to the protocol time point.

4.1 Medical examination and demographic measurements

4.1.1 Enrolment medical examination and demographic measurements

Each volunteer will undergo an enrolment medical examination up to 28 days prior to the Day 1 of Study Period 1. This will consist of the following:

- A written and approved informed consent form must be signed and dated before screening procedures are performed.
- Review the inclusion and exclusion criteria with the volunteer.
- Recording of demographic data – date of birth, sex, race.
- A standard medical/surgical history and drug history.
- A complete physical examination, including height and weight.
- A blood sample for standard clinical chemistry and haematology assessments.
- Mid-stream urine sample for urinalysis, alcohol and drugs of abuse screen.
- Vital signs (resting BP and pulse, sitting 5 minutes)
- Serum β-HCG (females)
- FSH to confirm post-menopausal (females)
- 12-Lead ECG
- Blood sample for HIV antibody/Hepatitis B and C screen
- Concomitant medication monitoring

Refer to Section 4.4 for detailed descriptions of the above assessments.

4.1.2 Post-study medical examination

Volunteers will return to the CPU for a follow-up visit (visit 4) within 3-5 days after being discharged from the unit. At the follow-up visit (visit 4) the following procedures will be performed:

- Complete physical examination with vital signs (resting BP and pulse, sitting 5 minutes)
- 12-lead ECG
- Blood sample for standard clinical chemistry and haematology assessments
- Mid-stream urine sample for urinalysis
- Serum β-HCG (females)
- AE and concomitant medication monitoring

4.2 Pharmacokinetic measurements

For timing of individual samples refer to the study plan (Table 2).

4.2.1 AZD6140 and metabolite

4.2.1.1 Determination of drug concentration in biological samples

Samples for measurement of drug concentration of AZD6140 and it active metabolite, AR-C124910XX in plasma will be analyzed by York Bioanalytical Solutions, Upper Poppleton, York, UK on behalf of Development Drug Metabolism and Pharmacokinetics (DMPK) & Bioanalysis, Mölndal, AstraZeneca using fully validated bioanalytical methods. The lower limit of quantification (LLOQ) will be 5 and 2.5ng/mL, respectively. Details of the methods used will be provided in the clinical study report (CSR). Samples will be disposed of after the CSR is finalized.

4.2.1.2 Collection and processing of samples for determination of AZD6140/AR-C124910XX

Venous blood samples (4mL) for determination of AZD6140 and AR-C124910XX concentrations in plasma will be taken at the times presented in the study plan (Table 2).

When the intravenous infusion is given, the cannula for blood sampling must be inserted into the arm contralateral to the arm with the infusion line. The cannula used for infusion must never be used for blood sampling. If a cannula cannot be inserted or is not functional, venipuncture must be performed in the arm contralateral to the arm with the infusion line. The arm for infusion may be used for blood sampling when it is more than 24 hours after dose administration.

Blood will be collected according to site procedure. Disposable needles and disposable lithium heparinized tubes (22-040-069 Greiner VACUETTE North America No. 454029) shall be used. Individual venipunctures for each time point may be performed or an indwelling catheter may be used. If an indwelling catheter is used, the catheter should be kept patent with isotonic saline; the saline will be withdrawn (1mL) and discarded prior to the blood sample being taken. Blood samples (4mL) will be collected into a lithium-heparinized tube. The heparin and blood will be carefully mixed. The sample will be placed on ice until centrifugation, which will begin within 30 minutes after the sample is obtained. The sample will be centrifuged for 10 minutes at 4°C at a relative centrifugal force of 1500g. The resulting plasma will be split into two aliquots and transferred to two 1.8mL polypropylene tubes (Nunc Cryovial, Fisher Scientific No 12-565-163N, NNI No. 375418) with screw cap and immediately frozen upright at -20°C or below in a non frost-free freezer and kept frozen at this temperature before, during and after transport to the designated laboratory. One of the aliquots will be labeled and shipped as detailed below. The other aliquot will be labeled and retained at the site as backup and shipped for analysis if needed.

The samples will be analyzed within the timeframe after collection for which the stability in the samples has been validated and found acceptable. Results from analyses stored longer than the period stated will not be reported

4.2.2 Labelling and shipping of plasma samples

4.2.2.1 Labelling of AZD6140/AR-C124910XX plasma samples

The labels supplied by AstraZeneca must be applied to the plasma sample tubes. The labels should including the following information:

1. Study Number: D5130C000038
2. Volunteer Number:
3. Barcode as registered into Initiator
4. Day/Nominal Time
5. Matrix: PLASMA
6. Analyte: AZD6140

Labels will consist of a printed-paper component and be compatible at storage at -20 °C.

4.2.2.2 Shipment of AZD6140/AR-C124910XX samples

All PK plasma samples accompanied by the specimen shipment logs will be shipped via an agreed upon overnight courier (World Courier). The frozen samples must be packed securely to avoid breakage during transit, should be double bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure they remain frozen for at least

72 hours to allow for delays in shipment. The samples from each volunteer will be placed in separate bags labelled as instruction in section 4.2.2.1. All applicable shipping regulations must be followed.

Documentation sufficient to identify each sample must be included in the shipment.

At the time the samples are shipped,
, and the designated laboratory identified below must be notified by email and fax. Fax notifications will include a copy of the specimen shipment log. Contact information is as follows:

Samples should only be shipped on Monday through Wednesday. Do not ship on or the day before a legal holiday.

