AstraZeneca

Clinical Study Report: Appendix 12.1.1	
Drug Substance	AZD6140
Document No.	SC-532-5238
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Study Code	SC-532-5238
Appendix Date	

Appendix 12.1.1
Protocol and protocol amendments

AstraZeneca

Clinical Study Protocol

Drug Substance	AZD6140
Study Code	SC-532-5238
Date	

Version No 02

An Open, Crossover Study To Evaluate The Absorption Characteristics of AZD6140 From an Immediate Release Tablet Compared to an Oral Suspension and to Assess the Regional Absorption of AZD6140 in Healthy Volunteers

The following amendment(s) have been made to this protocol since the date of preparation:

Amendment No. **Date of amendment**

PROTOCOL SYNOPSIS

An Open, Crossover Study To Evaluate The Absorption Characteristics of AZD6140 From an Immediate Release Tablet Compared to an Oral Suspension and to Assess the Regional Absorption of AZD6140 in Healthy Volunteers

Investigator

Study centre(s) and number of subjects planned

This will be a single centre study. Twelve healthy male or female volunteers will be entered into the study, for at least 10 to complete.

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

Objectives

The primary objective of the study is to examine by assessment of plasma concentrations of AZD6140 and the metabolite AR-C126910XX the regional absorption characteristics of AZD6140 from the proximal small bowel, distal small bowel and ascending colon to aid in the design of a modified release tablet formulation.

Secondary objectives of the study are:

1. to compare the pharmacokinetic parameters obtained from an immediate release tablet formulation (100 mg), with that obtained from an oral suspension (100 mg).

2. to gain information about the safety and tolerability of AZD6140 administered under these conditions by assessment of Adverse Events, 12-lead ECGs, blood pressure and pulse, clinical chemistry, haematology and urinalysis.

Study design

This will be a single centre, open crossover study.

Target subject population

Twelve healthy male and female volunteers (minimum of 10 to complete, maximum of 12 to dose).

Investigational product, dosage and mode of administration

1. AZD6140 Immediate Release tablet 100 mg – single dose

2. AZD6140 Oral suspension 100 mg – single dose

3. AZD6140 suspension/powder 100 mg within the Enterion™ capsule – 3 single doses (to be confirmed - see Section 3.4.1.1).

Comparator, dosage and mode of administration

None.

Duration of treatment

There will be 5 treatment limbs. On each limb subjects will receive a single dose of study treatment. The first 2 study periods will last approximately 24 hours. The third, fourth and fifth study periods will last approximately 28, 31 or 48 hours, depending on the treatment allocation. Subjects will be required to return to the clinical unit at 36 hours either post-dose or post-activation for all regimens. Each capsule administration will be separated by a washout period of no less than 96 hours.

Endpoints

- **Pharmacodynamic**

  Scintigraphic imaging – Gastric emptying time, small intestinal transit time, ileo-caecal junction (ICJ) arrival time, residence time at ICJ, colon arrival time, colon transit time, total transit time, time and anatomical location on successful Enterion activation.

- **Safety**

  Haematology, clinical chemistry, urinalysis, blood pressure, pulse, 12-lead ECG and adverse events.

- **Pharmacokinetic**

  The plasma concentration data for AZD6140 and the metabolite AR-C126910XX will be analysed using standard pharmacokinetic methods to yield the following parameters:

AUC, AUC_t, $t_{1/2}$, C_{max}, t_{max}.

Individual and mean plasma concentrations and pharmacokinetic parameters will be summarised and presented in tabular format and/or graphically by AstraZeneca R&D Charnwood. Descriptive statistics will be applied to the data.

Statistical methods

All data will be summarised using suitable summary statistics, where appropriate. No formal statistical analysis will be performed on any of the data.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Table 1 Abbreviations and specialist terms

Abbreviation or specialist term	Explanation
ADP	Adenosine Diphosphate
AE	Adverse event (see definition in Section 4.4.2.1).
AIDS	Acquired immunodeficiency syndrome
AMOS	AstraZeneca Monitoring System
APA	ADP-induced platelet aggregation
APTT	Activated partial thromboplastin time
ARSAC	Administration of Radioactive Substances Advisory Committee
AUC	Total area under the plasma concentration-time curve
AUC_t	Area under the plasma concentration-time curve from time zero to the time of the last measurable plasma concentration
B	Basophils
BP&P	Blood pressure and pulse
C_{max}	Maximum plasma concentration
CRF	Case Report Form
DTPA	Diethylenetriaminepentaacetic acid
ECG	Electrocardiogram
ERC	Ethical Review Committee
FSH	Follicular stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
HRT	Hormone replacement therapy
ICH	International Conference on Harmonisation
ICJ	Ileo-caecal Junction
IEC	Independent Ethics Committee
^{111}In	111-Indium
IPS	Investigational Products
IR	Immediate release
IRB	Institutional Review Board
MCH	Mean cell haemoglobin
MCHC	Mean cell haemoglobin concentration
MCV	Mean cell volume

Abbreviation or specialist term	Explanation
NSAIDS	Non steroidal anti-inflammatory drugs
OAE	Other significant adverse event (ie an adverse event of special interest in this clinical development; see definition in Section 4.4.2.1). The classification of OAEs will be performed by AstraZeneca drug safety physicians after the study is complete.
OTC	Over-the-counter
Principal investigator	The investigator who leads the study conduct at an individual study centre.
PK	Pharmacokinetics
PT	Prothrombin time
RBC	Red blood cells
SAE	Serious adverse event (see definition in Section 4.4.2.1).
SAP	Statistical Analysis Plan
^{99m}Tc	99m-Technetium
$t_{½}$	Plasma terminal half-life
t_{max}	Time for the plasma concentration to reach C_{max}
WBC	White blood cells

1. INTRODUCTION

1.1 Background

AZD6140 (formally AR-C126532XX) is [1S-[1α,2α,3β(1*S**,2*R**),5β]]-3-[7-[2-(3,4-difluorophenyl)cyclopropylamino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol]. It is a potent, selective and competitive P_{2T} -receptor antagonist antiplatelet agent[1,2]. It is orally active and does not require metabolic activation, unlike clopidogrel and ticlopidine, which are incompletely active as P_{2T} receptor antagonists in humans. *In vitro* studies indicate that metabolism by rat, dog and human hepatocytes and microsome preparations are minor. Pre-clinical studies indicate that it can produce long-lasting and complete inhibition of adenosine diphosphate (ADP)-induced platelet aggregation (APA) *ex vivo*. Although sparingly soluble in water, it is 85-90% bioavailable as an oral suspension in canine oral dosing studies. It is also typical of its class in completely protecting against thrombosis in the canine femoral artery cyclic flow model at doses that do not cause bleeding time extension. The first human study SC-532-5169 indicated dose linearity up to 100 mg (oral dosing), with incomplete inhibition of the platelet aggregation using the impedance technique. In addition a maximum tolerated dose was not identified. Subsequent preliminary data indicate complete inhibition of platelet aggregation at doses of 100 mg to 400 mg (SC-532-5171). Safety data generated from these 2 studies have indicated that over the dose range of 0.1 to 400 mg, there are no clinically significant adverse events with AZD6140. In both studies performed to date mean changes seen in lancet bleeding time were transient and were generally no greater than 4-fold that of baseline values. These effects were mainly seen at doses greater than 100 mg. Also, data from SC-532-5171 have indicated that, although doses of 300 and 400 mg provide once daily dosing coverage to produce a 24-hour inhibition of platelet aggregation between approximately 60 – 100%, the pharmacokinetics of the compound are such that using an extended release formulation could reduce the necessary dose of AZD6140 to produce this effect. *In vitro* studies in animal tissues relating to the absorption of AZD6140 from different regions of the gut have given conflicting results and the most meaningful data can now be obtained by means of a regional absorption study in man.

The Enterion™ site-specific delivery capsule represents a novel, easy to use, non-invasive methodology for assessing regional drug absorption from the gastrointestinal tract. The capsule is 32 mm in length and 10 - 12 mm in diameter and is capable of delivering suspensions (and other formulations) to specific sites of the GI tract. The location of the capsule is determined using gamma scintigraphy, thereby resulting in significantly lower radiation doses to the volunteers compared to other capsule technologies such as the high frequency capsule. This permits more frequent imaging in comparison to investigations involving other radiological techniques. This results in more accurate assessment of anatomical location of the device. The capsules contain a drug chamber with a wide port and activation is confirmed by means of a signal that is emitted from the capsule when activation occurs and is relayed back to the activation unit.

1.2 Rationale for this study

The rationale for this study is to investigate the absorption of AZD6140 from the proximal small bowel, distal small bowel and ascending colon in healthy volunteers. This will provide reliable information on the regional absorption of this compound that has not been available from *in-vitro* investigations. Regional absorption is to be compared with that of a standard suspension formulation which has been used in the 2 previous studies with AZD6140 and also a standard instant release tablet (IR) formulation as a preliminary 'solid' dosage form reference.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to examine by assessment of plasma concentrations of AZD6140 and the metabolite AR-C126910XX the regional absorption characteristics of AZD6140 from the proximal small bowel, distal small bowel and ascending colon to aid in the design of a modified release tablet formulation.

2.2 Secondary objectives

Secondary objectives of the study are:

1. to compare the pharmacokinetic parameters obtained from an immediate release tablet formulation (100 mg), with that obtained from an oral suspension (100 mg).

2. to gain information about the safety and tolerability of AZD6140 administered under these conditions by assessment of Adverse Events, 12-lead ECGs, blood pressure and pulse, clinical chemistry, haematology and urinalysis.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

This will be a single centre, open crossover study in 12 healthy male and female volunteers (maximum of 12 to dose, minimum of 10 to complete). This study will be carried out under the Administration of Radioactive Substances Advisory Committee (ARSAC) certificate, under certificate RPC-497-1215-(14123), certificate holder Dr G Hooper.

Visit 1 (enrolment) will take place up to 21 days prior to dosing. After collection of written informed consent, subjects will be screened for eligibility. Subjects who fulfil the eligibility criteria will progress to Visit 2. At Visit 2, subjects will be randomised to receive either

100 mg AZD6140 suspension or 100 mg AZD6140 immediate release (IR) tablet. Subjects randomised to suspension at Visit 2 will receive the IR tablet at Visit 3 and *visa versa*. At Visit 4, subjects will be randomised to the order in which the following limbs are conducted (Visits 4, 5, and 6):

- Enterion capsule containing oral suspension or powder (100 mg) released into proximal small bowel.

- Enterion capsule containing oral suspension or powder (100 mg) released into the distal small bowel.

- Enterion capsule containing oral suspension or powder (100 mg) released into the ascending colon (to be confirmed - see Section 3.4.1.1).

Subjects will attend the clinic for the final follow up visit (Visit 7) 7 to 10 days after the completion of Visit 6.

Figure 1 Study flow chart

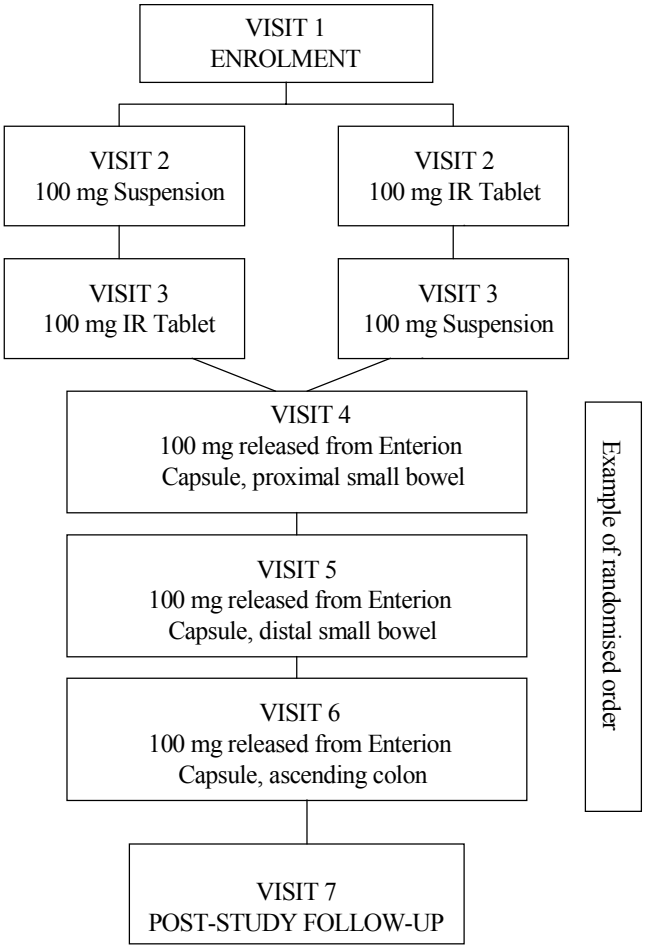

Table 2 Study plan

Assessments	Visit 1 Enrolment	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7 Follow-up
Informed consent	✓						
Inc./Excl. criteria	✓	✓	✓	✓	✓	✓	
Medical/Surgical History	✓						
Physical Exam	✓						✓
Virology screen	✓						
AZD6140 Dose		✓	✓	✓	✓	✓	
12-Lead ECG	✓	✓	✓	✓	✓	✓	✓
BP & Pulse rate	✓	✓	✓	✓	✓	✓	✓
Safety bloods	✓	✓	✓	✓	✓	✓	✓
Urinalysis	✓	✓	✓	✓	✓	✓	✓
Scintagraphic Images				✓	✓	✓	
Drugs of abuse	✓	✓	✓	✓	✓	✓	
PK Samples		✓	✓	✓	✓	✓	
Adverse Events		✓	✓	✓	✓	✓	✓

3.2 Rationale for study design, doses and control groups

The study's open design is to optimise the number of volunteers completing each segment of the study. Crossing over the release sites for the Enterion allows some flexibility in that, if a site is missed by rapid passage beyond that site, drug can be delivered at a lower site and the randomisation changed to allow the next limb to dose at the earlier GI site. Similarly, by crossing over the tablet and suspension as the first 2 limbs of the study, baseline pharmacokinetic data will be obtained for the majority of subjects and maximise the numbers receiving both tablet and suspension.

