Clinical Study Protocol

Drug Substance	Selumetinib
Study Code	D1532C00069
Edition Number	1

A Phase I, Randomized, Open-label, Single-center, Crossover Study to Assess the Effect of Food on the Pharmacokinetics of a 75 mg Single Oral Dose of Selumetinib in Healthy Male Volunteers Aged 18 to 45 Years

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

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

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

AstraZeneca

PROTOCOL SYNOPSIS

A Phase I, Randomized, Open-label, Single-center, Crossover Study to Assess the Effect of Food on the Pharmacokinetics of a 75 mg Single Oral Dose of Selumetinib in Healthy Male Volunteers Aged 18 to 45 Years

Principal Investigator

Study center and number of subjects planned

This study will be conducted at a single study center,

A total of 34 healthy male volunteers will be randomized (17 healthy volunteers per treatment sequence) in order to ensure at least 30 evaluable healthy volunteers complete the study.

Study period		Phase of development
Estimated date of first healthy volunteer enrolled	Q4 2013	I
Estimated date of last healthy volunteer completed	Q1 2014	

Objectives

Primary Objective

To investigate the effect of food, in comparison to fasting conditions, on the exposure of selumetinib after a single 75 mg dose in healthy volunteers.

Secondary Objectives

The secondary objectives of the study are:

1. To investigate the pharmacokinetics of selumetinib under fed and fasting conditions.

2. To investigate the pharmacokinetics of N-desmethyl selumetinib under fed and fasting conditions.

3. To further assess the safety and tolerability of selumetinib by assessment of adverse events, laboratory variables, 12-lead electrocardiograms, and vital signs.

Exploratory Objective

The exploratory objective of the study is to collect an optional pharmacogenetic sample from consenting healthy volunteers for exploratory investigation to determine whether variability in pharmacokinetic and safety parameters can be explained by differences in the healthy volunteer's genotype.

Study design

This study is designed as a Phase I, open-label, randomized, single-center, 2-period crossover study in healthy male volunteers in order to investigate the effect of food on the PK of a single dose of selumetinib 75 mg.

The study will consist of 4 visits. Visit 1 will be a screening visit. Visits 2 and 3 will be treatment visits and the healthy volunteers will be resident at the study center from Day -1 until Day 3 for both visits. Healthy volunteers will be randomized on Day 1 of Visit 2 to 1 of 2 'treatment' sequences (fasted then fed or fed then fasted) and will receive selumetinib on Day 1 of Visit 2 and Visit 3. Visit 4 will be the follow-up visit and will take place 7 to 10 days after discharge from Visit 3.

Target subject population

Healthy male volunteers aged 18 to 45 years (inclusive) who are non-smokers and have a calculated creatinine clearance greater than 50 mL/min using the Cockcroft-Gault formula. Healthy volunteers with current or past history of central serous retinopathy or retinal vein thrombosis, intra-ocular pressure greater than 21 mmHg or uncontrolled glaucoma will be excluded.

Number of subjects:

A total of 34 healthy volunteers aged 18 to 45 years (inclusive) will be included. Healthy volunteers who are discontinued or withdraw from the study will not be replaced, unless the total number of evaluable healthy volunteers falls below 30. This number of healthy volunteers was chosen based on the desire to gain adequate information while exposing as few healthy volunteers as possible to study procedures.

Investigational product, dosage and mode of administration

Treatment A: selumetinib capsules in the fasted state, healthy volunteers will receive a single oral dose of 75 mg selumetinib (3 x 25 mg capsules) after fasting overnight for at least 10 hours followed by an additional fasting period of at least 4 hours postdose.

Treatment B: selumetinib capsules in the fed state, healthy volunteers will receive a high fat breakfast in accordance with the Food and Drug Administration guidance after fasting overnight for at least 9.5 hours. The entire high fat breakfast should be consumed within

30 minutes and a single oral dose of 75 mg selumetinib (3 x 25 mg capsules) will be administered 30 minutes after the start of the high fat breakfast followed by a fasting period of at least 4 hours postdose.