Plasma samples will be shipped to:

4.3 Pharmacodynamic measurements (Not applicable)

4.4 Safety measurements

4.4.1 Laboratory safety measurements

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters will be taken on the days listed given in the study plan (Table 1).

If any of the tests performed on the samples taken after investigational product administration show clinically significantly abnormal results as judged by the investigator, new blood samples will be obtained and tests repeated until the results return to baseline or the cause is assessed. The investigator will provide an evaluation of the clinical importance of the deviation. The development of any clinically relevant deterioration in any laboratory parameter may constitute an AE if it leads to discontinuation of the study drug or if it fulfils the criteria of seriousness. The investigator will record on the laboratory report whether the abnormality is Clinically Significant (CS) or Not Clinically Significant (NCS).

If aspartate aminotransferase (AST), alanine aminotransferase (ALT) or bilirubin elevations are >3 x upper limit of normal (ULN) at any time, the AstraZeneca monitor/study physician should be informed immediately.

The following laboratory variables will be measured:

Table 4 Safety Laboratory Tests to be Monitored During the Study

Clinical chemistry	Haematology	Urinalysis
Glucose	Haemoglobin	Specific gravity
Blood urea nitrogen	Haematocrit	pH
Creatinine	Erythrocytes (RBCs)	Glucose
Sodium	Leukocytes (WBCs)	Ketones
Potassium	Platelet Count	Protein
Bicarbonate	Leukocyte Differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)	Blood
Calcium		Microscopic analysis of formed elements[a]
Chloride		
Creatine Kinase		
Protein, Total		
Albumin		

Clinical chemistry	Haematology	Urinalysis
Magnesium		
Uric acid		
Bilirubin, Total		
Bilirubin, Direct		
Alkaline phosphatase		
AST		
ALT		
Gamma glutamyl transferase		

[a] If a urine sample is positive for protein or blood, a microscopic examination of the urine sediment will be performed and values will be recorded on the appropriate eCRF.

4.4.1.1 Urine drug screen

Urine will be tested for the following drugs of abuse: methadone, benzodiazepines, cocaine and/or metabolites, amphetamines, tetrahydrocannabinol (THC), opiates, methamphetamines (including ecstasy), phencyclidine (PCP), and barbiturates.

If a volunteer tests positive for drugs of abuse they will be excluded from entering, or continuing in the study. If the drug is illegal, advice will be offered and the volunteer will be removed from the volunteer panel.

Tests results will be confirmed negative prior to assignment of a volunteer number (or continuation in the study), but will not be entered into the database.

4.4.1.2 Urine ethanol testing

Urine ethanol will be measured at the time specified in Table 1. Test results will be confirmed negative prior to assignment of a volunteer number (or continuation in the study), but will not be entered into the database.

4.4.1.3 HIV and hepatitis screens

Testing for the HIV antibody, HBsAg, and Hepatitis C antibody is to be performed on all volunteers at screening only. Tests results will be confirmed negative prior to assignment of a volunteer number but will not be entered into the database.

4.4.1.4 Serum pregnancy test

All female volunteers only will have a serum β-HCG test performed on the days specified in the study plan (Table 1). If at any point a pregnancy test result is positive, the volunteer will not be allowed to proceed in the study.

Refer to Section 8.4 for instructions regarding the reporting and follow up of pregnancies. No study medication may be given to a female volunteer who has not had negative results on the initial serum pregnancy test as well as the subsequent serum pregnancy tests. The results of the pregnancy test will be recorded on the CRF as "positive" or "negative".

4.4.2 Electrocardiographic measurements

For timing of individual measurements refer to study plan (Table 1).

4.4.2.1 Resting 12-lead ECG

Twelve-lead ECGs will be obtained after the volunteer has been lying down for 10 minutes. ECGs will be documented in the CRF by recording date, time, heart rate, and overall assessment as normal and abnormal.

All ECGs will be recorded and evaluated by the investigator. If indicated additional ECG assessments can be made at the discretion of the investigator. These assessments should be entered as an unscheduled assessment on the appropriate CRF.

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 or not clinically significant. The reason for the abnormality will be recorded on the CRF.

4.4.3 Vital signs

4.4.3.1 Blood pressure and heart rate

For timing of individual measurements refer to study plan (Table 1). Blood pressure and heart rate will be measured as per CPU procedures with an appropriate cuff size. Volunteers will be sitting 5 minutes before assessments. During Study Period 1 and Study Period 2, blood pressure and heart rate will be captured electronically.

4.4.4 Other safety measurements

For timing of individual measurements refer to study plan (Table 1).

4.4.4.1 Complete physical examination

The complete physical examination will include an assessment of the following: general appearance, skin, head and neck (including eyes, ears and throat), lymph nodes, thyroid, musculoskeletal/extremities (including spine), cardiovascular, lungs, abdomen, and neurological systems.

Complete physical examination data to be recorded on the CRF will include: 1) normal/abnormal/not done, and 2) a description of any abnormalities. Except for the screening examination, if there has been no change from the previous exam, only that information need be recorded.

4.4.4.2 Height and weight

Height (cm) and weight (kg) will be measured without shoes. BMI will be calculated as weight (kg)/height $(m)^2$ and will not be reported on the CRF.