The dose selected was restricted by the size of the drug chamber in the Enterion capsule. A dose of 100 mg was selected as the best dose to fit into the chamber and also that which is predicted to give evaluable PK data out to the 36-hour timepoint (ie with approximately 30% of the exposure, 36-hour concentrations of AZD6140 will be greater than the Limit of Quantification of the assay).

3.3 Selection of study population

3.3.1 Study selection record

The investigator is responsible for keeping a record of subjects who were considered for enrolment but were never enrolled.

3.3.2 Inclusion criteria

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

1. Provision of written informed consent

2. Be male or post-menopausal (cessation of regular menses for more than 12 months and an FSH of >20 IU).

3. Aged between 18 and 65 years of age, inclusive.

4. Have a Body Mass Index (BMI) between 18 and 30 $kg \cdot m^{-2}$, inclusive.

5. Have normal physical examination, laboratory values, 12-lead ECG and vital signs, unless the investigator considers an abnormality to be clinically irrelevant.

6. Subject must be able to demonstrate ability to swallow an empty size 000 gelatin capsule.

3.3.3 Exclusion criteria

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

1. A 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 unless considered clinically irrelevant by the investigator.

2. A history of intolerance or hypersensitivity to drugs with a similar chemical structure (eg adenine nucleoside antivirals and immunosuppressant drugs) or their excipients.

3. Personal or family history of bleeding disorders, suspicion of vascular malformations, including aneurysms, history of important bleeding such as haematemesis or epistaxis, or rectal bleeding (including that from haemorrhoids within the last 3 months).

4. Consumption of aspirin in any form, or of any other nonsteroidal anti-inflammatory drugs, within 2 weeks prior to Visit 1.

5. Surgery or significant trauma within 3 months prior to Visit 1.

6. Clinically significant out-of-range values for prothrombin time or activated partial thromboplastin time as judged by the investigator.

7. Diagnosed hypertension, or supine blood pressure, after a period of acclimatisation ≥150/90 mmHg or <90/40 mmHg.

8. A 5-minute resting supine heart rate outside the range 40-90 bpm.

9. Participation in any clinical study with an investigational drug in the 4 months prior to the study, or participation in a study with a new formulation of a marketed drug in the previous 3 months prior to Visit 1.

10. Donation of blood or plasma in total >500 mL within 3 months of Visit 1.

11. Symptoms of a clinically significant illness within 4 weeks of Visit 1.

12. Use of any prescribed medication in the 3 weeks prior to Visit 2 (except hormone replacement therapy (HRT)) or over the counter preparations (for aspirin/NSAIDS see exclusion 4) (excluding paracetamol up to 4 g daily) in the 7 days prior to Visit 2 (for more detailed information see Section 3.4.5).

13. A significant history of alcohol abuse or consumption of more than 21 units of alcohol (male) or 14 units (female) per week.

14. A significant history of drug abuse or a positive drugs of abuse test, unless due to a declared medication.

15. Evidence of having serum hepatitis or subject who carries the hepatitis B surface antigen or hepatitis C antibodies.

16. Subjects considered by the investigator to be at risk of transmitting through blood or other body fluids the agents responsible for AIDS (Acquired Immunodeficiency Syndrome) or other sexually transmitted disease or hepatitis. This will be achieved by the use of a card (similar to that used by the National Blood Transfusion Service) which asks a potential subject if they have reason to believe that they may fall into any category included on the card. If the verbal answer is in the affirmative then they will be excluded from the study.

17. Subjects who smoke more than 15 cigarettes per day or ½ oz of tobacco per week, or use nicotine or any other nicotine-containing products and who will be unable to abstain from smoking during the treatment periods. Subjects who have a breath carbon monoxide reading of greater than 20 ppm.

18. Radiation exposure from clinical trials, including that from the present study and from diagnostic X-rays, but excluding background radiation, exceeding 5 mSv in the last 12 months or 10 mSv in the last 5 years. No subject whose occupational exposure is monitored will participate in the study.

19. Acute diarrhoea or constipation in the last 14 days before the predicted first study day. If screening occurs >14 days before the first study day, this criterion is to be determined on the first study day. Diarrhoea will be defined as the passage of liquid faeces and/or a stool frequency of greater than 3 times per day. Constipation will be defined as failure to open the bowels more frequently than every other day.

20. Subjects who have had dental procedures (excluding minor scale and polish) in the 4 weeks prior to Visit 1.

21. Presence of non-removable metal objects such as metal plates, screws etc, in abdominal region of body.

22. Subjects who are employed in work involving sharp objects.

23. Subjects who cannot abstain from contact sports for the duration of the study (ie Visits 1 to 7).

3.3.4 Discontinuation of subjects from treatment or assessment

3.3.4.1 Criteria for discontinuation

Subjects may be discontinued from study treatment and assessments at any time, at the discretion of the investigator(s). Specific reasons for discontinuing a subject from this study are:

1. Withdrawal of informed consent.

2. Development of exclusion criteria, pregnancy or other safety reasons.

3. Incorrect enrolment or randomisation of the subject.

4. Intolerance of study related procedures.

Both AstraZeneca and the investigator reserve the right to terminate the study at any time. Once dosing with radiopharmaceuticals has begun, the study will not be terminated without careful consideration being given to the risk and benefit of those subjects already dosed. In these circumstances, termination must be agreed with both the Ethics Committee and the ARSAC certificate holder.

3.3.4.2 Voluntary discontinuation by a subject

Subjects are free to discontinue their participation in the study at any time, without prejudice to further treatment. Subjects who discontinue from the study should always be asked about the reason(s) for their discontinuation and about the presence of any adverse events. If possible, they should be seen and assessed by an investigator(s). Adverse events should be followed up.

3.3.4.3 Incorrectly enrolled or randomised subjects

Not applicable. See final paragraph of Section 3.3.4.1.

3.3.4.4 Procedures for discontinuation

If any subject is required to discontinue the study, the investigator must assess if and when the subject should return to the unit for a post-study follow-up. If the subject has been dosed, a follow-up visit should be conducted.

The Case Report Forms (CRF) should be completed (STTERM module) to reflect the reason for the subject's discontinuation in the study.

3.3.5 Restrictions

3.3.5.1 Dietary restrictions

Subjects should abstain from taking caffeine-containing beverages or foods (tea, chocolate, cocoa and cola etc) from 12 midnight on the day prior to admission to the clinic (Day 0), until they leave the clinic on Day 1. Subjects should abstain from alcohol for 24 hours prior to each study day until they leave the clinic on Day 1.

On all dosing occasions the subjects will fast from midnight prior to admission (Day 0). During Visits 2 and 3 subjects will attend the unit at approximately 07:00 hours and will be dosed around 08:00. They will continue to fast until 5 hours post-dose, when they will be served with a light lunch. Dinner will be served at approximately 9 hours post-dose, all meal times will be recorded in the CRF.

During Visits 4, 5 and 6 subjects will be provided with a light breakfast of toast and jam at approximately 07:00 on Day 0. Dosing will commence approximately 4 hours later, at 11:00. Each subject will drink 200 mL of water at 2 hours post-dose. Lunch will be served at 5 hours post-dose and dinner at 9 hours post-dose. Decaffeinated fluids will be allowed *ad libitum* after lunch on the days of dosing (see Appendix H for description of all meals).

Subjects must not eat anything likely to disturb gastrointestinal transit (eg curry and high fat foods such as fish and chips) for 24 hours prior to each study day.

All subjects will refrain from smoking from midnight on the day before dosing and whilst in the clinic.

3.3.5.2 Activity restrictions

Subjects should abstain from strenuous activity or any contact sports for 3 days before dosing until the end of the study. Strenuous activity is considered to be anything that is different from the subject's normal physical routine.

Subjects will be asked to abstain from donating blood during the course of the study until 3 months after the last visit.

All subjects will be admitted to the unit at approximately 07:00 hours on the morning of dosing (Day 0) and will remain in the unit during Day 0.

On Visits 2 and 3 subjects will be allowed to leave the premises 24 hours after dosing (Day 1) once they have been passed fit for discharge by the study physician.

On Visits 4, 5 and 6 subjects will be allowed to leave the premises 24 hours after activation of the capsule once they have been passed fit for discharge as above.

All subjects will be required to return to the clinic for performance of the 36-hour post-dose/activation timepoint. If the 36-hour timepoint falls in the middle of the night, subjects will be given the option of staying within the unit between the 24- and 36-hour timepoints.

3.4 Treatments

3.4.1 Investigational products

3.4.1.1 Identity of investigational product

AZD6140 Suspension

Compound Number:	AZD6140
Dosage Form:	10.3 g suspension per single dose unit containing 100 mg AZD6140
Excipients:	1% Carboxymethylcellulose 0.1% Polysorbate 80 Made up to volume with 'Water for Injection'

AZD6140 Immediate Release Tablet

Compound Number:	AZD6140
Dosage Form:	Immediate release tablet containing 100 mg AZD6140
Excipients:	Lactose monohydrate Ph Eur Microcyrstalline cellulose Ph Eur Polyvinylpyrrolidone K30 Ph Eur Croscarmellose sodium Ph Eur Magnesium stearate Ph Eur White film coating

AZD6140 Suspension/Powder-Enterion

Compound Number:	AZD6140
Dosage Form:	Enterion capsule containing 100 mg AZD6140 A ^{111}In-chloride marker (1 MBq) will be incorporated into the radioactive tracer port in the end cap of the capsule. This marker will remain in the device throughout the gastrointestinal tract. A ^{99m}Tc-DTPA drink will also be given at the same time as the Enterion capsule to highlight the GI tract.

The procedure that will be used to prepare the Enterion capsules for each study day will be documented in a Manufacturing Protocol. Dependent on *in vitro* dissolution tests (to simulate the bowel environment) AZD6140 will be presented in the Enterion capsule as either a suspension or raw drug powder. The decision about which formulation to be used will be made by AstraZeneca R&D Charnwood and Pharmaceutical Profiles Ltd.

The Enterion capsules are constructed to prevent leakage of material from the capsule prior to activation. Leakage tests are performed to confirm that the formulation does not leak from the capsule *in vitro*. The tests involve incubating capsules containing the test formulation in a dissolution vessel. Aliquots of the incubation media are then removed at various timepoints to test for the presence of the drug.

In order to ensure that the formulation is effectively and efficiently released from the capsule a test activation will be performed. The test involves activation (opening) of the capsule in the air and quantifying the amount of drug released.

3.4.1.2 Labelling

AZD6140 suspension and tablets for Visits 2 and 3 will be manufactured, labelled with flag labels and supplied by AstraZeneca R&D Charnwood. AZD6140 suspension will be supplied in single dose units, in amber vials. AZD6140 IR tablets will be supplied in single unit dose bottles, one tablet packed into each 50 mL HDPE plastic bottle with clic loc cap. AZD6140 active ingredient and excipients will be supplied by AstraZeneca R&D Charnwood to fill the Enterion capsule and filling will be carried out by either AstraZeneca R&D Charnwood or Pharmaceutical Profiles depending on the outcome of *in vitro* testing. Details of this will be recorded in the Manufacturing Protocol. Radiolabelling of the Enterion capsule will be performed by Pharmaceutical Profiles.

Labelling will be in accordance with Good Manufacturing Practice (GMP) and will include subject number and visit number.

3.4.1.3 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. The storage location will be locked and only accessible to authorised study site personnel.

The suspension will be kept in a secure place under adequate storage conditions, between 2 and 8°C. Both the tablets and the raw drug powder should be stored between 2 - 30°C, protected from light and high humidity.

3.4.1.4 Accountability

The investigator (or delegate) is responsible for maintaining drug accountability records for study drugs. This will be performed according to standard procedures at the unit.

Unused study drugs may be dispatched directly to the Waste Management Group at AstraZeneca R&D Charnwood, following discussion with the study monitor.

3.4.2 Doses and treatment regimens

All subjects will receive a single dose of all following study treatments:

1. IR tablet 100 mg – taken with 200 mL water.

2. Oral suspension 100 mg – taken with 200 mL water.

Limbs 1 and 2 will be randomised between Visits 2 and 3. Subjects will be admitted to the clinic at approximately 07:00 on the morning of dosing (Day 0). Both doses will be taken around 11:00 hours. Subjects will remain within the clinic until discharge after the 24-hour post-dose timepoint. They will then return to the clinic for performance of the 36-hour post-dose timepoint.

3. Oral suspension/powder (100 mg) released into proximal small bowel via the Enterion capsule.

4. Oral suspension/powder (100 mg) released into the distal small bowel via the Enterion capsule.

5. Oral suspension/powder (100 mg) released into the ascending colon via the Enterion capsule.

Limbs 3, 4 and 5 will be randomised between Visits 4, 5 and 6. A 200 mL ^{99m}Tc-DTPA drink will be taken with each dose to provide an outline of the gastrointestinal tract. Subjects will be admitted to the clinic at approximately 07:00 on the morning of dosing (Day 0). All doses will be taken around 11:00 hours on Day 0. The capsule will be activated to release the suspension/powder at the target region of the bowel according to randomisation. The timing of this will vary between subjects. Subjects will remain within the clinic until discharge after

the 24-hour post-activation timepoint. They will then return to the clinic for performance of the 36-hour post-activation timepoint.