Comparator, dosage and mode of administration

None

Duration of treatment

A single dose of selumetinib will be administered on Day 1 of Visits 2 and 3 with a washout period of at least 7 days between administrations.

Outcome variable(s):

- Pharmacokinetics

  The primary endpoints will be maximum concentration in plasma (C_{max}), area under plasma concentration-time curve from time zero to infinity (AUC), area under plasma concentration-time curve from time zero to the last quantifiable concentration ($AUC_{(0-t)}$) determined from selumetinib fed and fasted plasma concentration data.

  The secondary endpoints will be time to C_{max} (t_{max}), area under the plasma concentration-time curve from time zero to 12 hours postdose ($AUC_{(0-12)}$), terminal rate constant (λ_z), terminal half-life ($t_{½}$), apparent systemic plasma clearance (CL/F), apparent volume at distribution equilibrium (V_{ss}/F), apparent volume at distribution (V_z/F), mean residence time (MRT) for selumetinib and AUC, C_{max}, t_{max}, $t_{½}$, $AUC_{(0-12)}$, and $AUC_{(0-t)}$ for the N-desmethyl metabolite.

- Safety

  The primary safety endpoints will include adverse events, physical examinations, ophthalmologic assessments, vital signs, clinical laboratory assessments, and 12-lead electrocardiograms.

Statistical methods

Following log-transformation, C_{max}, AUC, and $AUC_{(0-t)}$ of selumetinib and N-desmethyl selumetinib will be separately analysed using a linear mixed-effects analysis of variance model. Transformed back from the logarithmic scale, geometric least-squares means together with confidence intervals (2-sided 95%) for C_{max}, AUC, and $AUC_{(0-t)}$ will be estimated and presented. Also, ratios of geometric least squares means (fed/fasted) together with confidence intervals (2-sided 90%) will be estimated and presented.

An analysis of selumetinib and N-desmethyl selumetinib t_{max} using the Wilcoxon Signed Rank Test, and the Lehman median estimator of difference (fed-fasted) and 90% confidence intervals will also be presented.

Analyses will be conducted separately for selumetinib and the metabolite N-desmethyl selumetinib, however, it should be noted that sample size was determined according to the precision of the food effect of selumetinib, rather than the metabolite.

These analyses of food effect will require healthy volunteers to have evaluable pharmacokinetic data in both study periods.

The adverse events will be coded using the Medical Dictionary for Regulatory Activities for system organ class and preferred term. Adverse events will be summarized for each treatment group by system organ class and preferred term. Medications will be classified according to the AstraZeneca Drug Dictionary.

Tabulations and listing of data for frequency and severity of adverse events and results of clinical laboratory tests, vital signs, electrocardiograms, and physical examinations will be presented by treatment. The safety data will be presented by treatment and will include all healthy volunteers who received at least one dose of investigational product. For clinical laboratory tests, listings of values for each healthy volunteer will be presented with abnormal or out of range values flagged.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
$\%AUC_{ex}$	Percentage of AUC obtained by extrapolation
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve from time zero to infinity
$AUC_{(0-12)}$	Area under the plasma concentration-time curve from time zero to 12 hours postdose
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from time zero to the last quantifiable concentration
BLQ	Below the LLOQ
BMI	Body mass index
CI	Confidence interval
CL/F	Apparent systemic plasma clearance
C_{max}	Maximum concentration in plasma
CrCL	Creatinine clearance
CV	Coefficient of variation
DAE	Discontinuation of the investigational product due to an AE
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GRand	Global randomization system
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
IATA	International Air Transport Association
IB	Investigator's Brochure

Abbreviation or special term	Explanation
ICH	International Conference on Harmonization
IRB	Institutional Review Board
λ_z	Terminal rate constant
LIMS	Laboratory Information Management System
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase kinase
MR	Metabolite to parent ratio
MRT	Mean residence time
N	Number of data points
NA	Not applicable
ND	Not determined
NOEL	No observed effects level
NSCLC	Non-small cell lung cancer
OAE	Other significant AE
PICTS	Phase I Clinical Trial System
PK	Pharmacokinetic(s)
Rsq	Coefficient of determination
SAE	Serious adverse event
SD	Standard deviation
SPF	Sun protection factor
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal half-life
t_{max}	Time to C_{max}
ULN	Upper limit of normal
V_{ss}/F	Apparent volume at distribution equilibrium
V_z/F	Apparent volume at distribution