4.4.4.3 Brief physical examination

The brief physical examination will include an assessment of the following: abdomen, lungs, and the cardiovascular system.

Brief physical examination data to be recorded on the CRF will include 1) normal/abnormal/not done, and 2) a description of any abnormalities. If there has been no change from the previous exam, only that information need be recorded.

4.4.4.4 Demographics and informed consent

The volunteer's signed and dated informed consent must be obtained before conducting any procedure specifically for the study (Refer to Section 7.3). Demographics (date of birth, sex, race, date of signed informed consent) for each volunteer will be obtained and collected on the appropriate CRF.

4.4.4.5 Inclusion and exclusion criteria

The inclusion and exclusion criteria must be assessed and reviewed with each volunteer according to the study plan (Table 1) in order to establish and confirm their eligibility to participate in the study.

4.4.4.6 Medical history

A detailed medical history including surgical and medication histories will be recorded for each volunteer at the initial screening and updated at admission to the CPU. Significant medical conditions that have occurred within the past 2 years or conditions that are ongoing (i.e., headache, backache, indigestion) are to be recorded in the appropriate CRF.

The medication history must identify any known drug allergies, present or history of drug abuse and use of chronic medications. All medications and over-the-counter (OTC) products (including vitamins and herbal products) taken within 2 weeks prior to Day –1 of Study Period 1 are to be recorded on the CRF.

4.5 Genetic measurements and co-variables

4.5.1 Collection of samples for genetic research

A single venous blood sample (10mL) will be collected into a polypropylene tube containing ethylenediamine tetra-acetic acid (EDTA) and gently inverted a minimum of 5 times to mix thoroughly. Tubes will be labelled with the protocol study number, centre number, enrolment code and volunteer number and date of sample collection. No personal identifiers (volunteer name, initials or date of birth) will be placed on the tube or accompanying documentation. A record of the date of the volunteer consent to the genetic

research and the date of the blood sample collection will be recorded in the appropriate section of the CRF.

Genotype is a stable parameter; therefore if for any reason the blood sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. The genetic blood sample should ideally be drawn through the same cannula used to draw blood samples required for the main study.

4.5.1.1 Sample processing and shipping

Samples will be frozen (-20°C or below) and transported to the relevant DNA extraction laboratory within one month of collection and must remain frozen at all times. Processing, labelling and shipping instructions are provided in Appendix D.

Where possible samples should be shipped in batches and shipment should be coordinated with the receiving site to ensure that samples arrive within working hours. A requisition sheet, detailing the protocol study number, centre number, enrolment number and/or randomisation code and date of sample collection, should accompany the shipment.

Ship samples to:

Management of genetic blood sample collection, DNA extraction, transport and ultimate archiving of DNA samples will be co-ordinated via the Clinical Genotyping Group (CGG). CGG can be contacted at:

4.5.1.2 Storage and coding of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain volunteer confidentiality.

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

The blood samples and data for genetic analysis in this study will be coded. Each blood sample will be labelled with the study number and volunteer number. Only the investigator will be able to link the blood sample to the individual volunteer. The sample and data will not be labelled with a personal identifier. The link between the volunteer enrolment/randomisation code and the DNA number will be maintained in a secure environment. The link will facilitate the correlation of genotype with the clinical data, allow regulatory audit and retrieval of samples for destruction in the case of withdrawal of consent.

All DNA samples will be stored under secure conditions with restricted access at AstraZeneca. The blood, DNA samples or data derived from the samples may be made available to groups or organizations working with AstraZeneca on this study or as part of the development drug project. However, the samples and any results will remain the property of AstraZeneca at all times. AstraZeneca will not give blood, DNA samples or data derived from the samples to any other parties, except as required by law.

Samples will be stored for a maximum of 20 years, from the date of the completion of the study, after which they will be destroyed.

DNA is a finite resource that is used up during analysis. Samples will be stored and used until no further analyses are possible. Further samples will not be acquired from the volunteer.

4.5.1.3 Summary of genetic assessments and analysis

The purpose of the genetic research is to generate data for use in future retrospective analyses. Future analyses will explore genetic factors that may influence the disposition, efficacy, safety and tolerability to AZD6140 in this protocol. The results of the genetic research will not form part of the clinical study report for this study. The results may be pooled with genetic data from other studies on AZD6140 to generate hypotheses to be tested in future studies.

4.6 Volume of blood sampling

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

Table 5 Volume of blood to be drawn from each volunteer

Assessment		Sample volume (mL)	Samples (n)	Total volume (mL)
AZD6140 PK Samples		4	44	176
Blood discarded from indwelling catheter for PK samples		1	44	44
Blood Samples for Genotyping		10	1	10
Safety	Clinical chemistry & Pregnancy	8.5	6	51
	Haematology	4	6	24
	PT, aPTT*	4.5	1	4.5
	Virology Screen	8.5	1	8.5
Total				**318**

*PT, aPTT will be done at screening only per CPU procedures. Results will not be recorded in the CRF.

4.7 Adverse Events

The methods for collecting adverse events are described below.

4.7.1 Adverse Events

4.7.1.1 Definitions

The definitions of adverse events (AEs), serious adverse events (SAEs) and other significant adverse events (OAEs) are given below. It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The principal investigator is responsible for ensuring this.

Adverse event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (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, including run-in or washout periods, even if no study treatment has been administered.

Serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils 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
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the volunteer or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (i.e., their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant case report form (CRF) must answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by any of the following – study medication – other medication?" For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix B to the Clinical Pharmacology Study Protocol.

Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as "yes".

Other Significant Adverse Events (OAE)

OAEs will be identified by the Study Delivery Team Physician in consultation with the appropriate Global Drug Safety Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the volunteer from study treatment, will be classified as OAEs. Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative may be written and included in the Clinical Study Report.

4.7.1.2 Recording of adverse events

Adverse events will be collected from the point of dosing (Study Period 1, Day 1) through completion of the follow-up visit (visit 4). Serious adverse events will be collected from

the time the informed consent is signed at screening (visit 1) through completion of the follow-up visit (visit 4).

The volunteer will be told to report any AE occurring during the study to the investigator or his personnel. Open standardized AE questioning, such as "Have you had any health problems since the previous visit?" will be done by the investigators or their personnel at each contact with the volunteer. The AE open standardized questioning should be done discreetly in order to prevent the volunteer from influencing each other.

Any AEs observed or reported by a volunteer and/or staff, will be recorded in the CRF. Any AE including clinical findings not resolved at the follow-up visit, will be followed up at an additional visit or telephone contact within 7 days after the follow-up visit or until resolved or explained.

Laboratory and vital sign abnormalities will not be recorded as an AE unless any criterion for an SAE is fulfilled, the volunteer discontinues the study due to the result(s), or the investigator insists that it should be reported as an AE. If a laboratory value or vital sign is associated with clinical signs and symptoms, the signs and symptoms should be reported as an AE and the associated laboratory or vital signs should be considered additional information. Any sign or symptom that fulfils the SAE definition (Appendix B) or is the reason for discontinuation of treatment of investigational products should be reported accordingly.

The following variables will be recorded for each AE noted:

- Onset, resolution
- Intensity (mild/moderate/severe)
- Action(s) taken
- Outcome of the AE
- Causality of the AE (yes or no)
- Whether it constitutes an SAE or not

The intensity rating is defined as:

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 4.7.1.1. An AE of severe

intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Should an overdose (accidental or deliberate) occur it must be reported in accordance with the procedures described in Section 8.3, regardless of whether the overdose was associated with any symptoms or not. All symptoms associated with the overdose should be reported as AEs.

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 8.4. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

4.7.1.3 Reporting of serious adverse events

Investigators and other site personnel must inform appropriate AstraZeneca representatives of any SAE that occurs in the course of the study within 1 day (i.e., immediately but no later than the end of the next business day) of when he or she becomes aware of it.

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

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

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 day as described above. For a non-serious AE that become serious but which is not fatal or life threatening a report should be received within 5 days.

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the CRF. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

5. STUDY MANAGEMENT

5.1 Monitoring

5.1.1 Study monitoring

The monitoring of this study will be performed in accordance with the principles of Good Clinical Practice (GCP) as laid out in the International Conference on Harmonization (ICH) document "Good Clinical Practice: Consolidated Guideline".

The specific requirements of the genetic part of the study will be discussed with the investigator(s) and other personnel involved with the study.

5.1.2 Data verification

It is a prerequisite of this study that the study monitor has direct access to source data for data verification. This will be done by comparing data from the CRFs with those in the volunteer's medical notes (permission from the volunteer will be sought as part of the consent process). Such verification is an essential element of quality control, as it allows the rectification of transcription errors and omissions.

Monitoring including source data verification should routinely be performed prior to the transfer of data to Data Management.

Source verification of the genetic consent of participating volunteers will be performed and make sure that the investigational team is adhering to the specific requirements of the genetics aspects of the study.

5.2 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, an Ethics Committee may visit the centre to perform audits or inspections, including source data verification. The purpose of an AstraZeneca audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH and any applicable regulatory requirements. The investigator should contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at his or her centre.

5.3 Training of staff

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

Before the first volunteer is entered into the study the investigational staff will have an opportunity to discuss the procedures associated with the collection of blood samples,

extraction of DNA and genetic testing with AstraZeneca personnel. The ethical considerations specific to genotyping and the importance of the informed consent process will be made clear. The requirements for the collections of the volunteer' samples will also be made clear.

5.4 Changes to the protocol

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

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol must be notified to or approved by each Ethics Committee, and in many countries also the local regulatory authority, before implementation. Local requirements must be followed.

If a protocol amendment requires a change to a particular centre's Master Informed Consent Form, then AstraZeneca and the centre's IEC or IRB must be notified. Approval of the revised Master Informed Consent Form by AstraZeneca and by the IEC or IRB is required before the revised form is used.

AstraZeneca will distribute amendments and new versions of the protocol to each principal investigator(s) who in turn is responsible for the distribution of these documents to his or her Ethics Committee, and to the staff at his or her centre. The distribution of these documents to the regulatory authority will be handled according to local practice.

5.5 Study agreements

The principal investigator at each centre must comply with all the terms, conditions, and obligations of the study agreement for this study. In the event of any inconsistency between this protocol and the study agreement, this protocol shall prevail.

Specific reference to genetics should be included in the agreement. The contractual obligations should not include any additional payment for collecting the samples, unless special processing is required.

5.6 Study timetable and end of study

The study is expected to start in and to be completed in .

End of study is defined as data base lock, which is the time point after no volunteer will be exposed to study related activities.