Investigational Products (IPS), AstraZeneca R&D Charnwood will provide a Subject/Treatment allocation sheet, providing the treatment sequence for each subject. During the course of the study it may be necessary to revise the allocation of the treatments administered at Visits 4, 5 and 6, for individual subjects, for example, to accommodate rapid gastrointestinal transit. In the event of a missed activation where the treatment cannot be reallocated, the capsule will not be activated. In this instance a subject may be asked to return to the clinical unit for an additional study day providing the amount of blood that will be taken from the subject over the study is still within the range accepted by the Ethics Committee and that the radiation dose will not exceed the yearly limit. Furthermore, should retrospective analysis indicate that the capsule has been activated in the incorrect site, the subject may be asked to return for an additional study day. Additional study days will be approved by the Principal Medical Investigator and AstraZeneca R&D Charnwood and the Ethics Committee.

Each dosing occasion will be separated by a washout of no less than 96 hours.

3.4.3 Method of assigning subjects to treatment groups

At enrolment (Visit 1) subjects will be allocated an enrolment code (E code). The E code will be made up of 7 digits. The first 5 digits will be pre-printed onto the CRF and will remain the same throughout the study (E00100). The final 2 digits will be allocated sequentially by the investigator to each subject in ascending order, starting with 50. Hence for the first subject enrolled the E code will be E0010050, for the second it will be E0010051 and so on.

As the subject qualifies for the randomisation phase of the study at Visit 2, subjects will be allocated the next sequential subject number starting with 001. Subjects who fail to complete the study after the start of Visit 2 will not be replaced.

Subject eligibility will be established before treatment randomisation. Subjects will be randomised strictly sequentially, as subjects are eligible for enrolment/randomisation. If a subject discontinues from the study, the subject number will not be reused, and the subject will not be allowed to re-enter the study.

3.4.4 Blinding and procedures for breaking the blind

As this is an open study, blinding is not required (see Section 3.2).

3.4.5 Pre-study, concomitant and post-study treatment(s)

Subjects should abstain from taking medication (with the exception of paracetamol and HRT) which would interfere with the scientific conclusions of the study including over-the-counter preparations.

As a minimum, subjects should refrain from taking prescribed medications from 3 weeks prior to the first dosing occasion (Visit 2) until completion of the sample period at Visit 6 and OTC

preparations including herbal remedies and vitamin preparations from 7 days prior to the first dosing occasion (Visit 2) until completion of the sample period at Visit 6.

However, decisions about inclusion in the study should take into account the long half-life of some drugs and a longer period of exclusion may be necessary.

Aspirin is specifically prohibited from 3 weeks prior to Visit 2 until completion of the sample period at Visit 6 due to a potential increase in bleeding risk.

Other medication, which is considered necessary for the subject'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 CRF.

3.4.6 Treatment compliance

All doses will be taken while subjects are in the unit and observed by trained staff. Where radiolabelled dosage forms are being administered, compliance will be detected by scintigraphy. Where non-radiolabelled dosage forms are being given, the person responsible for dosing will check the subject's mouth to ensure that the formulation has been swallowed.

4. STUDY MEASUREMENTS AND ENDPOINTS

4.1 Primary endpoint

The primary endpoint for the study is the plasma concentration profile of AZD6140 and the metabolite AR-C126910XX when released from the Enterion capsule in the proximal and distal small bowel and the ascending colon.

4.2 Screening and demographic measurements

The following data will be collected at Enrolment (Visit 1) and recorded in the CRF:

- Demographics (gender, date of birth, race, height (cm), weight (kg), body mass index ($kg \cdot m^{-2}$))
- caffeine intake, alcohol breath test and alcohol intake, smoking history
- Safety clinical chemistry and haematology
- Safety urinalysis
- Virology status (Hepatitis B and C)
- Drugs of abuse test

- Medical and surgical history
- Physical examination
- 12-lead ECG
- BP and pulse (supine and standing).

4.3 Pharmacodynamic measurements and endpoints

4.3.1 Scintigraphic Imaging Techniques

4.3.1.1 Methods of assessment

On study days when the Enterion capsule is taken (Visits 4, 5 and 6), an anterior anatomical marker containing 0.05MBq ^{111}In will be taped to the skin where the midclavicular line meets the right costal margin so that it lies in approximately the same transverse plane as the pylorus.

Anterior scintigraphic images, each of 50 seconds duration, will be recorded at frequent intervals until device activation, using a gamma camera (General Electric Maxicamera) with a 40 cm field of view and fitted with a medium energy parallel hole collimator. Images will be recorded at approximately 10-minute intervals until device activation and also for the 4-hour period post-activation. Thereafter images will be acquired at 20-minute intervals until 8 hours post-activation and then every 60 minutes until 12 hours post-activation. Images will then be taken at 18, 24 and 36 hours post-activation. If the Enterion capsule has not reached the target site by midnight on the day of dosing, the imaging schedule will be reduced to allow the subject to rest. The location of the capsule will be reviewed for every subject and the imaging schedule will be reduced accordingly. For the majority of subjects, the schedule will be as follows: images will be recorded at hourly intervals between midnight and 02:00 hours, no images will be recorded between 02:00 and 04:00 hours, images will be recorded hourly between 04:00 and 07:00 hours. Thereafter, images will be recorded in accordance with the standard schedule (ie 10-minute intervals until device activation). Any deviation from this imaging schedule will be recorded.

The subjects will remain moderately active during the study period and all images will be acquired with the subjects standing in front of the gamma camera. The images will be recorded using a Park Medical Micas X computer system and will be stored on digital audio tape (DAT) for subsequent analysis. Subjects will be allowed to leave the unit once all assessments at 24 hours post-activation have been completed. They will be required to return to the clinic for the 36-hour post-activation assessments. If the 36-hour timepoint falls in the middle of the night, subjects will be given the option of staying within the unit between the 24- and 36-hour timepoints.

During the course of the study period the scintigraphic images will be visually assessed as they are acquired in order to determine the gastric emptying and the arrival time at the target site. At this point, device activation will occur releasing the contents. For the proximal small

bowel, activation will take place immediately on gastric emptying. For the distal small bowel, activation will take place approximately 90 minutes after gastric emptying if the capsule looks to be at the target location. For the ascending colon activation limb, activation will always be targeted to the ascending colon (ie as early in the large bowel as possible – including the hepatic flexure). However, in a small number of cases transit of the capsule through the ascending colon can be rapid. Therefore, it is possible that successful activation may occur in the transverse colon. Given that the absorption characteristics of the ascending and transverse colon are similar, transverse activation will be accepted as complete data for a maximum of two subjects. The actual time of activation will be recorded on the CRF. Confirmation that the activation process has been successful will be achieved by means of an opening signal produced by the activation equipment.

The scintigraphic data from the study will be analysed in accordance with the current version of Pharmaceutical Profiles' Standard Operating Procedure N 1011 Gut Qualitative Analysis.

The data will be analysed to obtain the following parameters:

Gastric emptying time
Small intestinal emptying time
Ileo-caecal junction (ICJ) arrival time
Residence time in ICJ
Colon arrival time
Colon transit time
Total transit time
Anatomical location and time of successful Enterion activation.

The recorded time of movement of the capsule from the stomach to the small intestine will be taken as the mid-time between the times recorded for the 2 images about the transition. The times for the ICJ arrival and colon arrival will be determined in the same manner. Small intestinal transit time will be calculated by subtracting the gastric emptying time from the time at which colon arrival occurs. ICJ residence time will be calculated by subtracting the ICJ arrival time from the colon arrival time.

4.4 Safety measurements and endpoints

4.4.1 Summary of safety objectives and endpoints

Table 3 shows how the safety endpoints of this study relate to the study objectives.

Table 3 Safety objectives and endpoints relating to each objective

Objective	Endpoints	Summary statistic for analysis (including timepoint and population)	Planned analysis	Significance of results
To assess the safety and tolerability of 100 mg AZD6140 when given as an IR tablet, an oral suspension and suspension/powder delivered to 3 different sites in the GI tract	Haematology, clinical chemistry urinalysis, ECG and BP & Pulse.	Change from baseline (pre-dose at each visit)	Summary statistics (mean, SD, min, max)	Clinical review of all values outside the reference ranges
	Incidence, nature and severity of Adverse Events	Incidence rate summarised by treatment limb	Summary of AEs during each study period	Individual subject safety monitoring

The methods for collecting safety data are described below.

4.4.2 Adverse Events

4.4.2.1 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 are familiar with the content of this section. The principal investigator is responsible for ensuring this.

a) 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 (eg nausea, chest pain), signs (eg tachycardia, enlarged liver) or the abnormal results of an investigation (eg laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

b) Serious Adverse Event

A serious adverse event is an AE occurring during any study phase (ie 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 hospitalisation or prolongation of existing hospitalisation

- results in persistent or significant disability or incapacity
- is a congenital abnormality or birth defect
- is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above?

The causality of SAEs (ie their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant 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 the drug?" For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix F.

c) Other significant adverse event

An AstraZeneca expert will identify OAEs 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 subject 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 will be written and included in the Clinical Study Report.

4.4.2.2 Recording of adverse events

Adverse events will be collected throughout the study from Visit 1. Direct questions will also be asked at the following timepoints:

Visits 2 and 3: On admission (Day 0) and at 1, 2, 4, 12, 24 and 36 hours

Visits 4, 5 and 6: On admission (Day 0) and at 1, 2, 4, 12, 24 and 36 hours post-activation

Visit 7 post-study follow-up.

All adverse events, whether or not causally related to the study drug, must be documented immediately by the investigator on the appropriate Adverse Event form in the subject's CRF. This must include:

- a brief description of the event
- date of onset (and time, if relevant)
- date of resolution (and time, if relevant)
- intensity*
- seriousness of the event

- action with respect to the study drug and also any other actions taken
- a causality rating (see below).

All adverse events should be followed up either to resolution, or to a point where no further improvement is expected by the investigator.

*Definitions used for intensity

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.

The investigator is required to assess the causal relationship to the study drug according to the following classifications:

Probable: Time relationship exists. No other possible causative factors exist. Improvement on dechallenge has occurred. A specific laboratory investigation (if performed) has confirmed the relationship.

Possible: Time relationship exists. Other possible causative factors may exist. Improvement on dechallenge may or may not have been seen.

Unlikely: Time relationship is non-existent or doubtful and/or other factors certain or probable to have been causative.

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

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 9.4, Procedures in case of pregnancy. Pregnancy in itself is not regarded as an AE.

4.4.2.3 Reporting of serious adverse events

When the investigator becomes aware of a SAE during the course of the study, the SAE must be reported to the local monitor or other AstraZeneca representative within one (1) day and a completed written SAE report must be sent within four (4) calendar days. Follow-up information should reported by the investigator within one day and in writing within 4 calendar days.

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

Serious Adverse Events should be reported to the following personnel:

OR

4.4.3 Laboratory safety measurements and variables

4.4.3.1 Methods of assessment

Safety blood sampling

Blood samples will be collected for clinical chemistry and haematology at the following timepoints:

Visit 1 (enrolment).

Visits 2 and 3: pre-dose and 24 hours post-dose.

Visits 4, 5, and 6: pre-dose and 24 hours post activation.

Visit 7 (follow-up).

See Section 7.6 for information on numbers of samples and blood volume.

The following clinical chemistry parameters will be measured in plasma: urea ($mmol \cdot L^{-1}$), creatinine ($\mu mol \cdot L^{-1}$), total cholesterol ($mmol \cdot L^{-1}$), triglycerides ($mmol \cdot L^{-1}$), glucose ($mmol \cdot L^{-1}$), sodium ($mmol \cdot L^{-1}$), potassium ($mmol \cdot L^{-1}$), calcium ($mmol \cdot L^{-1}$), urate ($\mu mol \cdot L^{-1}$), total protein ($g \cdot L^{-1}$), albumin ($g \cdot L^{-1}$), albumin/globulin ratio (ratio), total bilirubin ($\mu mol \cdot L^{-1}$), alkaline phosphatase ($IU \cdot L^{-1}$), lactate dehydrogenase ($IU \cdot L^{-1}$), aspartate transaminase ($IU \cdot L^{-1}$), alanine transaminase ($IU \cdot L^{-1}$), gamma-glutamyltransferase ($IU \cdot L^{-1}$) and C-reactive protein ($IU \cdot L^{-1}$).

At enrolment the clinical chemistry blood sample will also be used to test for FSH (IU).

Clinical chemistry samples will be taken into a 2.7 mL lithium heparin tube.

The following haematology parameters will be measured: haemoglobin ($g \cdot dL^{-1}$), RBC ($10^{12} \cdot L^{-1}$), haematocrit ($L \cdot L^{-1}$), MCHC ($g \cdot dL^{-1}$), MCH (pg), MCV (fL), reticulocytes (%RBC), platelets ($10^{9} \cdot L^{-1}$), WBC ($10^{9} \cdot L^{-1}$) and differential count (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils ($10^{9} \cdot L^{-1}$)) and large unstained cells ($10^{9} \cdot L^{-1}$), PT (s) and APTT (s).

Haematology samples will be taken into a 1.2 mL EDTA tube. PT and APTT samples will be taken into a 1.4 mL citrate tube.

Urinalysis

Fresh mid-stream urine samples (approximately 20 mL) will be collected at the following timepoints:

Visit 1 (enrolment).

Visits 2 and 3: pre-dose and 24 hours post-dose.

Visits 4, 5, and 6: pre-dose and 24 hours post activation.

Visit 7 (follow-up).

The following parameters will be measured: pH, protein, glucose, ketones, blood, bilirubin, nitrite and urobilinogen ($\mu mol \cdot L^{-1}$).

If positive values are reported for protein or blood and are considered to be of possible clinical significance, the urinalysis will be followed up with urine microscopy. The results will be reviewed by the investigator.

Microscopy data will not be entered onto the database, this information will be collected to support clinical management of the subject.