1. INTRODUCTION

1.1 Background

Selumetinib is a potent, selective, uncompetitive inhibitor of mitogen-activated protein kinase kinase (MEK), licensed for development by AstraZeneca Pharmaceuticals (hereafter referred to as AstraZeneca or the sponsor) from Array BioPharma and is in development for the treatment of solid tumors. Array BioPharma was responsible for the first in man study of selumetinib. The remainder of the clinical development program for oncology indications is the responsibility of AstraZeneca. Phase II studies are ongoing in patients with non-small cell lung cancer (NSCLC) and patients receiving adjuvant treatment for differentiated thyroid cancer, and a Phase III study in advanced NSCLC is planned.

1.1.1 Summary of relevant preclinical and clinical information to date

Preclinical experience with selumetinib is described in the Investigator's Brochure.

Selumetinib (AZD6244 hyd-sulfate) was not mutagenic or clastogenic in vitro, but produced increases in micronucleated immature erythrocytes in mouse bone marrow micronucleus studies. Investigatory studies showed this to be predominantly via an aneugenic mechanism and this is entirely consistent with disruption of normal spindle function due to the known pharmacological action of selumetinib. With selumetinib, a no observed effects level (NOEL) of 24 mg/kg/day (for 2 days) was established for induction of micronuclei.

Reproductive toxicology data indicate that selumetinib can have adverse effects on embryofetal development and survival at dose levels that do not induce maternal toxicity in mice. Healthy volunteers will be asked to adhere to strict restrictions regarding contraception use and avoid semen donation.

approximately 1760 patients with cancer and 27 healthy male volunteers had received selumetinib in clinical studies. Clinical experience with selumetinib as monotherapy and in combination with other anti-cancer agents is described in the Investigator's Brochure.

1.2 Rationale for conducting this study

A food effect has previously been observed in patients administered selumetinib (Study D1532C00020) with maximum concentration in the sampled matrix (C_{max}) and area under the concentration-time curve in the sampled matrix from zero to infinity (AUC) being reduced by 62% and 19% respectively under fed conditions. A delay in time to C_{max} (t_{max}) was also observed. The previous food effect study was performed on a formulation that will not be the final to be marketed formulation. The current study will assess the food effect on the to be marketed capsules.

The primary objective of this study to assess any differences in pharmacokinetics (PK) of selumetinib at a dose of 75 mg when administered in the fasted state compared to the fed state.

1.3 Clinical safety

1.3.1 Adverse events in healthy volunteers

In a Phase I study conducted in healthy male volunteers aged 18 to 55 years, to compare the PK profiles of selumetinib from different formulations (Study D1532C00066), healthy volunteers received single doses of 75 mg selumetinib as a capsule formulation on three occasions and a single dose of 35 mg selumetinib solution on one occasion. Selumetinib was well tolerated in this study with no clinically important trends in hematology, biochemistry, urinalysis, vital signs, or electrocardiogram (ECG) parameters, or left ventricular ejection fraction (measured by echocardiogram). The most common adverse events (AEs) reported were contact dermatitis (due to ECG electrodes) (25.9%), headache (11.1%), raised creatine phosphokinase (due to physical exertion) (11.1%), and nasal congestion (7.4%). No serious adverse event (SAE) was reported in the study.

AstraZeneca will immediately notify the principal investigator if any additional safety information becomes available during the study.

1.3.2 Adverse events within 24 hours of selumetinib treatment in cancer patients

A summary of AEs reported within 24 hours of a single dose of 75 mg selumetinib monotherapy treatment in advanced cancer patients is provided in Table 1. Adverse event data are available from Study D1532C00005 and Study D1532C000020 (65 advanced cancer patients in total). The most frequently reported AEs were decreased blood potassium (3/65 patients [4.5%]), diarrhea, headache, and nausea (each reported for 2/65 patients [3.0%]). The event of decreased blood potassium occurred in 3 patients. All 3 patients had a low potassium value at baseline. All events (further decrease or similar value/baseline) were considered unrelated to selumetinib by the investigator. Confounding factors included concomitant medications such as diuretics and steroids. These events were not considered to be clinically significant findings. All other AEs were reported in only 1 patient each.