5.7 Data management

5.7.1 Case report forms

Paper CRFs (pCRFs) will be used to record all data not captured electronically. The forms will be in triplicate on carbonless paper. Data should be recorded directly and legibly from

the source documents onto the pCRFs in black ballpoint pen. Corrections to the pCRFs should be made legibly, initialled, and dated. Correction fluid or covering labels must not be used. The top and middle sheets will be collected and forwarded to data management personnel. The bottom sheet will be retained in the Investigator Study File

The AstraZeneca Monitor will check data at the monitoring visits to the investigational site. The Investigator, together with the AstraZeneca Monitor, will ensure that the data in the pCRFs are accurate, complete and legible.

QDS Data Management will enter the pCRF data on an ongoing basis into their standard commercial database. The data will be verified and cleaned with electronic data checks comprised of validated computer programs and manual data review. Any missing, impossible or inconsistent recordings in the pCRFs will be referred back to the Investigator using a data clarification form (DCF) by QDS via AstraZeneca R&D Wilmington, and be documented for each individual volunteer before Clean File Data status is declared. Responses should be received by QDS Data Management and updated within an agreed number of days upon generating the data queries. These timelines will be reduced nearing Clean File. Clean File will be declared when all of the following have been completed: all data discrepancies are resolved or accepted; all SAEs have been reconciled with the clinical database; all coding is complete and has been medically reviewed and approved; and quality control of the database against the pCRF and relevant data sources has been completed.

5.7.2 Electronic data capture at bedside

During the study days, data will be captured electronically at bedside using Initiator PRO.

The Investigator will ensure that the captured data are correct before exported from the Initiator PRO data capture system. Any changes made during validation will be documented with a full audit trail within the Electronic Data Capture application.

Any missing, impossible or inconsistent entries discovered after the data have been exported from the Initiator PRO data capture system will be referred back to the Investigator using data query forms, and be documented for each individual volunteer before clean file status is declared.

5.7.3 Genetic data

In the case of genotypic data, only the date the volunteer gave consent to participation in the genetic research and the date the blood sample was taken from the volunteer will be recorded in the CRF and database.

The genotypic data generated from the study will be stored in the AstraZeneca Laboratory Information Management System (LIMS) database or other appropriate system. This database is a secure database, which is separate from the database used for the main study. Some or all of the datasets from the main study may be duplicated within the AstraZeneca LIMS database for exploratory genetic analysis.

5.8 Reporting of genotypic results

Results from any genetic research performed will be reported separately from the clinical study report. AstraZeneca will not provide individual genotype results to volunteers, their family members, any insurance company, an employer, clinical study investigator, general physician or any other third party, unless required to do so by law. The volunteer's DNA will not be used for any purpose other than those described in the study protocol.

Individual volunteers will not be identified in any report or publication resulting from this work. The data and results of this study may be reviewed with collaborators and published, but neither the volunteer's name nor any other personal identifiers will appear in any publication or report.

6. PHARMACOKINETIC, PHARMACODYNAMIC, SAFETY, GENETIC AND STATISTICAL METHODOLOGY

6.1 Pharmacokinetic / pharmacodynamic evaluation

6.1.1 Calculation or derivation of pharmacokinetic variables

The pharmacokinetic analyses will be performed by Clinical Pharmacokinetics, Clinical Pharmacology, AstraZeneca, Wilmington, DE USA.

Plasma concentrations of AZD6140 and its metabolite ARC124910XX will be listed and depicted graphically as a function of time after single oral and intravenous doses.

PK parameters- 1) C_{max}, t_{max}, $t_{½}$, AUC $_{(0-t)}$ and AUC for AZD6140 and AR-C124910XX after intravenous and oral doses; 2) AUMC, MRT (IV) for AZD6140 and AR-C124910XX; and CL, V_{ss}, and V_z for AZD6140 after intravenous dosing and 3) AUMC, MRT oral and MAT after oral dosing for AZD6140 and AR-C124910XX , as well as CL/F for AZD6140 after oral dosing; will be estimated using non-compartmental analysis. Metabolite: parent C_{max} and AUC ratios will be calculated following IV and oral dosing. C_{max} will be estimated as the highest measured concentration and t_{max} is the time to maximum concentration after single dose administration. The terminal elimination rate constant (λz) will be calculated by log-linear regression of the terminal portion of the plasma concentration-time profile. The terminal elimination half-life ($t_{½}$) will be calculated as $0.693/\lambda z$. AUC and AUMC will be calculated using the linear trapezoidal method up to the last measurable concentration (AUC $_{0-t}$) and thereafter by extrapolation of the terminal elimination phase to infinity. AZD6140 CL and CL/F will be estimated as the ratio of AZD6140 dose and AUC after intravenous and oral doses, respectively. Mean residence time (MRT) will be calculated as the ratio of AUMC to AUC with a correction for non-instantaneous infusion input following intravenous administration. Mean absorption time (MAT) will be estimated as the difference between MRT oral and MRT IV. Steady state volume of distribution (V_{ss}) will be estimated as the product of CL and MRT iv, and terminal phase volume of distribution, V_z, will be estimated as the ratio of CL to λz.

6.2 Safety evaluation (Not applicable)

6.3 Genetics as a co-variate

6.3.1 Calculation or derivation of genetic variables

Not applicable.