All the samples will be labelled with the study number, enrolment code, gender, visit number and study timepoint. They will be analysed by the Department of Clinical Pathology AstraZeneca R&D Charnwood, according to standard methods. The laboratory will provide up-to-date reference ranges throughout the study.

Virology

At enrolment a 1.2 mL sample will also be taken into a lithium heparin tube and used to test for Hepatitis B surface antigen and C antibodies.

All the samples will be labelled with the study number, enrolment code and study timepoint. They will be analysed by the Department of Clinical Pathology AstraZeneca R&D Charnwood according to standard methods. The results will be reviewed by the investigator, to ensure eligibility for the study.

The hepatitis data will not be entered onto the database.

Drugs of abuse screen

An aliquot of the urine sample at enrolment (Visit 1), Day 0 at Visits 2 to 6 and will be tested for drugs of abuse (including cannabis) using SureStep test kits.

If a positive result is obtained, the subject must be withdrawn from the study unless an adequate explanation exists such as the inadvertent use of codeine.

The drugs of abuse data will not be entered onto the database.

4.4.4 Other safety measurements and variables

4.4.4.1 Methods of assessment

Vital signs

Supine and standing blood pressure (mmHg) and pulse (bpm) will be measured. Supine blood pressure will be measured after 5 minutes in the supine position. Standing blood pressure will be measured after 2 minutes standing.

Supine and standing blood pressure and pulse measurements will be taken at the following timepoints:

Visit 1 (enrolment).

Visits 2 and 3: pre-dose, 1, 2, 4, 12 and 24 hours post-dose.

Visits 4, 5 and 6: pre-dose, pre-activation, 1 (standing only), 2 (standing only), 4 (standing only), 12 (standing only) and 24 hours post-activation.

Visit 7 (follow-up).

Blood pressure and pulse will be recorded using a semi-automatic blood pressure recording device (Omron) with an appropriate cuff size.

12-lead ECG

A 12-lead ECG and rhythm strip will be recorded at the following timepoints:

Visit 1 (enrolment).

Visits 2 and 3: pre-dose, 1, 2, 4, 12 and 24 hours post-dose.

Visits 4, 5 and 6: pre-dose, pre-activation, 1, 2, 4, 12 and 24 hours post-activation.

Visit 7 (follow-up).

The ECG will be performed using an automated machine (Schiller) which is programmed to provide an electronic interpretation of the electrocardiogram. These reports may be qualified by the investigator since the programme cautiously overstates potential abnormalities. A medically qualified person will assess the ECG parameters, and make an overall evaluation. Data obtained from the ECG traces (PR, QRS, QT, QTc interval, sinus rhythm, overall evaluation and any comments) will be directly entered into the study database by Data Management personnel, AstraZeneca R&D Charnwood.

Physical examination

Physical examinations will be performed at enrolment (Visit 1) and at the post-study follow-up visit (Visit 7). A medically qualified person will perform this examination.

4.5 Pharmacokinetic measurements and parameters

4.5.1 Summary of pharmacokinetic objectives and endpoints

Table 4 shows how the pharmacokinetic endpoints of this study relate to the study objectives.

Table 4 Pharmacokinetic objectives and endpoints relating to each objective

Objective	Endpoints	Summary statistic for analysis (including timepoint and population)	Planned analysis	Significance of results
Comparison of PK parameters of AZD6140 and the metabolite AR-C126910XX when released into proximal and distal small bowel and ascending colon	Plasma concentration of AZD6140 and the metabolite AR-C126910XX	Concentration data, C_{max}, t_{max}, AUC, AUC_t, $t_{½}$	Subjective comparison, graphical representation of AZD6140 and the metabolite AR-C126910XX concentration versus time	Comparison of the AZD6140 and metabolite concentrations will show the degree to which the oral suspension/powder is absorbed from different sites of the gut
Comparison of PK parameters of AZD6140 and the metabolite AR-C126910XX given as an IR tablet and an oral suspension	Plasma concentration of AZD6140 and the metabolite AR-C126910XX	Concentration data, C_{max}, t_{max}, AUC, AUC_t, $t_{½}$	Subjective comparison, graphical representation of AZD6140 and the metabolite AR-C126910XX concentration versus time	Comparison of the AZD6140 and metabolite concentrations will show whether the IR formulation is suitable for progressing to Phase II

The methods for collection of biological samples and derivation of pharmacokinetic parameters are presented below.

4.5.2 Collection of biological samples

4.5.2.1 Pharmacokinetic blood samples

Blood samples of 5.5 mL (4.5 mL for analysis, 1.0 mL discarded) for the determination of AZD6140 and the metabolite AR-C126910XX will be taken during the study at the following timepoints:

Visits 2 and 3:

Pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24 and 36 hours after dosing.

Visits 4, 5 and 6:

Pre-dose, pre-activation and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24 and 36 hours after activation.

See Section 7.6 for information on numbers of samples and blood volume.

Blood samples will be collected into lithium heparin tubes and placed on ice until centrifugation. The samples must be centrifuged (3000 rpm at 4°C for 10 minutes) within 30 minutes of sampling to obtain plasma. The resultant plasma will be transferred into a plain polypropylene tube (screw cap) and frozen upright at or below -20°C. All plasma samples must be labelled with the study number, subject number and study timepoint. The labels must maintain their integrity despite contact with moisture. The frozen samples will be shipped, on dry ice, on an ongoing basis for analysis under the guidance of AstraZeneca.

4.5.2.2 Faecal sampling

From the time of dosing all subjects will be instructed to collect all faecal samples (Visits 4, 5 and 6 only). If the capsule has not been passed prior to the subject leaving the unit, the subject will be instructed to bring all samples to the unit each day until the capsule has been recovered. Once recovered the capsule will be visually examined to confirm that the drug has been released. It will then be stored at -20°C until dispatch for residual drug analysis or for disposal.

4.5.3 Drug concentration measurements, and calculation or derivation of pharmacokinetic parameters

The plasma concentration data for AZD6140 and the metabolite AR-C126910XX will be analysed using standard pharmacokinetic methods to yield the following parameters:

AUC, AUC_t, $t_{½}$, C_{max} and t_{max}.

The pharmacokinetic evaluation will be carried out by, or under the guidance of, the Clinical Pharmacokinetic Section of the Department of Experimental Medicine at AstraZeneca R&D Charnwood, using an appropriate pharmacokinetic software package. Non-compartmental methods will be used if appropriate.

5. DATA MANAGEMENT

Data will be validated and quality checked by the AstraZeneca Monitor at the centre throughout the study. The original, edited CRFs will be returned to Data Management at AstraZeneca.

The data will be entered onto the AMOS database at AstraZeneca. The entered data will be manually checked against the originals and additional computerised checks will be run. Any missing, impossible or inconsistent entries in the CRF will be referred back to the investigator via the monitor within 3 working days of entering data using data query forms. Responses should be received and updated within 3 working days of generation.

Safety data comprising clinical chemistry, haematology and urinalysis will be reported by the department of Clinical Pathology at AstraZeneca R&D Charnwood and loaded into AMOS. Original paper printouts of the results will be sent to the study clinical investigator for comment and signature and then filed with the remainder of the CRFs.

Final quality control checks will be completed and error rates reported prior to a meeting to discuss the declaration of a clean data file. Protocol deviations detected during blind review of the data and during the data entry process will be considered for their effect on the analysis of the data. All decisions on the evaluability of data from each subject must have been made and documented in the Statistical Analysis Plan before declaration of clean file. The date of clean file will be documented within one day of the clean file meeting. The database will be locked and SAS® datasets will be extracted for the statistical analysis of the data.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Determination of sample size

No formal sample size calculations were performed. The sample size of 10 subjects was deemed to be adequate to provide definitive information on plasma concentrations of AZD6140.

6.2 Statistical evaluation

6.2.1 Methods of statistical analysis

Statistical and safety analyses will be carried out by, or under the guidance of, the Statistics Department AstraZeneca R&D Charnwood. Statistical analyses will be performed according to the Statistical Analysis Plan. The Statistical Analysis Plan will be prepared before database lock.

Where standard summary statistics are referenced, these will include (but not be limited to) the mean, standard deviation, median, minimum and maximum for continuous data, and counts and frequency percentages for categorical data.

6.2.2 Study endpoints

The primary endpoint for this study is the plasma concentration of AZD6140 and the metabolite AR-C126910XX when released from the Enterion capsule in the proximal and distal small bowel and the ascending colon.

PK parameters derived from the Enterion limbs of the study, as well as plasma concentrations of AZD6140 and the metabolite AR-C126910XX when given as an IR tablet and an oral suspension are considered to be secondary endpoints.

6.2.3 Statistical analyses

All pre-treatment group characteristics will be summarised and presented using standard summary statistics. No statistical hypothesis tests will be carried out on baseline data.

No formal statistical tests will be done on any pharmacokinetic data. The plasma concentration data will be summarised, by timepoint. PK parameters will be calculated for each subject, and summarised by treatment limb. Individual and mean plasma concentrations and pharmacokinetic parameters will be summarised and presented in tabular format and/or graphically. Descriptive statistics will be applied to the data.

Adverse Events

Adverse events will be summarised by System Organ Class and Astra Preferred Term, using Astra Adverse Event Terminology. All adverse events will be noted as being emergent during pre-treatment (prior to any study drug being given to the subject), or treatment-emergent (if they appear following administration of study drug). If an adverse event is treatment-emergent, it will be assumed to be emergent due to the last dose level having been administered to that subject.

All adverse event data will be listed for all subjects. Separate listings of all serious adverse events, deaths or other significant adverse events, as assessed by the study responsible physician, will be presented.

Adverse event data will be summarised by causality (whether there is a reasonable possibility that the event is causally related to study drug ‘Yes’ or ‘No’) and intensity, and by causality and seriousness, by treatment emergence category. Summaries will be presented by treatment limb.

Laboratory data

All laboratory safety data, incorporating haematology, clinical chemistry and urinalysis data, will be listed, with deviations from the normal ranges explicitly noted on the listings.

Numerical laboratory safety data will be summarised using standard summary statistics by scheduled timepoint. Raw values will be summarised for the Visit 1, pre-dose baseline measurements and follow-up measurements, and within-subject changes from baseline for the post-treatment measurements. Summaries will be presented by treatment limb.

Discrete laboratory safety data will be summarised showing the number of subjects at each level of measurement at each scheduled timepoint. These summaries will be presented by treatment limb.

Figures comparing the post-treatment measurements against the pre-treatment measurement will be produced for each numerical laboratory safety measurement. These figures will be presented by treatment limb.

Vital signs data

Vital signs data will be summarised using standard summary statistics by scheduled timepoint. Summaries will present raw values for each visit including pre-dose baseline measurements, and within-subject changes from baseline for all other measurements. These summaries will be presented by treatment limb.

Vital signs measurements will be presented as mean plots across time, presented by treatment limb.

ECG data

ECG data will be summarised using standard summary statistics by scheduled timepoint. Numerical summaries will present summaries of raw values for each visit, including pre-dose baseline measurements, and within-subject changes from baseline for all other measurements. These summaries will be presented by treatment limb.

ECG intervals will be presented as mean plots across time, presented by treatment limb.

Physical examination data

Abnormal physical examinations will be listed and summarised by treatment limb. For the summaries, the number of abnormalities within each examination category will be used for Visit 1, and data at Visit 7 will be categorised as either normal; abnormal but unchanged from Visit 1; and newly abnormal.

Other safety data

All other safety data will be listed and summarised using suitable summary statistics, where appropriate.

All subjects allocated to treatment will be included in the analysis set and all data will be assigned to the treatment received. Exclusions from this analysis set will be documented in the statistical analysis plan prior to clean file; examples include, but are not limited to, major deviations in the administration of study compound or co-administration of medications expected to affect the data.

7. STUDY MANAGEMENT

7.1 Monitoring

Before the study begins, a representative of AstraZeneca will visit the investigational site to

- determine the adequacy of the facilities
- discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives.

During the study, a monitor from AstraZeneca or company representing AstraZeneca will have regular contacts with the investigational site, including visits to

- provide information and support to the investigator(s)
- confirm that facilities remain acceptable
- confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRFs, and that investigational product accountability checks are being performed
- perform source data verification (a comparison of the data in the CRFs with the subject's records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each subject (eg clinic charts).

The monitor or another AstraZeneca representative will be available between visits if the investigator(s) or other staff at the centre need information and advice.

7.2 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) 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, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator should contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at his or her centre.

7.3 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.

7.4 Changes to the protocol

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

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol must be notified to or approved by the IEC, 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 Written Informed Consent Form, then AstraZeneca and the centre's IEC must be notified. Approval of the revised Written Informed Consent Form by AstraZeneca and by the IEC is required before the revised form is used.

AstraZeneca will distribute amendments and new versions of the protocol to the principal investigator, who in turn is responsible for the distribution of these documents to his or her IEC, 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.

Administration changes to the protocol will be handled according to AstraZeneca's Standard Operating Procedures.

7.5 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 study agreement shall prevail.

7.6 Volume of blood sampling and handling of biological samples

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

Table 5 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	N of samples	Total volume (mL)
Pharmacokinetic		5.5	68	374
Safety	Clinical chemistry (Visit 1)	4.5	1	4.5
	Clinical chemistry (Visits 2-7)	3	11	33
	Haematology (Visit 1)	3	1	3
	Haematology (Visits 2-7)	2	11	22
Total				436.5

7.7 Study timetable and termination

PAG Submission:

PAG Meeting:

ERC Submission:

ERC Meeting:

First Subject In:

8. ETHICS

8.1 Ethics review

The final study protocol, including the final version of the Written Informed Consent Form, must be approved or given a favourable opinion in writing by an IEC as appropriate. The investigator must submit written approval (or a written contract for studies conducted in Japan) to AstraZeneca before he or she can enrol any subject into the study.