Table 1 Number (n) and percentage (%) of patients with adverse events within 24 hours of selumetinib treatment

MedDRA Preferred Term	Total n=65		D1532C00005 (A)[a] n=7		D1532C00005 (B)[a] n=28		D1532C00020 n=30	
	n	%	n	%	n	%	n	%
Blood potassium decreased	3	4.5	0	0	0	0	3	9.9
Diarrhea	2	3.0	1	14.3	0	0	1	3.3
Headache	2	3.0	0	0	0	0	2	6.6
Nausea	2	3.0	1	14.3	0	0	1	3.3
Abdominal pain	1	1.5	1	14.3	0	0	0	0
Anemia	1	1.5	0	0	0	0	1	3.3
Constipation	1	1.5	1	14.3	0	0	0	0
Decreased appetite	1	1.5	0	0	0	0	1	3.3
Dehydration	1	1.5	1	14.3	0	0	0	0
Dry skin	1	1.5	1	14.3	0	0	0	0
Dyspnea exertional	1	1.5	1	14.3	0	0	0	0
Dysuria	1	1.5	1	14.3	0	0	0	0
Fatigue	1	1.5	0	0	0	0	1	3.3
Frequent bowel movements	1	1.5	0	0	0	0	1	3.3
Pain in extremity	1	1.5	0	0	0	0	1	3.3
Somnolence	1	1.5	0	0	0	0	1	3.3
Syncope vasovagal	1	1.5	0	0	0	0	1	3.3
Tachycardia	1	1.5	1	14.3	0	0	0	0
Vision blurred	1	1.5	0	0	1	3.6	0	0
Vomiting	1	1.5	0	0	0	0	1	3.3
Wheezing	1	1.5	0	0	0	0	1	3.3

MedDRA: Medical Dictionary for Regulatory Activities

a Study D1532C00005 (A; 25, 50, 75, 100 mg bd hyd-sulfate) and (B; single dose 75 mg hyd-sulfate vs 100 mg free-base) are 75 mg selumetinib capsule formulation.

1.3.3 Potential adverse events

In advanced cancer patients, clinical experience with selumetinib as monotherapy and in combination with other anti-cancer agents is described in the current version of the

selumetinib Investigator's Brochure (IB). Section 5.4 of the IB acts as Reference Safety Information of the IB and lists those events that are to be regarded as expected for regulatory reporting purposes.

- Gastrointestinal: diarrhoea, nausea, vomiting, stomatitis (oral mucositis), dry mouth
- Skin and subcutaneous: rashes (including dermatitis acneiform and exfoliative rash), dry skin, paronychia
- General: facial and/or peripheral edema, fatigue/asthenia, pyrexia
- Respiratory: dyspnea
- Eye: blurred vision
- Physical assessments: increased blood pressure, reduced left ventricular ejection fraction

Laboratory changes: increases in serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT), hypoalbuminemia, hyperphosphatemia, which may be associated with an increase in calcium x phosphate product requiring therapeutic intervention.

Patients in previous studies had metastatic cancer, had received previous treatment with chemotherapy and/or radiotherapy and have taken selumetinib for a long period of time.

Further information on selumetinib can be found in the IB.

1.4 Benefit/risk and ethical assessment

Selumetinib will be administered to healthy male volunteers purely for research and development purposes and those healthy volunteers receiving investigational product are not expected to benefit from the study.

All AEs, identified and potential risks identified through review of the preclinical and clinical studies conducted to date will be managed in accordance with standard clinical practice.

2. STUDY OBJECTIVES

2.1 Primary objective

To investigate the effect of food, in comparison to fasting conditions, on the exposure of selumetinib after a single 75 mg dose in healthy volunteers.