6.4 Statistical methods and determination of sample size

6.4.1 Statistical evaluation

Statistical analysis will be carried out by Quality Data Services (QDS), King of Prussia under the direction of Biostatistics at AstraZeneca, Wilmington, using SAS (version 8). Graphics required for presentation in the text portion of the Clinical Study Report (CSR) will be done using SAS or Sigmaplot 2000. Other graphics intended for supplemental figures and individual time plots will be done using SAS.

6.4.2 Description of variables in relation to hypotheses

6.4.2.1 Primary objective

In order to assess the absolute bioavailability of AZD6140 following oral and intravenous administration, the dose-normalized AUC values for the two formulations of AZD6140 will be computed.

6.4.2.2 Secondary objectives

Characterization of the pharmacokinetics of AZD6140 following oral and intravenous administration of AZD6140 will be based on single dose C_{max}, $t_{max,}$ $AUC_{(0-t)}$, AUC, $t_{1/2}$, and CL/F of AZD6140.

Characterization of the pharmacokinetics of AR-C124910XX following oral and intravenous administration of AZD6140 will based on single dose C_{max}, t_{max}, $AUC_{(0-t)}$, AUC, $t_{1/2}$ of AR-C124910XX; and AR-C124910XX:AZD6140 C_{max} and AUC ratios.

Characterization of the pharmacokinetics of AZD6140 and AR-C124910XX after oral administration of AZD6140 will be based on single dose AUMC, MRT oral and MAT and CL/F for AZD6140.

Characterization of the pharmacokinetics of AZD6140 and AR-C124910XX after intravenous administration of AZD6140 will be based on single dose AUMC, MRT (IV) and CL, V_{ss}, and V_z for AZD6140.The safety and tolerability of AZD6140 will be examined by collection of adverse events, vital signs, and clinical laboratories.

The examination of the safety and tolerability of AZD6140 will be conducted based on AE, clinical lab, vital sign and ECG data.

6.4.3 Description of analysis sets

6.4.3.1 Pharmacokinetics analysis set

The pharmacokinetics analysis set will include all volunteers who provide sufficient data to estimate the pharmacokinetic parameters of AZD6140 and AR-C124910XX following administration of each formulation involved in the contrast of interest with no deviations, which would interfere with the absorption, distribution, metabolism, or excretion of AZD6140.

6.4.3.2 Safety analysis set

The safety analysis set will include all volunteers who receive at least one dose of study medication.

6.4.4 Methods of statistical analyses

The aim of this analysis is to determine the absolute bioavailability of AZD6140 following oral and intravenous administration.

The primary variables will be AUC (oral), AUC (IV), (Dose (IV) and Dose(oral) which are used in the calculation of Primary Endpoint F (Absolute bioavailability), where F= (AUC (oral)/AUC (IV))* (Dose (IV)/Dose(oral)).

The primary contrast will be AZD6140(90 mg oral dose) vs. AZD6140(15 mg intravenous infusion).

Unless otherwise specified, descriptive statistics will include N, mean, standard deviation, minimum, median, and maximum.

A comprehensive statistical analysis plan will be prepared and finalized prior to database lock.

6.4.4.1 Pharmacokinetics

Only data from volunteers in the PK analysis set will be summarized and formally analyzed. All PK and plasma concentration data will be listed. Any data excluded from the analysis will be flagged accordingly.

The absolute bioavailability (F), where F=(AUC(oral)/Dose(oral)/(AUC(IV)/Dose(IV)), of AZD6140 following oral and intravenous administration will be analyzed as follows: Dose-normalized AUC values for the two formulations of AZD6140 will logarithmically transformed. An ANOVA model will then be fit using these log-scale values. The effect of formulation will be the primary contrast [log(AUC(oral)/Dose(oral))-log(AUC(IV)/Dose(IV))]. The effect of formulation will be estimated using the 1smean and its 95% confidence interval. The 1smean and 95% confidence interval will then be exponentiated in order to estimate the absolute bioavailability. The lsmeans and 95% confidence intervals will also be calculated and exponentiated for each treatment formulation

PK parameters and plasma concentration data for each moiety (AZD6140, AR-C124910XX) will be summarized using descriptive statistics by AZD6140 formulation. Descriptive statistics will also include geometric mean and CV for all parameters except t_{max}, which will be summarized using only N, minimum, median and maximum. Geometric mean and individual plasma concentration-time profiles will be presented by AZD6140 formulation. AUC and C_{max} for each moiety will also be presented graphically as a function of AZD6140 formulation.

6.4.4.2 Safety

Only data from volunteers in the safety analysis set will be summarized and formally analyzed. Any data excluded from the analysis will be flagged accordingly.

Adverse events will be analyzed using frequency distribution by formulation. Clinical laboratory results, vitals signs and ECGs will be analyzed by formulation and protocol time point.

6.4.5 Determination of sample size

No formal sample size calculation was performed for this study. Ten evaluable volunteers were selected as a compromise between obtaining information on the absolute bioavailability of AZD6140 and exposing the minimum number of volunteers to AZD6140.

6.5 Interim analyses (Not applicable)

6.6 Data monitoring committee (Not applicable)

7. ETHICS

7.1 Ethics review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favourable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to AstraZeneca before he or she can enrol any volunteer into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit volunteers for the study. The protocol must be re-approved by the Ethics Committee annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the Ethics Committee according to local regulations and guidelines.