The principal investigator(s) is responsible for informing the IEC of any amendment to the protocol in accordance with local requirements. In addition, the IEC must approve all advertising used to recruit subjects for the study. The protocol must be reapproved by the IEC annually, as local regulations require.

Either the investigator(s) or AstraZeneca must submit progress reports to the IEC according to local regulations and guidelines. The principal investigator(s) must also provide the IEC and the ARSAC certificate holder with any reports of serious adverse events from the study site.

8.2 Ethical conduct of the study

The study will be performed in accordance with the ethical principles in the Declaration of Helsinki (see Appendix C), Good Clinical Practice, and applicable regulatory requirements.

8.3 Subject information and consent

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

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

The principal investigator(s) must store the original, signed Written Informed Consent Form. A copy of the signed Written Informed Consent Form must be given to the subject.

A sample Written Informed Consent Form is enclosed (Appendix B). If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

8.4 Subject data protection

The Written Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. Subjects in this database will be identified by initials or subject number only. The Written Informed Consent Form will also explain that for data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an IEC may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.

9. EMERGENCY PROCEDURES

9.1 AstraZeneca emergency contact procedure

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

Outside of normal working hours, contact AstraZeneca R&D Charnwood switchboard on and ask to be put in contact with the person on call for the AZD6140 clinical team.

9.2 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.

9.3 Procedures in case of overdose

Overdose is unlikely to occur in this study as all doses are given as single units and subjects will be dosed within the clinical unit.

Since there is no known specific antidote to this novel compound the volunteers should be treated symptomatically.

9.4 Procedures in case of pregnancy

Although females who are not of child-bearing potential will be selected for this study, in the most unlikely event that pregnancy occurs, the following details will be relevant.

Pregnancy itself is not regarded as an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject 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.

10. REFERENCES

1. Current Investigator Brochure for AZD6140.

2. RAC1 Briefing Document for the AZD6140 Oral P_{2T} Program.

AstraZeneca

Clinical Study Protocol: Appendix A

Study Code SC-532-5238

IND No.

Appendix Date

Version No 02

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

Study Title

An Open, Crossover Study To Evaluate The Absorption Characteristics of AZD6140 From an Immediate Release Tablet Compared to an Oral Suspension and to Assess the Regional Absorption of AZD6140 in Healthy Volunteers

I agree to the terms of this study protocol

AstraZeneca Research and Developme
site representative

SIGNATURE OF PRINCIPAL INVESTIGATOR

Title of report

An Open, Crossover Study To Evaluate The Absorption Characteristics of AZD6140 From an Immediate Release Tablet Compared to an Oral Suspension and to Assess the Regional Absorption of AZD6140 in Healthy Volunteers

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.: 2173

Signature:

AstraZeneca

Clinical Study Protocol: Appendix B

Study Code SC-532-5238

Appendix Date

Version No 02

Appendix B
Sample written informed consent form

Pharmaceutical Profiles

SUBJECT INFORMATION SHEET

PPL-502

Pharmacoscintigraphic Evaluation of the Regional Drug Absorption of AZD6140.

You are being invited to take part in a research study. Before you decide to participate it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with your friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

The aim of this study is to assess the drug absorption properties of a drug (AZD6140). This will be done by comparing the concentration of the drug in the blood when it is delivered to different regions of the human gut (proximal small bowel, distal small bowel and colon) by a site-specific capsule. The concentration of the drug in your blood after you have taken a tablet or liquid formulation will also be compared.

Why have I been chosen?

You have been selected at random from our volunteer database because you appear to fulfill the entry requirements for the study.

To qualify for this study you:

- Must be a healthy male or post-menopausal female volunteer aged 18-65 years;
- Must be of normal weight for your height;
- Must be a non-smoker or smoke fewer than 15 cigarettes per day or ½ oz tobacco per week ;
- Must have a breath carbon monoxide reading of less than 20 ppm;
- Must not have a history of drug or alcohol abuse. Regular alcohol consumption in males and females must be <21 and <14 units week, respectively
- Must produce a negative result upon testing for drugs of abuse;
- Must not have serum hepatitis or carry antibodies for hepatitis, unless due to a declared medication;
- Must not be part of a social group at risk of transmitting AIDS;
- Must not have a history or presence of neurological, heamatological, psychiatric, gastrointestinal, liver or kidney disease;
- Must not have a history of intolerance or hypersensitivity to similar drugs. These include antivirals such as acyclovir (Aciclovir, Zovirax®) and famciclovir (Famvir);

- Must not have a personal or family history of bleeding disorders. These include the presence of aneurysms (swollen blood vessels), bleeding disorders such as vomiting blood or nose bleeds, or rectal bleeding (this includes the presence of haemorrhoids (piles) within the last 3 months);
- Must be able to swallow a size 000 gelatin capsule;
- Must not have taken asprin within 2 weeks of the start of the study;
- Must not have had an operation or significant trauma during the 3 months prior to screening;
- Must not have had any significant illness within the 4 weeks prior to screening;
- Must not have suffered from significant stomach pain or indigestion either chronically or within 4 weeks prior to screening for the study;
- Must have normal blood clotting, as determined by our doctors;
- Must have normal blood pressure and resting heart rate;
- Must be free from acute diarrhoea or constipation in the 14 days before the first study day. Diarrhoea will be defined as the passage of liquid faeces and/or a stool frequency of greater than three times per day. Constipation is defined as a failure to open the bowels more frequently than every other day;
- Must not have participated in a research study within the last 4 months with an investigational drug, or 3 months with a newly marketed formulation;
- Must not have used any prescribed medication in the previous 3 weeks (except hormone replacement therapy (HRT)).
- Must not have taken any other over the counter preparations or vitamin and/or herbal supplements eg. St Johns Wort within seven days of the study;
- Must be free from non-removable metal objects such as metal plates, screws etc. in the abdominal area;
- Must not have had dental procedures (excluding minor scale and polish) in the 4 weeks prior to the pre-study medical;
- Must not have donated blood in the previous three months. You are also advised not to donate blood during the 14 weeks following completion of the study;
- Must not be monitored for radiation dosage at your place of work.

Do I have to take part?

No - it is up to you whether or not to take part. If you decide to take part, the study will be explained to you by either a nurse or a doctor. You will be given this information sheet to keep and will also be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time without giving a reason. This will not affect the standard of care you receive. If you withdraw from the study after you have been dosed, you must attend a post-study medical. This is for your own benefit.

The investigator is also free to withdraw you from the study at any time.

What will happen to me if I take part?

Pre-study Medical:

You will be required to attend a pre-study medical examination. This will last for approximately one and a half hours.

- At the pre-study medical you will be asked about your medical history. You will also undergo the following: physical examination, blood and urine testing which will include tests for hepatitis C virus (HCV), hepatitis B virus (HBV) and for drugs of abuse, including cannabis. Your heart will be monitored by performing an electrocardiograph (ECG) test;

Acceptance into the study is not guaranteed and is subject to the results and tests carried out at this pre-study medical being approved by a physician.

Study Days:
If you are accepted into the study, you will be required to attend 5 study days to be held on dates which you will be informed of in separate correspondence. One of the study days will be approximately 28 hours in length, one of the study days will be approximately 31 hours in length and one of the study days will be 48 hours in length. Each study day will be separated by at least 96 hours. You will be required to return to the clinical site at 36 hours post dose/activation. Representatives from the company sponsoring the research study may be present on study days to witness routine study day procedures.

- When you arrive for a study day, you will be asked some questions about your health since your last visit. In addition to this, your breath will be tested for the presence of alcohol and carbon monoxide. Your urine will be tested for the presence of drugs of abuse.
  Please note: If your pre-dose breath alcohol is positive, your study day will be re-arranged. If your carbon monoxide level is greater than 20 ppm you will be excluded from the study.
- If your study day is re-arranged, you will be required to return for an additional study day on a mutually agreed date.
- You will have a flexible plastic tube (cannula) put into an arm vein, in order to allow blood samples to be taken throughout the study day. If your arms are hairy it may be necessary to shave a small area to allow the plastic tube to be put in place. More than one attempt may be needed to put the tube in the vein and it is possible you may experience some bruising at the site of cannulation. Occasionally, during the later stages of the study day, the cannula may fail to operate. If this situation arises it may be necessary for us to take blood using a syringe and needle. The total volume of blood taken from you during the course of the study, including the pre- and post-study medicals will be 436.5 mL.
- On your first two study days you will swallow either a tablet or liquid formulation of the study drug at 8am. These are not radiolabelled. No pictures will be taken, but blood samples will be taken up to 24 hours after dosing at regular intervals. A blood sample will also be taken at 36 hours after dosing when you return to the clinic.
- On your third, fourth and fifth study days you will swallow a site specific delivery capsule (Enterion) at approximately 11am contain ng AZD6140 which will be opened once it reaches the proximal small bowel, distal small bowel or colon. The capsule contains a small amount of radioactivity. You will then be required to remain at Pharmaceutical Profiles for 24 hours after the capsule has been opened and return to the clinical site for a picture and a blood sample at 36 hours after the capsule has been opened.

Please note: The length of time taken for the Enterion capsule to reach the site of activation will vary from individual to individual and can be as long as 24 hours. Therefore you should plan to be at the Pharmaceutical Profiles for at least 60 hours. However, in some cases you may be free to leave several hours earlier than this.

- Pictures of your intestines will be recorded immediately after dosing and at 10 minute intervals until 4 hours after your capsule has been activated. Pictures will then be recorded at 20 minute intervals between 4 and 8 hours post-capsule activation and thereafter every hour until 12 hours post-activation. You will then have an image taken at 18, 24 and 36 hours post-activation.
- On each study day you will have blood samples taken at regular intervals up until either 24 hours post dose (study days one and two), or 24 hours post capsule activation (study days three, four and five). You will also have a blood sample taken at 36 hours post dose (study days 1 and 2) or 36 hours post activation (study days 3, 4 and 5).
- On your first two study days you attend the study site on the morning of dosing and will remain fasted until 5 hours post dose. Food will be provided for you throughout the study days at strictly specified times. You must eat the food provided, and nothing else.
- On study days three, four and five you must fast from midnight on the day prior to dosing and will remain fasted until approximately 7am. You will then be provided with a light breakfast and then you will remain fasted until 5 hours post-dose. Food will be provided for you throughout the study days at strictly specified times. You must eat the food provided, and nothing else.
- You will be informed of any significant new findings that develop during the course of the studywhich may affect your decision to remain in the study.

Please note: In the unlikely event of a capsule being opened at an incorrect location within the gastrointestinal tract or not being opened at all because the capsule moved quickly and the activation site was missed, you may be invited to take part in an additional study day. It will be up to you whether you take part or not. If you decide to take part, the additional requirements will be explained to you by either a doctor or a nurse. A maximum of 87 mL extra blood will be taken from you (making a total of 523.5 mL. You will also receive an extra radiation dose of 0.46 mSv, which is less than the dose of radiation received from one abdominal X-ray, giving a total radiation exposure of 1.84 mSv. You will receive an additional inconvenience payment for the extra study day. Any additional study days will require approval by the Ethics Committee before they are conducted.

Post-study Medical:

Once you have completed the study, or if you withdraw from the study part-way through, you will be required to attend a post-study medical. This will take place within 14 days of your last study day. It will last approximately 30 minutes and a date and time will be arranged with you individually.

- At the post-study medical, you will be given a partial physical examination and blood samples will be taken for routine testing to ensure that you are in the same physical condition as you were before you started the study.

What do I have to do?

- You **must** discuss any special dietary requirements (e.g. vegetarian, vegan, dislike of certain foods) before volunteering.
- You must not eat anything likely to disturb gastrointestinal transit (e.g. curry or fatty foods such as fish and chips) for 24 hours prior to the study days.
- You must not drink any alcohol, in the 24 hours prior to each study day.
- You must not smoke from midnight on the day before dosing. Smoking is not allowed during study periods.
- You must fast from midnight on the day before dosing; a small beaker of water is allowed before arrival at the Clinical Unit.
- You must not drink liquids or eat food containing caffeine or xanthine for the duration of each study period (i.e. from midnight on the day before dosing until you leave the clinical unit).
  Please note: Drinks that contain caffeine and xanthines include coffee, tea and a number of soft drinks (e.g. cola drinks, Dr. Pepper, Mountain Dew, Lucozade and Red Bull. Chocolate also contains caffeine and xanthines)
- You must arrive at the Clinical Unit at 0700 on the morning of dosing;
- You are requested to wear trousers that do not have metal fastenings, for example tracksuit bottoms.
- You will undergo all the study day procedures as described in the 'What will happen to me if I take part' section of this information sheet.
- You must keep belongings such as credit cards away from the area around the device used to open the capsule. This is because the device generates a magnetic field that may damage the information contained within such objects.
- You must tell the investigators if you experience any symptoms of any type during the course of the study.
- On study days when you receive the site specific delivery capsule you will be required to collect your faeces in the container provided and return these to the study day staff so that we can retrieve the capsule for further analysis. If the capsule has not been recovered by the time you leave the unit, you will be required to bring all samples to the Clinical Unit each day until the capsule has been passed.
- You will be informed of any significant new findings that develop during the course of the study.

What is the drug or procedure that is being tested?

The drug that is being tested (AZD6140) is being developed for the treatment of blood clots and other conditions which are caused by specific cells (platelets) sticking together. The safety of this drug has been studied in two previous human studies, dosing 37 subjects, at doses up to 400 mg (4 times the dose to be used in this study). Studies showed that the drug was well tolerated, although one volunteer had an increased bleeding time after taking the drug. In the very unlikely event that you are ill as a result of taking the drug, there is no specific antidote to this novel compound and therefore blood transfusion is the only counter therapy.

Please Note: The drug that you will be taking contains gelatin.