2.2 Secondary objectives

The secondary objectives of the study are:

1. To investigate the PK of selumetinib under fed and fasting conditions.

2. To investigate the PK of N-desmethyl selumetinib under fed and fasting conditions.

3. To further assess the safety and tolerability of selumetinib by assessment of AEs, laboratory variables, 12-lead ECGs, and vital signs.

2.3 Exploratory objective

To collect an optional pharmacogenetic sample from consenting subjects for exploratory investigation to determine the variability in PK or safety parameters can be explained by differences in the healthy volunteer's genotype.

The exploratory analysis will be reported separately.

3. STUDY PLAN AND PROCEDURES

This clinical study protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This study is designed as a Phase I, open-label, randomized, single-center, 2-period crossover study in healthy male volunteers in order to investigate the effect of food on the PK of a single dose of selumetinib 75 mg. A total of 34 healthy male volunteers aged between 18 and 45 years (inclusive) will be enrolled in the study. Screening procedures will only be performed for healthy volunteers who provide informed consent.

The study will consist of 4 visits. Visit 1 will be a screening visit and will take place within 28 days of Visit 2. Visits 2 and 3 will be the treatment visits and the healthy volunteers will be resident at the study center from Day -1 until Day 3 for both visits. Healthy volunteers will be randomized to 1 of 2 'treatment' sequences on Day 1 of Visit 2 and will receive selumetinib on Day 1 of Visit 2 and Visit 3:

- Sequence 1: 75 mg selumetinib oral dose in a fasted state (Treatment A) followed by a second 75 mg selumetinib oral dose in the fed state (Treatment B) with a washout period of at least 7 days between doses.

- Sequence 2: 75 mg selumetinib oral dose in the fed state (Treatment B) followed by a second 75 mg selumetinib oral dose in the fasted state (Treatment A) with a washout period of at least 7 days between doses.

Visit 4 will be the follow-up visit and will take place 7 to 10 days after discharge from Visit 3.

For Treatment A, selumetinib in the fasted state, healthy volunteers will receive a single oral dose of 75 mg selumetinib after fasting overnight for at least 10 hours and will remain fasted until 4 hours postdose. No water will be allowed from 1 hour before administration until 1 hour after administration, except for water required to swallow the selumetinib capsules.

For Treatment B, selumetinib in the fed state, healthy volunteers will received a high fat breakfast in accordance with the Food and Drug Administration (FDA) guidance (Food and Drug Administration 2002) after fasting overnight for at least 9.5 hours. The entire high fat meal should be consumed within 30 minutes and a single oral dose of 75 mg selumetinib will be administered 30 minutes after the start of the high fat breakfast. Following breakfast, healthy volunteers will be fasted for at least 4 hours postdose. No water will be allowed from 1 hour before administration until 1 hour after administration, except for water required to swallow the selumetinib capsules. The high fat breakfast will have a total of approximately 800 to 1000 calories with approximately 50% of the calorific content made up from fat. The meal will therefore derive approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat respectively.

Other than the high fat breakfast for Treatment B, all other meals and snacks will be standardized and will be provided at the same time in each treatment period (Visits 2 and 3).

The study flow chart is presented in Figure 1.