Where there is a genetic research, approval must be obtained for this genetic research and the associated genetic informed consent from the Ethics Committee. It must be clearly stated in the approval that this genetic research is approved. The investigator must submit written approval to AstraZeneca before any volunteer participates in this genetic research.

7.2 Ethical conduct of the study

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

7.3 Informed Consent

The principal investigator at each centre will ensure that the volunteer is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Volunteers must also be notified that they are free to discontinue from the study at any time. The volunteer should be given the opportunity to ask questions and allowed time to consider the information provided.

The volunteer's signed and dated informed consent must be obtained before conducting any procedure specifically for the study.

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

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

7.4 Volunteer data protection

The Master Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, Volunteers will authorize the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data

legislation. All data processed by AstraZeneca will be identified by randomisation code/study code/ initials.

The Master Informed Consent Form will also explain that for data verification purposes, authorized representatives of AstraZeneca, a regulatory authority, an IRB or IEC may require direct access to parts of the hospital or practice records relevant to the study, including volunteers' medical history.

All data protection and confidentiality principles, described in the main study protocol, are applicable to this genetic research.

Reference to participation in this genetic research should not be recorded into the volunteer' general medical records. All notes should be kept within the clinical study records.

Due to the exploratory nature of this genetic research, there will be no routine communication of results to volunteer. AstraZeneca will not provide individual genotype results to any volunteer, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the volunteer, however, it must be recognized that there are exceptional circumstances where individuals may see both genetic data and a volunteer's personal identifier, for example in the case of a medical emergency, when AstraZeneca Physicians and investigators might know the volunteer' identity and might have access to the genetic data, or during regulatory audit where designated authorities must be permitted access to the relevant files.

8. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

8.1 AstraZeneca emergency contact procedure

In the case of a medical emergency, contact AstraZeneca personnel shown below.

•

•

For Serious Adverse event reporting

•

8.2 Procedures in case of medical emergency

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study. **A medical emergency usually constitutes an SAE and should be reported as such, see Section 4.7.1.3.**

8.3 Procedures in case of overdose

Use of study medication in doses in excess of that specified in the protocol should not be recorded in the CRF as an AE of 'Overdose' unless there are associated symptoms or signs.

An overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the CRF.

An overdose with associated non-serious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the CRF. In addition, the overdose should be reported on the separate AZ "Clinical Study Overdose Report Form."

An overdose without associated symptoms should not be recorded as an AE in the CRF. The overdose should be reported on the separate AZ "Clinical Study Overdose Report Form".

8.4 Procedures in case of pregnancy

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the volunteer was discontinued from the study.

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

9. REFERENCES

None

AstraZeneca

Clinical Pharmacology Study Protocol Appendix A	
Drug Substance	AZD6140
Study Code	D5130C00038
Appendix Edition Number	1
Appendix Date	

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

An open-label, single-centre, randomised, two-period, crossover study to determine the absolute bioavailability of AZD6140 in healthy male and female volunteers

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

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

AstraZeneca Research and Development site representative

ASTRAZENECA SIGNATURE(S)

An open-label, single-centre, randomised, two-period, crossover study to determine the absolute bioavailability of AZD6140 in healthy male and female volunteers

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

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

AstraZeneca Research and Development site representative

SIGNATURE OF PRINCIPAL INVESTIGATOR

An open-label, single-centre, randomised, two-period, crossover study to determine the absolute bioavailability of AZD6140 in healthy male and female volunteers

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

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations.

Centre No.: 01

Signature:

AstraZeneca

Clinical Pharmacology Study Protocol: Appendix B

Drug Substance	AZD6140
Study Code	D5130C00038
Appendix Edition Number	1
Appendix Date	

Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

<<*Examples of such events are:*

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

AstraZeneca

Clinical Pharmacology Study Protocol: Appendix C

Drug Substance	AZD6140
Study Code	D5130C00038
Appendix Edition Number	1
Appendix Date	

Appendix C
WHO Risk Categories

Risk group	Shipping Requirement	Pathogen	Risk to individuals	Risk to the community	Examples of Pathogens and their Risk groups
1	Standard Diagnostic (IATA PI650)	A micro-organism that is unlikely to cause human disease.	NONE OR VERY LOW	NONE OR VERY LOW	Most bacteria, fungi and viruses
2	Standard Diagnostic (IATA PI650)	A pathogen that can cause human or animal disease but is unlikely to be a serious hazard to laboratory workers, the community, livestock or the environment. Laboratory exposures may cause serious infection, but effective treatment and preventive measures are available and the risk of spread of infection is limited.	MODERATE	LOW	Legionella pneumophila E. Coli 0157
3	Standard Diagnostic (IATA PI650)	A pathogen that usually causes serious human or animal disease but does not ordinarily spread from one infected individual to another. Effective treatment and preventive measures are available.	HIGH	LOW	HIV Hepatitis B Hepatitis C
4	High risk(IATA PI602)	A pathogen that usually causes serious human or animal disease and that can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventive measures are not usually available.	HIGH	HIGH	Lassa Fever Ebola Virus

If a subject is being withdrawn due to a suspected infection in WHO risk categories 2, 3 and 4 no biological samples from this subject are allowed to be sent to the laboratory. Samples will be destroyed according to normal routines at the study site.