The site specific delivery capsule is a large capsule (approximately 35 mm long and 12 mm in diameter) which has been designed as a means of evaluating the regional absorption of drugs from the gastrointestinal tract. The capsule will remain closed until it is opened by an external magnetic field, at which point the drug will be released from the space inside the capsule. In this study, the capsules will be opened in the proximal small bowel, the distal small bowel and the colon.

What are the side effects of taking part?

AZD6140 is an anti-platelet agent that will be used to treat blood clots. AZD6140 stops blood clotting, therefore if you cut yourself during the study you may bleed for longer than usual. Measuring bleeding times in other studies from small cuts in the skin, it has been shown that at doses greater than 100 mg, transitory increases of generally less than 4 times the normal has been seen. Since the drug is also experimental, there may be unknown side-effects.

What are the possible disadvantages and risks of taking part?

- By taking part in the study you will be exposed to ionising radiation. The Department of Health has authorised the administration of radioactive substances for this study. The maximum total radiation dose to you from taking part will be 1.84mSv, which is less than the dose received from three abdominal X-rays.
- As stated above, there is also a possibility that you may experience side effects after receiving the single dose of AZD6140.

What are the possible benefits of taking part?

You will not receive any medical benefit from taking part in this study, however the results of the study will help the development of a modified release formulation, which may benefit patients with blood clots.

What if something goes wrong?

Compensation for any injury caused by taking part in this study will be in accordance with the guidelines of the Association of the British Pharmaceutical Industry (ABPI). In line with these guidelines, the Sponsor company will therefore compensate you if you are caused injury directly by your participation in the study. Your right under the law to claim compensation for injury where you can prove negligence is not affected. Copies of the guidelines are available on request.

In the event of a research related injury occurring you should contact Dr Heather Wray, Pharmaceutical Profiles, Mere Way, Ruddington Fields, Nottingham, NG11 6JS; telephone number 0115 974 9000.

Will my taking part in this study be kept confidential?

If you consent to take part in the research study, your privacy will be fully protected. Your medical records may be inspected by the company sponsoring the research for purposes of analysing the results. They may also be looked at by people from Pharmaceutical Profiles and regulatory authorities to check that the study is being carried out correctly. Your name, however, will not be

disclosed outside Pharmaceutical Profiles with the exception that for your own safety, your GP will be told that you have taken part in this study, and will be notified if any of the results from your blood and urine tests are significantly abnormal or if any serious adverse events occur. For the same reason, brief details of your involvement in this trial may be revealed to other units, such as the University of Nottingham and AstraZeneca (Charnwood), that carry out clinical trials.

What will happen to the results of the research study?

The results of the study will be analysed and given to the sponsor Pharmaceutical Company in the form of a research report that is usually prepared by Pharmaceutical Profiles. The results will then be used in the further development of the treatment that is being tested. The results may also be sent (either as paper copies or as electronic data) to countries outside the UK which do not have the same data protection laws. You will not be identified by name in the research report or in any of the data that leaves Pharmaceutical Profiles, whether paper or electronic.

Who is organising and funding the research?

Pharmaceutical Profiles are organising the research study which is being paid for by a sponsor Pharmaceutical Company. You will be given an inconvenience payment of £1145 plus travel expenses for taking part in the study. It is important for you to note that this payment will be reduced if you do not complete the study and that the payment will not be increased in the event of study days being postponed.

Who has reviewed the study?

The study has been approved by the Quorn Research Review Committee (QRRC) which is an independent Ethics Committee. The study has also been reviewed and approved by the physician who holds the ARSAC (Administration of Radioactive Substances Advisory Committee) certificate for the research, Dr Gerry Hooper. Dr Hooper is also the secretary of the Ethics Committee. Approval from both these parties must be obtained before the study can be performed.

Contact for further information:

If you would like any further information, or have any further questions please contact Georgina Singleton (Volunteer Recruitment Co-ordinator) or Dr Heather Wray (Principal Medical Investigator) at Pharmaceutical Profiles, Mere Way, Ruddington Fields, Nottingham, NG11 6JS; telephone number: 0115 9749000

Thank you for considering taking part in this study.

CONSENT FORM

PPL- 502

Subject identification for this study: .....

Title of Project: An Open, Crossover Study To Evaluate The Absorption Characteristics of AZD6140 From An Immediate Release Tablet Compared to an Oral Suspension and to Assess the Regional Absorption of AZD6140 in Healthy Volunteers

Investigator: Pharmaceutical Profiles Limited

1. I confirm that I have read and understand the information sheet dated 04 June (version 2) for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care legal rights being affected.

3. I understand that sections of any of my medical notes may be looked at responsible individuals from Pharmaceutical Profiles, the sponsor Pharmaceutical Company or regulatory authorities where it is relevant to my taking part in research. I give my permission for these individuals to access my records.

4. I agree to take part in the above study:

Name of Volunteer	Signature	Date
Name of Person taking consent	Signature	Date
Researcher	Signature	Date

AstraZeneca

Clinical Study Protocol: Appendix C

Study Code SC-532-5238

Appendix Date

Version No 02

Appendix C

Declaration of Helsinki

Recommendations guiding physicians in biomedical research involving human subjects.

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975 and the 35th World Medical Assembly, Venice, Italy, October 1983 and the 41st World Medical Assembly Hong Kong, September 1989 and the 48th General Assembly, Somerset West, Republic of South Africa, October 1996.

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of The World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient´s interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient".

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject´s physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject´s freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give a consent, the minor´s consent must be obtained in addition to the consent of the minor´s legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical research combined with professional care (Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I,2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-therapeutic biomedical re-search involving human subjects

(Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient´s illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

AstraZeneca

Clinical Study Protocol: Appendix D

Study Code SC-532-5238

Appendix date

Draft No. final

Appendix D
Investigators and study administrative structure

STAFF AT INVESTIGATIONAL SITE

Centre No.	Centre address	**Name** (First name, Last name)	Qualifications	Position	Role in the study

ASTRAZENECA STUDY PERSONNEL

Address	**Name** (First name, Last name)	**Qualifications**	**Position**	**Role in the study**

AstraZeneca

Clinical Study Protocol: Appendix E

Study Code SC-532-5238

Appendix date

Version No 02

Appendix E
Insurance and indemnity

INSURANCE AND INDEMNITY

AstraZeneca's liability is covered by a liability insurance policy with AstraZeneca Insurance Company Limited, policy No: L/702938.

With respect to any liability directly or indirectly caused by the investigational products in connection with this Clinical Study, AstraZeneca assumes liability by law on behalf of the investigator(s) and his assistants for possible injury to the subject provided the investigator(s) and his assistants have followed the instructions of AstraZeneca in accordance with this protocol and any amendments thereto, that the investigational products administered to the subject in this Clinical Study have been supplied by AstraZeneca and that the investigator and his assistants have in general performed this clinical study in accordance with scientific practice and currently acceptable techniques and know-how.

AstraZeneca can forward a letter of indemnity if needed by the investigator(s)/institution.

AstraZeneca

Clinical Study protocol: Appendix F

Study Code SC-532-5238

Appendix date

Version No 02

Appendix F
Additional safety information

1. 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 adverse event 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 adverse event occurred in a more severe form it might have caused death (ie hepatitis that resolved without hepatic failure).

Hospitalisation

Out-patient treatment in an emergency room is not in itself a serious adverse event, 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 adverse events 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 a situation where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardise 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. 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

2. FURTHER GUIDANCE ON THE ASSESSMENT OF CAUSALITY

The following factors should be considered when deciding if there is a "reasonable possibility" that an adverse event (AE) may have been caused by the investigational product.

- **Time course of events and 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 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**. Has a specific laboratory investigation 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.

AstraZeneca

Clinical Study Protocol: Appendix G

Study Code SC-532-5238

Appendix Date

Version No 02

Appendix G
Study Procedures

STUDY PROCEDURES

Visit 1 - Enrolment

- Demographics (gender, date of birth, race, height (cm), weight (kg), body mass index ($kg \cdot m^{-2}$))
- caffeine intake, alcohol breath test and alcohol intake, smoking history
- Safety clinical chemistry and haematology
- Safety urinalysis
- Virology status (Hepatitis B and C)
- Drugs of abuse test
- Medical and surgical history
- Physical examination
- 12-lead ECG
- BP and pulse (supine and standing).

Visits 2 and 3 – Oral IR Tablet Dosing Limb and Oral Suspension Limb

- Day 0 – admission to unit at approximately 07:00 hours

  - ♦ Pre-dose — PK blood, clinical chemistry, haematology, urinalysis, drugs of abuse test, breath alcohol test, BP&P, 12-lead ECG, AEs.
  - ♦ 0 hours — Dose with AZD6140 IR tablet or AZD6140 suspension (approximately 08:00 hours).
  - ♦ 0.5 hours — PK blood.
  - ♦ 1 hour — PK blood, BP&P, ECG, AEs.
  - ♦ 1.5 hours — PK blood.
  - ♦ 2 hours — PK blood, BP&P, ECG, AEs.
  - ♦ 3 hours — PK blood.
  - ♦ 4 hours — PK blood, BP&P, ECG, AEs.
  - ♦ 5 hours — Lunch.
  - ♦ 6 hours — PK blood.
  - ♦ 8 hours — PK blood.

- 9 hours Dinner.
- 12 hours PK blood, BP&P, ECG, AEs.

- Day 1
  - 18 hours PK blood.
  - 24 hours PK blood, Clinical chemistry, haematology, urinalysis, BP&P, ECG, AEs. Breakfast.
  - 36 hours PK blood, AEs.

Visits 4, 5 and 6 – AZD6140-Enterion Limbs

- Day 0 – admission to unit at approximately 07:00 hours.
  - -4 hours light breakfast (approx 07:00).
  - Pre-dose PK blood, clinical chemistry, haematology, urinalysis, drugs of abuse test, breath alcohol test, BP&P, 12-lead ECG, AEs.
  - 0 hours Dose with Enterion capsule with ^{99m}Tc-DTPA drink (approx 11:00) and monitor transit of capsule through the GI tract using scintigraphic images.
  - 5 hours post-dose Lunch
  - 9 hours post-dose Dinner
  - **Take PK blood sample, ECG, BP&P immediately prior to release of AZD6140 when capsule reaches the target region of the GI tract according to randomisation.**
  - **Activation** Record actual time of activation in the CRF.
  - 0.5 hours PK blood.
  - 1 hour PK blood, BP&P, ECG, AEs.
  - 1.5 hours PK blood.
  - 2 hours PK blood, BP&P, ECG, AEs. 200 mL water.
  - 3 hours PK blood.
  - 4 hours PK blood, BP&P, ECG, AEs.
  - 6 hours PK blood.
  - 8 hours PK blood.
  - 12 hours PK blood, BP&P, ECG, AEs.

- Day 1
  - ♦ 18 hours PK blood.
  - ♦ 24 hours PK blood, Clinical chemistry, haematology, urinalysis, BP&P, ECG, AEs. Breakfast.
  - ♦ 36 hours PK blood, AEs.

Visit 7 – Post-Study Follow-Up

- Safety clinical chemistry and haematology
- Safety urinalysis
- Physical examination
- 12-lead ECG
- BP and pulse (supine and standing).

AstraZeneca

Clinical Study Protocol: Appendix H

Study Code SC-532-5238

Appendix Date

Version No 02

Appendix H
Study Day Meals

Study Day Meals

Light Breakfast (Day 0, Visits 4, 5 and 6 only)

1 slice of toast and butter with jam or marmalade

Decaffeinated beverage

Standard Breakfast (24 hours post-dose on all visits)

1 bowl cornflakes

2 slices of toast and butter with jam or marmalade

1 glass orange juice

Decaffeinated beverage

Lunch (5 hours post-dose – all visits)

2 filled rolls (selection of fillings)

1 bag of crisps

1 piece of fruit

Decaffeinated beverage

Dinner (9 hours post-dose – all visits)

Selection of pre-defined meals

Decaffeinated beverage

AstraZeneca

Clinical Study Protocol Amendment	
Amendment No.	1
Study Code	SC-532-5238
Date	[redacted]

An Open, Crossover Study to Evaluate the Absorption Characteristics of AZD6140 From an Immediate Release Tablet Compared to an Oral Suspension and to Assess the Regional Absorption of AZD6140 in Healthy Volunteers

Sponsor:

AstraZeneca R&D Charnwood, Bakewell Road, Loughborough, Leics LE11 5RH.

Centres affected by the amendment:

Single Centre Study – Pharmaceutical Profiles Ltd.

The protocol for the study is to be amended as follows:

Amendment 1.1

Protocol Synopsis, Page 2, Subsection – Objectives

Delete paragraph: "The primary objective of the study is to examine by assessment of plasma concentrations the regional absorption characteristics of AZD6140 from the proximal small bowel, distal small bowel and ascending colon to aid in the design of a modified release tablet formulation."

Replace with: "The primary objective of the study is to examine by assessment of plasma concentrations of AZD6140 and the metabolite AR-C126910XX the regional absorption characteristics of AZD6140 from the proximal small bowel, distal small bowel and ascending colon to aid in the design of a modified release tablet formulation."

Amendment 1.2

Synopsis, Page 3, Subsection – Endpoints, Pharmacokinetic

Delete paragraph: "The plasma concentration data for AZD6140 will be analysed using standard pharmacokinetic methods to yield the following parameters:"

Replace with: "The plasma concentration data for AZD6140 and the metabolite AR-C126910XX will be analysed using standard pharmacokinetic methods to yield the following parameters:"

Amendment 1.3

Page 12, Section 2.1 Primary objective

Delete paragraph: "The primary objective of the study is to examine by assessment of plasma concentrations the regional absorption characteristics of AZD6140 from the proximal small bowel, distal small bowel and ascending colon to aid in the design of a modified release tablet formulation."