Figure 1 Study flow chart

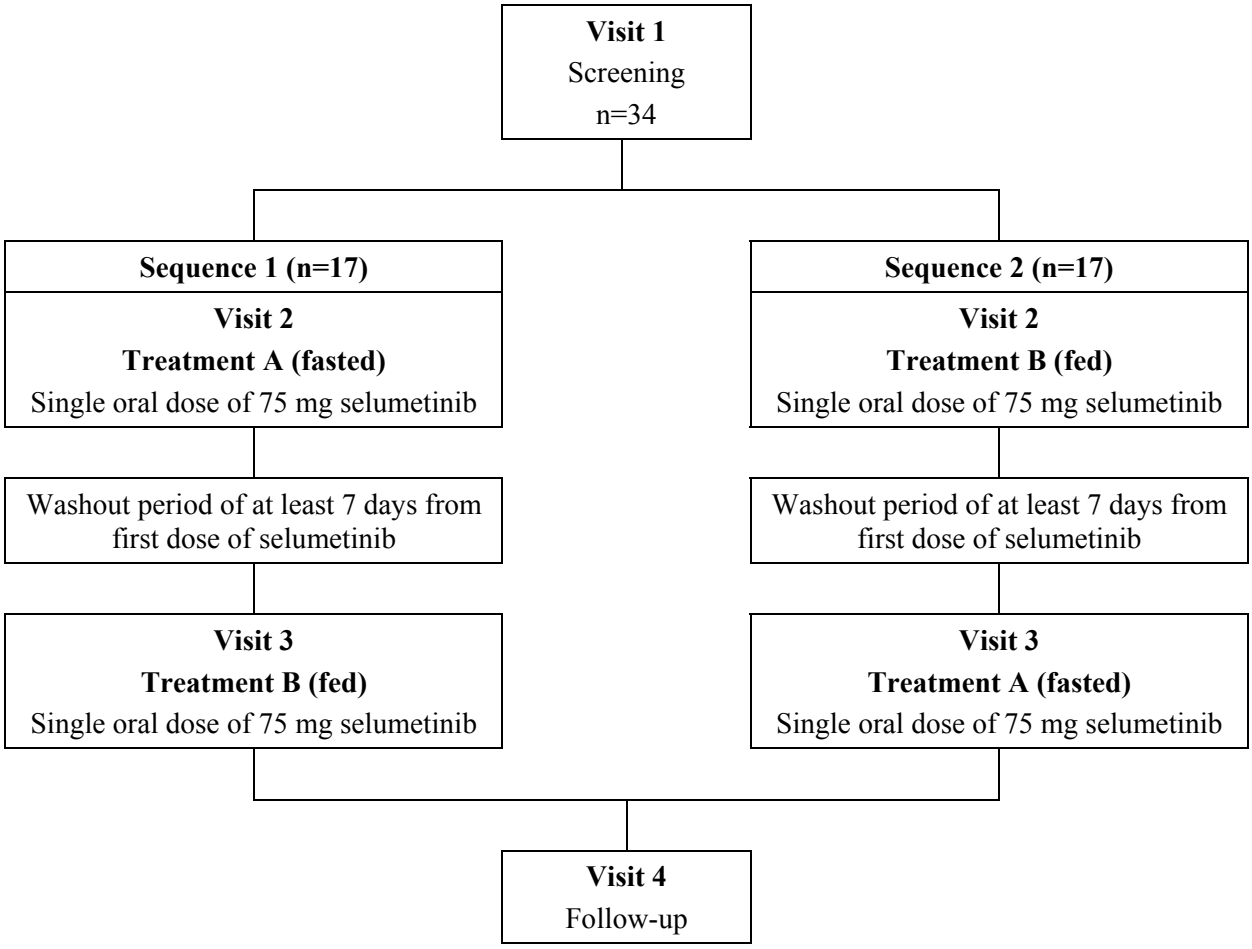

Table 2 Schedule of assessments

	Visit 1	Visits 2 and 3[a]				Visit 4
Assessments	**Screening** ≤28 days before Visit 2	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Follow-up** 7 to 10 days after discharge from Visit 3
Informed consent for study participation	X					
Optional informed consent for genotyping	X					
Eligibility criteria	X	X[b]				
Demography	X					
Medical/surgical/smoking history	X					
Hepatitis B, C, and HIV screen	X					
Ophthalmic examination[c]	X[c]	X[c]				
Drug of abuse, alcohol, and cotinine screen	X	X				
Height and weight[d]	X	X				X
Physical examination	X	X[e]			X[e]	X
Vital signs[f]	X	X	X	X	X	X
Hematology, clinical chemistry, urinalysis[g]	X	X		X	X	X
Randomization			X[b]			
Investigational product administration			X			
12-Lead electrocardiogram[h]	X		X			X
Optional pharmacogenetic sampling		X[i]				

Assessments	Visit 1	Visits 2 and 3[a]				Visit 4
	Screening ≤28 days before Visit 2	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Follow-up** 7 to 10 days after discharge from Visit 3
Pharmacokinetic blood sampling[j]			X	X	X	
Standard meals[k]			X	X	X	
Concomitant medications recording	X	X	X	X	X	X
Adverse event recording		X	X	X	X	X
Serious adverse event recording	X	X	X	X	X	X