Clinical Pharmacology Study Protocol Appendix D	
Drug Substance	AZD6140
Study Code	D5130C00038
Appendix Edition Number	1
Appendix Date	

Appendix D
Instructions for Blood Collection, Storage and Transport in Clinical Genetics Studies

Collection

Ideally, blood should be collected into ***9/10ml polypropylene tubes*** containing the ***anticoagulant EDTA***. Recommended tubes are detailed in the table below. **Part numbers may vary between countries. Please check tubes are suitable before ordering them**. After collection, blood tubes must be gently ***inverted*** several times to ensure thorough mixing of EDTA with the sample to prevent clotting.

Polypropylene Collection Tube	Part #	Comments
	1066 US 1066.001 UK	SARSTEDT Monovette® EDTA KE - 9ml
	367525 USA/UK	Becton-Dickinson Vacutainer™ K2E - 10ml
	455036 USA/UK	Greiner Bio-one Vacuette® K3E EDTA K3 - 9ml

Table of recommended blood tubes for genotyping sample collection

- ***Glass tubes MUST NOT be used*** as they may break during transport and freeze-thaw cycles.
- ***Heparin MUST NOT be used as an anticoagulant*** as it may interfere with downstream genotyping methodology.

The collection tubes must be labelled with the following information:

- Unique sample ID (compliant with protocol)
- Study ID (& Study Centre ID, if available)
- Date of sample collection

DNA Processing Laboratories have encountered scanning incompatibility due to inclusion of hidden digits in barcode labels. If barcode labels are to be used, a sample will be requested at a later date. All labels must be freezer-proof.

2. STORAGE AT THE STUDY CENTRE AND TRANSPORT

After collection, blood samples must be stored appropriately at the site of collection and transported to the Central Handling Facility, or Designated DNA Processing Laboratory, ***as soon as possible***. The table below shows guidelines for sample storage and transport:

Option	***Storage Temperature at Study Centre***	***Maximum Duration***	***Transport Temperature***	***Delivery Time***
1	+ 4°C (fridge)	24 hours	0 - 4°C (ice bricks)	24 hours
2	+ 4°C (fridge)	24 hours	Less than -20°C (dry ice)	24 -72 hours
3	-20°C (freezer) or -70°C	Up to 1 month	Less than -20°C (dry ice)	24 -72 hours

Table to show the recommended storage conditions for blood samples immediately after collection

- ***IF BLOOD SAMPLES ARE TO BE STORED AT -20°C OR LESS, NON-FROST FREE FREEZERS MUST BE USED TO PREVENT REPEATED FREEZE-THAW OF BLOOD WHICH MAY REDUCE YIELD & QUALITY OF THE DNA OBTAINED***
- ***SAMPLES MUST NOT BE THAWED AND THEN RE-FROZEN AT ANY POINT***

The Central Handling Facility, or Designated DNA Processing Laboratory, must be notified of the shipment of any samples prior to dispatch. Ideally, the dispatch note must be sent by either fax or email and must contain the following information:

- Study ID, number of samples & list of sample ID's
- Courier name, airway bill number & date of shipment
- Shipment condition (wet ice or dry ice)
- Contact name & address

Considerations should be made to ensure that the samples are delivered during working hours and within 24 -72 hours of dispatch.

3. RECOMMENDED PACKAGING INSTRUCTIONS

For safety reasons all blood samples must be contained. Samples should be individually placed in a clip-lock bag labelled with the sample ID and sealed. Samples may then be batched and again sealed within a second clip-lock bag labelled with the study ID. For ease of further packaging and protection from damage, samples should then be placed within another plastic bag labelled with the study ID and study centre ID. A bio-safety label should also be applied.

Sample Shipment.

IATA (International Air Transport Association) approved polystyrene transport boxes must be used.

For samples transported on wet ice:

The box should contain frozen ice blocks and protective packaging (polystyrene flocking), to allow for a minimum of 24 hours transport.

For samples transported on dry ice:

The box should contain dry-ice pellets (if pellets are not available then blocks may be used if protective packaging such as polystyrene flocking is included) to allow for a minimum of 72 hours transport.

Each package must be sealed in a cardboard box labelled with the courier airway bill.

4. STORAGE AT THE CENTRAL HANDLING FACILITY OR DESIGNATED DNA PROCESSING LABORATORY

i. Central Handling Facility (short term storage)

Blood/EDTA samples can be stored temporarily at the Central Handling Facility and subsequently transported to the Designated Processing Laboratory following the guidelines below:

Storage Temperature at Central Handling Facility	Maximum Duration	Transport Temperature	Delivery Time
-20°C (freezer) or -70°C	6 months	Less than -20°C (dry ice)	24 -72 hours

- ***IF BLOOD SAMPLES ARE TO BE STORED AT -20°C OR LESS, NON-FROST FREE FREEZERS MUST BE USED TO PREVENT REPEATED FREEZE-THAW OF BLOOD WHICH MAY REDUCE YIELD & QUALITY OF THE DNA OBTAINED***

- ***SAMPLES MUST NOT BE THAWED AND THEN RE-FROZEN AT ANY POINT***

ii. Designated DNA Processing Laboratory (final destination)

ON ARRIVAL AT THE DESIGNATED DNA PROCESSING LABORATORY, BLOOD/EDTA SAMPLES SHOULD BE STORED AT -20°C OR -70°C (FREEZER) UNTIL THEY ARE PROCESSED. IDEALLY, SAMPLES SHOULD BE PROCESSED WITHIN 6 MONTHS OF COLLECTION.