Replace with: "The primary objective of the study is to examine by assessment of plasma concentrations of AZD6140 and the metabolite AR-C126910XX the regional absorption characteristics of AZD6140 from the proximal small bowel, distal small bowel and ascending colon to aid in the design of a modified release tablet formulation."

Amendment 1.4

Page 15, Table 2 Study plan

Insert ticks in the boxes under Visits 3 to 6 for Inclusion/Exclusion criteria.

Amendment 1.5

Page 17, Section 3.3.3 Exclusion criteria

Insert as new point 20: "Subjects who have had dental procedures (excluding minor scale and polish) in the 4 weeks prior to Visit 1."

Renumber existing point 20 to become point 21.

Amendment 1.6

Page 19, Section 3.3.5.2 Activity restrictions, 6th Paragraph

Insert as last sentence: "If the 36-hour timepoint falls in the middle of the night, subjects will be given the option of staying within the unit between the 24- and 36-hour timepoints."

Amendment 1.7

Page 24, Section 4.1 Primary endpoint

Delete paragraph: "The primary endpoint for the study is the plasma concentration profile of AZD6140 when released from the Enterion capsule in the proximal and distal small bowel and the ascending colon."

Replace with: "The primary endpoint for the study is the plasma concentration profile of AZD6140 and the metabolite AR-C126910XX when released from the Enterion capsule in the proximal and distal small bowel and the ascending colon."

Amendment 1.8

Page 25, Section 4.3.1.1 Methods of assessment, 3rd Paragraph

Insert as last sentence: "If the 36-hour timepoint falls in the middle of the night, subjects will be given the option of staying within the unit between the 24- and 36-hour timepoints."

Amendment 1.9

Page 33, Section 4.5.1 Summary of pharmacokinetic objectives and endpoints

Delete Table 4.

Replace with new Table 4:

Table 4 Pharmacokinetic objectives and endpoints relating to each objective

Objective	Endpoints	Summary statistic for analysis (including timepoint and population)	Planned analysis	Significance of results
Comparison of PK parameters of AZD6140 and the metabolite AR-C126910XX when released into proximal and distal small bowel and ascending colon	Plasma concentration of AZD6140 and the metabolite AR-C126910XX	Concentration data, C_{max}, t_{max}, AUC, AUC_t, $t_{½}$	Subjective comparison, graphical representation of AZD6140 and the metabolite AR-C126910XX concentration versus time	Comparison of the AZD6140 and metabolite concentrations will show the degree to which the oral suspension/powder is absorbed from different sites of the gut
Comparison of PK parameters of AZD6140 and the metabolite AR-C126910XX given as an IR tablet and an oral suspension	Plasma concentration of AZD6140 and the metabolite AR-C126910XX	Concentration data, C_{max}, t_{max}, AUC, AUC_t, $t_{½}$	Subjective comparison, graphical representation of AZD6140 and the metabolite AR-C126910XX concentration versus time	Comparison of the AZD6140 and metabolite concentrations will show whether the IR formulation is suitable for progressing to Phase II

Amendment 1.10

Page 34, Section 4.5.2.1 Pharmacokinetic blood samples

Delete paragraph: "Blood samples of 5.5 mL (4.5 mL for analysis, 1.0 mL discarded) for the determination of AZD6140 will be taken during the study at the following timepoints:"

Replace with: "Blood samples of 5.5 mL (4.5 mL for analysis, 1.0 mL discarded) for the determination of AZD6140 and the metabolite AR-C126910XX will be taken during the study at the following timepoints:"

Amendment 1.11

Page 34, Section 4.5.2.1 Pharmacokinetic blood samples, final paragraph, final sentence

Delete sentence: "The frozen sample will be transferred to the department of Development Drug Metabolism and Bioanalysis, AstraZeneca R&D Charnwood, on dry ice, after completion of each treatment period, for subsequent analysis."

Replace with: "The frozen samples will be shipped, on dry ice, on an ongoing basis for analysis under the guidance of AstraZeneca."

Amendment 1.12

Page 34, Section 4.5.3 Drug concentration measurements, and calculation or derivation of pharmacokinetic parameters

Delete paragraph: "The plasma concentration data for AZD6140 will be analysed using standard pharmacokinetic methods to yield the following parameters:"

Replace with: "The plasma concentration data for AZD6140 and the metabolite AR-C126910XX will be analysed using standard pharmacokinetic methods to yield the following parameters:"

Amendment 1.13

Page 36, Section 6.2.2 Study endpoints

Delete paragraphs: "The primary endpoint for this study is the plasma concentration of AZD6140 when released from the Enterion capsule in the proximal and distal small bowel and the ascending colon.

PK parameters derived from the Enterion limbs of the study, as well as plasma concentrations of AZD6140 when given as an IR tablet and an oral suspension are considered to be secondary endpoints."

Replace with: "The primary endpoint for this study is the plasma concentration of AZD6140 and the metabolite AR-C126910XX when released from the Enterion capsule in the proximal and distal small bowel and the ascending colon.

PK parameters derived from the Enterion limbs of the study, as well as plasma concentrations of AZD6140 and the metabolite AR-C126910XX when given as an IR tablet and an oral suspension are considered to be secondary endpoints."

Amendment 1.14

Appendix B, Sample written informed consent form

Delete Version 1 dated and replace with Version 2.

Amendment 1.15

Appendix G, Study Procedures, Page 3, line 2

Add at 12-hour timepoint: "PK blood"

Reasons for making the amendment:

1. Changes requested by the ERC prior to approval.

2. Additional analysis of the metabolite concentration requested by the AstraZeneca Project Team. Will have no additional effect on subject safety.

Signed agreement to the amendment:

I agree to the terms of this protocol amendment.

Study Code: SC-532-5238

Date
(day month, year)

I agree to the terms of this protocol amendment.

Study Code: SC-532-5238

Centre No.: 2173

AstraZeneca

Clinical Study Protocol: Appendix B

Study Code SC-532-5238

Appendix Date

Version No 02

Appendix B
Sample written informed consent form

Pharmaceutical Profiles

SUBJECT INFORMATION SHEET

PPL-502

Pharmacoscintigraphic Evaluation of the Regional Drug Absorption of AZD6140.

You are being invited to take part in a research study. Before you decide to participate it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with your friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

The aim of this study is to assess the drug absorption properties of a drug (AZD6140). This will be done by comparing the concentration of the drug in the blood when it is delivered to different regions of the human gut (proximal small bowel, distal small bowel and colon) by a site-specific capsule. The concentration of the drug in your blood after you have taken a tablet or liquid formulation will also be compared.

Why have I been chosen?

You have been selected at random from our volunteer database because you appear to fulfill the entry requirements for the study.

To qualify for this study you:

- Must be a healthy male or post-menopausal female volunteer aged 18-65 years;
- Must be of normal weight for your height;
- Must be a non-smoker or smoke fewer than 15 cigarettes per day or ½ oz tobacco per week ;
- Must have a breath carbon monoxide reading of less than 20 ppm;
- Must not have a history of drug or alcohol abuse. Regular alcohol consumption in males and females must be <21 and <14 units week, respectively
- Must produce a negative result upon testing for drugs of abuse;
- Must not have serum hepatitis or carry antibodies for hepatitis, unless due to a declared medication;
- Must not be part of a social group at risk of transmitting AIDS;
- Must not have a history or presence of neurological, heamatological, psychiatric, gastrointestinal, liver or kidney disease;
- Must not have a history of intolerance or hypersensitivity to similar drugs. These include antivirals such as acyclovir (Aciclovir, Zovirax®) and famciclovir (Famvir);

- Must not have a personal or family history of bleeding disorders. These include the presence of aneurysms (swollen blood vessels), bleeding disorders such as vomiting blood or nose bleeds, or rectal bleeding (this includes the presence of haemorrhoids (piles) within the last 3 months);
- Must be able to swallow a size 000 gelatin capsule;
- Must not have taken asprin within 2 weeks of the start of the study;
- Must not have had an operation or significant trauma during the 3 months prior to screening;
- Must not have had any significant illness within the 4 weeks prior to screening;
- Must not have suffered from significant stomach pain or indigestion either chronically or within 4 weeks prior to screening for the study;
- Must have normal blood clotting, as determined by our doctors;
- Must have normal blood pressure and resting heart rate;
- Must be free from acute diarrhoea or constipation in the 14 days before the first study day. Diarrhoea will be defined as the passage of liquid faeces and/or a stool frequency of greater than three times per day. Constipation is defined as a failure to open the bowels more frequently than every other day;
- Must not have participated in a research study within the last 4 months with an investigational drug, or 3 months with a newly marketed formulation;
- Must not have used any prescribed medication in the previous 3 weeks (except hormone replacement therapy (HRT)).
- Must not have taken any other over the counter preparations or vitamin and/or herbal supplements eg. St Johns Wort within seven days of the study;
- Must be free from non-removable metal objects such as metal plates, screws etc. in the abdominal area;
- Must not have had dental procedures (excluding minor scale and polish) in the 4 weeks prior to the pre-study medical;
- Must not have donated blood in the previous three months. You are also advised not to donate blood during the 14 weeks following completion of the study;
- Must not be monitored for radiation dosage at your place of work.

Do I have to take part?

No - it is up to you whether or not to take part. If you decide to take part, the study will be explained to you by either a nurse or a doctor. You will be given this information sheet to keep and will also be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time without giving a reason. This will not affect the standard of care you receive. If you withdraw from the study after you have been dosed, you must attend a post-study medical. This is for your own benefit.

The investigator is also free to withdraw you from the study at any time.

What will happen to me if I take part?

Pre-study Medical:

You will be required to attend a pre-study medical examination. This will last for approximately one and a half hours.

- At the pre-study medical you will be asked about your medical history. You will also undergo the following: physical examination, blood and urine testing which will include tests for hepatitis C virus (HCV), hepatitis B virus (HBV) and for drugs of abuse, including cannabis. Your heart will be monitored by performing an electrocardiograph (ECG) test;

Acceptance into the study is not guaranteed and is subject to the results and tests carried out at this pre-study medical being approved by a physician.

Study Days:
If you are accepted into the study, you will be required to attend 5 study days to be held on dates which you will be informed of in separate correspondence. One of the study days will be approximately 28 hours in length, one of the study days will be approximately 31 hours in length and one of the study days will be 48 hours in length. Each study day will be separated by at least 96 hours. You will be required to return to the clinical site at 36 hours post dose/activation. Representatives from the company sponsoring the research study may be present on study days to witness routine study day procedures.

- When you arrive for a study day, you will be asked some questions about your health since your last visit. In addition to this, your breath will be tested for the presence of alcohol and carbon monoxide. Your urine will be tested for the presence of drugs of abuse.
  Please note: If your pre-dose breath alcohol is positive, your study day will be re-arranged. If your carbon monoxide level is greater than 20 ppm you will be excluded from the study.
- If your study day is re-arranged, you will be required to return for an additional study day on a mutually agreed date.
- You will have a flexible plastic tube (cannula) put into an arm vein, in order to allow blood samples to be taken throughout the study day. If your arms are hairy it may be necessary to shave a small area to allow the plastic tube to be put in place. More than one attempt may be needed to put the tube in the vein and it is possible you may experience some bruising at the site of cannulation. Occasionally, during the later stages of the study day, the cannula may fail to operate. If this situation arises it may be necessary for us to take blood using a syringe and needle. The total volume of blood taken from you during the course of the study, including the pre- and post-study medicals will be 436.5 mL.
- On your first two study days you will swallow either a tablet or liquid formulation of the study drug at 8am. These are not radiolabelled. No pictures will be taken, but blood samples will be taken up to 24 hours after dosing at regular intervals. A blood sample will also be taken at 36 hours after dosing when you return to the clinic.
- On your third, fourth and fifth study days you will swallow a site specific delivery capsule (Enterion) at approximately 11am contain ng AZD6140 which will be opened once it reaches the proximal small bowel, distal small bowel or colon. The capsule contains a small amount of radioactivity. You will then be required to remain at Pharmaceutical Profiles for 24 hours after the capsule has been opened and return to the clinical site for a picture and a blood sample at 36 hours after the capsule has been opened.

Please note: The length of time taken for the Enterion capsule to reach the site of activation will vary from individual to individual and can be as long as 24 hours. Therefore you should plan to be at the Pharmaceutical Profiles for at least 60 hours. However, in some cases you may be free to leave several hours earlier than this.

- Pictures of your intestines will be recorded immediately after dosing and at 10 minute intervals until 4 hours after your capsule has been activated. Pictures will then be recorded at 20 minute intervals between 4 and 8 hours post-capsule activation and thereafter every hour until 12 hours post-activation. You will then have an image taken at 18, 24 and 36 hours post-activation.
- On each study day you will have blood samples taken at regular intervals up until either 24 hours post dose (study days one and two), or 24 hours post capsule activation (study days three, four and five). You will also have a blood sample taken at 36 hours post dose (study days 1 and 2) or 36 hours post activation (study days 3, 4 and 5).
- On your first two study days you attend the study site on the morning of dosing and will remain fasted until 5 hours post dose. Food will be provided for you throughout the study days at strictly specified times. You must eat the food provided, and nothing else.
- On study days three, four and five you must fast from midnight on the day prior to dosing and will remain fasted until approximately 7am. You will then be provided with a light breakfast and then you will remain fasted until 5 hours post-dose. Food will be provided for you throughout the study days at strictly specified times. You must eat the food provided, and nothing else.
- You will be informed of any significant new findings that develop during the course of the studywhich may affect your decision to remain in the study.

Please note: In the unlikely event of a capsule being opened at an incorrect location within the gastrointestinal tract or not being opened at all because the capsule moved quickly and the activation site was missed, you may be invited to take part in an additional study day. It will be up to you whether you take part or not. If you decide to take part, the additional requirements will be explained to you by either a doctor or a nurse. A maximum of 87 mL extra blood will be taken from you (making a total of 523.5 mL. You will also receive an extra radiation dose of 0.46 mSv, which is less than the dose of radiation received from one abdominal X-ray, giving a total radiation exposure of 1.84 mSv. You will receive an additional inconvenience payment for the extra study day. Any additional study days will require approval by the Ethics Committee before they are conducted.

Post-study Medical:

Once you have completed the study, or if you withdraw from the study part-way through, you will be required to attend a post-study medical. This will take place within 14 days of your last study day. It will last approximately 30 minutes and a date and time will be arranged with you individually.

- At the post-study medical, you will be given a partial physical examination and blood samples will be taken for routine testing to ensure that you are in the same physical condition as you were before you started the study.

What do I have to do?

- You **must** discuss any special dietary requirements (e.g. vegetarian, vegan, dislike of certain foods) before volunteering.
- You must not eat anything likely to disturb gastrointestinal transit (e.g. curry or fatty foods such as fish and chips) for 24 hours prior to the study days.
- You must not drink any alcohol, in the 24 hours prior to each study day.
- You must not smoke from midnight on the day before dosing. Smoking is not allowed during study periods.
- You must fast from midnight on the day before dosing; a small beaker of water is allowed before arrival at the Clinical Unit.
- You must not drink liquids or eat food containing caffeine or xanthine for the duration of each study period (i.e. from midnight on the day before dosing until you leave the clinical unit).
  Please note: Drinks that contain caffeine and xanthines include coffee, tea and a number of soft drinks (e.g. cola drinks, Dr. Pepper, Mountain Dew, Lucozade and Red Bull. Chocolate also contains caffeine and xanthines)
- You must arrive at the Clinical Unit at 0700 on the morning of dosing;
- You are requested to wear trousers that do not have metal fastenings, for example tracksuit bottoms.
- You will undergo all the study day procedures as described in the 'What will happen to me if I take part' section of this information sheet.
- You must keep belongings such as credit cards away from the area around the device used to open the capsule. This is because the device generates a magnetic field that may damage the information contained within such objects.
- You must tell the investigators if you experience any symptoms of any type during the course of the study.
- On study days when you receive the site specific delivery capsule you will be required to collect your faeces in the container provided and return these to the study day staff so that we can retrieve the capsule for further analysis. If the capsule has not been recovered by the time you leave the unit, you will be required to bring all samples to the Clinical Unit each day until the capsule has been passed.
- You will be informed of any significant new findings that develop during the course of the study.

What is the drug or procedure that is being tested?

The drug that is being tested (AZD6140) is being developed for the treatment of blood clots and other conditions which are caused by specific cells (platelets) sticking together. The safety of this drug has been studied in two previous human studies, dosing 37 subjects, at doses up to 400 mg (4 times the dose to be used in this study). Studies showed that the drug was well tolerated, although one volunteer had an increased bleeding time after taking the drug. In the very unlikely event that you are ill as a result of taking the drug, there is no specific antidote to this novel compound and therefore blood transfusion is the only counter therapy.

Please Note: The drug that you will be taking contains gelatin.

The site specific delivery capsule is a large capsule (approximately 35 mm long and 12 mm in diameter) which has been designed as a means of evaluating the regional absorption of drugs from the gastrointestinal tract. The capsule will remain closed until it is opened by an external magnetic field, at which point the drug will be released from the space inside the capsule. In this study, the capsules will be opened in the proximal small bowel, the distal small bowel and the colon.

What are the side effects of taking part?

AZD6140 is an anti-platelet agent that will be used to treat blood clots. AZD6140 stops blood clotting, therefore if you cut yourself during the study you may bleed for longer than usual. Measuring bleeding times in other studies from small cuts in the skin, it has been shown that at doses greater than 100 mg, transitory increases of generally less than 4 times the normal has been seen. Since the drug is also experimental, there may be unknown side-effects.

What are the possible disadvantages and risks of taking part?

- By taking part in the study you will be exposed to ionising radiation. The Department of Health has authorised the administration of radioactive substances for this study. The maximum total radiation dose to you from taking part will be 1.84mSv, which is less than the dose received from three abdominal X-rays.
- As stated above, there is also a possibility that you may experience side effects after receiving the single dose of AZD6140.

What are the possible benefits of taking part?

You will not receive any medical benefit from taking part in this study, however the results of the study will help the development of a modified release formulation, which may benefit patients with blood clots.

What if something goes wrong?

Compensation for any injury caused by taking part in this study will be in accordance with the guidelines of the Association of the British Pharmaceutical Industry (ABPI). In line with these guidelines, the Sponsor company will therefore compensate you if you are caused injury directly by your participation in the study. Your right under the law to claim compensation for injury where you can prove negligence is not affected. Copies of the guidelines are available on request.

In the event of a research related injury occurring you should contact

Will my taking part in this study be kept confidential?

If you consent to take part in the research study, your privacy will be fully protected. Your medical records may be inspected by the company sponsoring the research for purposes of analysing the results. They may also be looked at by people from Pharmaceutical Profiles and regulatory authorities to check that the study is being carried out correctly. Your name, however, will not be

disclosed outside Pharmaceutical Profiles with the exception that for your own safety, your GP will be told that you have taken part in this study, and will be notified if any of the results from your blood and urine tests are significantly abnormal or if any serious adverse events occur. For the same reason, brief details of your involvement in this trial may be revealed to other units, such as the University of Nottingham and AstraZeneca (Charnwood), that carry out clinical trials.

What will happen to the results of the research study?

The results of the study will be analysed and given to the sponsor Pharmaceutical Company in the form of a research report that is usually prepared by Pharmaceutical Profiles. The results will then be used in the further development of the treatment that is being tested. The results may also be sent (either as paper copies or as electronic data) to countries outside the UK which do not have the same data protection laws. You will not be identified by name in the research report or in any of the data that leaves Pharmaceutical Profiles, whether paper or electronic.

Who is organising and funding the research?

Pharmaceutical Profiles are organising the research study which is being paid for by a sponsor Pharmaceutical Company. You will be given an inconvenience payment of £1145 plus travel expenses for taking part in the study. It is important for you to note that this payment will be reduced if you do not complete the study and that the payment will not be increased in the event of study days being postponed.

Who has reviewed the study?

The study has been approved by the Quorn Research Review Committee (QRRC) which is an independent Ethics Committee. The study has also been reviewed and approved by the physician who holds the ARSAC (Administration of Radioactive Substances Advisory Committee) certificate for the research, Dr Gerry Hooper. Dr Hooper is also the secretary of the Ethics Committee. Approval from both these parties must be obtained before the study can be performed.

Contact for further information:

If you would like any further information, or have any further questions please contact Georgina Singleton (Volunteer Recruitment Co-ordinator) or Dr Heather Wray (Principal Medical Investigator) at Pharmaceutical Profiles, Mere Way, Ruddington Fields, Nottingham, NG11 6JS; telephone number: 0115 9749000

Thank you for considering taking part in this study.

CONSENT FORM

PPL- 502

Subject identification for this study: .....

Title of Project: An Open, Crossover Study To Evaluate The Absorption Characteristics of AZD6140 From An Immediate Release Tablet Compared to an Oral Suspension and to Assess the Regional Absorption of AZD6140 in Healthy Volunteers

Investigator: Pharmaceutical Profiles Limited

1. I confirm that I have read and understand the information sheet dated *)* for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care legal rights being affected.

3. I understand that sections of any of my medical notes may be looked at responsible individuals from Pharmaceutical Profiles, the sponsor Pharmaceutical Company or regulatory authorities where it is relevant to my taking part in research. I give my permission for these individuals to access my records.

4. I agree to take part in the above study:

Name of Volunteer	Signature	Date
Name of Person taking consent	Signature	Date
Researcher	Signature	Date

AstraZeneca

Clinical Study Protocol: Appendix G

Study Code SC-532-5238

Appendix Date

Version No 02

Appendix G
Study Procedures

STUDY PROCEDURES

Visit 1 - Enrolment

- Demographics (gender, date of birth, race, height (cm), weight (kg), body mass index ($kg \cdot m^{-2}$))
- caffeine intake, alcohol breath test and alcohol intake, smoking history
- Safety clinical chemistry and haematology
- Safety urinalysis
- Virology status (Hepatitis B and C)
- Drugs of abuse test
- Medical and surgical history
- Physical examination
- 12-lead ECG
- BP and pulse (supine and standing).

Visits 2 and 3 – Oral IR Tablet Dosing Limb and Oral Suspension Limb

- Day 0 – admission to unit at approximately 07:00 hours

  - ♦ Pre-dose — PK blood, clinical chemistry, haematology, urinalysis, drugs of abuse test, breath alcohol test, BP&P, 12-lead ECG, AEs.
  - ♦ 0 hours — Dose with AZD6140 IR tablet or AZD6140 suspension (approximately 08:00 hours).
  - ♦ 0.5 hours — PK blood.
  - ♦ 1 hour — PK blood, BP&P, ECG, AEs.
  - ♦ 1.5 hours — PK blood.
  - ♦ 2 hours — PK blood, BP&P, ECG, AEs.
  - ♦ 3 hours — PK blood.
  - ♦ 4 hours — PK blood, BP&P, ECG, AEs.
  - ♦ 5 hours — Lunch.
  - ♦ 6 hours — PK blood.
  - ♦ 8 hours — PK blood.

- 9 hours Dinner.
- 12 hours PK blood, BP&P, ECG, AEs.

- Day 1
  - 18 hours PK blood.
  - 24 hours PK blood, Clinical chemistry, haematology, urinalysis, BP&P, ECG, AEs. Breakfast.
  - 36 hours PK blood, AEs.

Visits 4, 5 and 6 – AZD6140-Enterion Limbs

- Day 0 – admission to unit at approximately 07:00 hours.
  - -4 hours light breakfast (approx 07:00).
  - Pre-dose PK blood, clinical chemistry, haematology, urinalysis, drugs of abuse test, breath alcohol test, BP&P, 12-lead ECG, AEs.
  - 0 hours Dose with Enterion capsule with ^{99m}Tc-DTPA drink (approx 11:00) and monitor transit of capsule through the GI tract using scintigraphic images.
  - 5 hours post-dose Lunch
  - 9 hours post-dose Dinner
  - **Take PK blood sample, ECG, BP&P immediately prior to release of AZD6140 when capsule reaches the target region of the GI tract according to randomisation.**
  - **Activation** Record actual time of activation in the CRF.
  - 0.5 hours PK blood.
  - 1 hour PK blood, BP&P, ECG, AEs.
  - 1.5 hours PK blood.
  - 2 hours PK blood, BP&P, ECG, AEs. 200 mL water.
  - 3 hours PK blood.
  - 4 hours PK blood, BP&P, ECG, AEs.
  - 6 hours PK blood.
  - 8 hours PK blood.
  - 12 hours PK blood, BP&P, ECG, AEs.

- Day 1
  - ♦ 18 hours PK blood.
  - ♦ 24 hours PK blood, Clinical chemistry, haematology, urinalysis, BP&P, ECG, AEs. Breakfast.
  - ♦ 36 hours PK blood, AEs.

Visit 7 – Post-Study Follow-Up

- Safety clinical chemistry and haematology
- Safety urinalysis
- Physical examination
- 12-lead ECG
- BP and pulse (supine and standing).

AstraZeneca

Clinical Study Protocol Administrative Change

Change No.	1
Study Code	SC-532-5238
Date	

An Open, Crossover Study to Evaluate the Absorption Characteristics of AZD6140 From an Immediate Release Tablet Compared To an Oral Suspension and to Assess the Regional Absorption of AZD6140 in Healthy Volunteers

Sponsor:

Centres affected by the administrative change

This is a single centre study.

The protocol for the study is to be changed as follows:

Administrative change 1.1

Protocol, page 22, section 3.4.2, Doses and treatment regimens, second paragraph:

Delete: '….. Both doses will be taken around 11:00 hours. ….'

Replace with: '….. Both doses will be taken around 08:00 hours. ….'

Administrative change 1.2

Appendix D, page 3, Investigators and study administrative structure, AstraZeneca study personnel table, second line:

Delete complete address for

Replace with:

Administrative change 1.3

Appendix D, page 3, Investigators and study administrative structure, AstraZeneca study personnel table, ninth (last) line:

Add the following qualifications and position to

Administrative change 1.4

Appendix D, page 3, Investigators and study administrative structure, AstraZeneca study personnel table:

Add the following personnel to this table:

Name:

Administrative change 1.5

Appendix D, page 3, Investigators and study administrative structure, AstraZeneca study personnel table:

Add the following personnel to this table:

Name:

Administrative change 1.6

Appendix D, page 3, Investigators and study administrative structure, AstraZeneca study personnel table:

Add the following personnel to this table:

Name:

Reasons for administrative changes:

Administrative change 1.1 has been made to correct a typographical error in the protocol. The dosing time is correct elsewhere in the protocol. Administrative changes 1.1 to 1.6 have been made to complete information in Appendix D which were not available at the time of protocol issue.

Signed agreement to the administrative change:

I agree to the terms of this administrative change.

Study Code: SC-532-5238

AstraZeneca

Clinical Study Protocol: Appendix D

Study Code SC-532-5238

Appendix date

Version 02

Appendix D
Investigators and study administrative structure

STAFF AT INVESTIGATIONAL SITE

Centre No.	**Centre address**	**Name** (First name, Last name)	**Qualifications**	**Position**	**Role in the study**

ASTRAZENECA STUDY PERSONNEL

Address	**Name** (First name, Last name)	Qualifications	Position	Role in the study

Continued

Address	**Name** (First name, Last name)	**Qualifications**	**Position**	**Role in the study**