HIV: human immunodeficiency virus

a Visits 2 and 3 will be separated by a washout period of at least 7 days between doses. Healthy volunteers will be resident at the study center from Day -1 until Day 3 for each visit.

b Visit 2 only.

c Ophthalmic examination (best corrected visual acuity, intra-ocular pressure, slit-lamp fundoscopy) will be conducted at screening or Visit 2 Day -1 and will only be repeated on occurrence of an adverse event.

d Height will only be recorded at screening.

e A brief physical examination will be performed.

f Supine pulse rate and blood pressure will be measured at screening, Visits 2 and 3 Day -1, Day 1 at predose, 1.5, 2, 4, 8, and 12 hours postdose, Day 2 (24 hours postdose), Day 3, and at follow-up. Pulse rate and blood pressure will be recorded after the electrocardiogram assessment.

g Blood samples will be collected at screening, Day -1, Day 2 (24 hours postdose), Day 3 (48 hours postdose), and at follow-up.

h The 12-lead electrocardiograms will be performed at screening, Day 1 at predose, 1.5, and 8 hours postdose, and at follow-up. Healthy volunteers should be resting in the supine position for 10 minutes before the electrocardiogram recording.

i The pharmacogenetic sample can be collected at any time during the study after optional informed consent has been signed.

j Blood samples (2 mL) will be collected to measure selumetinib and N-desmethyl metabolite at predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24 (Day 2), 36, and 48 hours (Day 3) postdose. When the pharmacokinetic sampling time points coincide with electrocardiogram and vital signs assessments, the other assessments should be performed before the pharmacokinetic sampling with the pharmacokinetic sampling taking place at the protocol specified time points.

k For Treatment A (fasted) healthy volunteers will not receive breakfast and selumetinib will be administered in the fasted state. For Treatment B (fed) healthy volunteers will receive a high fat breakfast which should be consumed within 30 minutes. Selumetinib will be administered 30 minutes after the start of the high fat breakfast. For both treatments, lunch will be provided 4 hours postdose (after completion of measurements at this time point), dinner will be provided 10 hours postdose, and a snack will be provided 14 hours postdose. Standard meals will be provided during the healthy volunteers' stay at the study center.

The study plan presented in Table 3 below outlines PK and ECG assessments for the 2 treatment sequences.

Table 3 PK and ECG schedule of assessments to be performed during Visit 2 and Visit 3

Study day	Protocol time (hours)	Pharmacokinetic blood sample	Electrocardiogram
-1			
1	Predose	X	X
1	0.5	X	
1	1	X	
1	1.5	X	X
1	2	X	
1	2.5	X	
1	3	X	
1	3.5	X	
1	4	X	
1	5	X	
1	6	X	
1	8	X	X
1	12	X	
2	24	X	
2	36	X	
3	48	X	

3.2 Rationale for study design, doses and control groups

This study is designed to further investigate the effect of food on the rate and extent of selumetinib (AZD6244 hyd-sulfate) absorption in healthy male volunteers in a study that is statistically sized to estimate the food effect ratio with sufficient precision according to observed within-subject variability of selumetinib AUC and C_{max}. A sample size of 30 evaluable healthy volunteers was chosen based on the desire to gain adequate information while exposing as few healthy volunteers as possible to the study procedures. Statistical implications of this sample size are shown in Section 12.3.

A high fat meal will be used in accordance with the FDA guidance (Food and Drug Administration 2002).

The results will support labeling statements with regard to posology.

Healthy male volunteers are considered appropriate for this study as the data generated will not be influenced by any disease process or concomitant medication.

The optional pharmacogenetic component is included in the study for exploratory investigation to determine whether variability in PK or safety parameters can be explained by differences in the healthy volunteer's genotype.

4. SUBJECT SELECTION CRITERIA

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

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

4.1 Inclusion criteria

For inclusion in the study, healthy volunteers should fulfill the following criteria:

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

2. Healthy male volunteers aged 18 to 45 years (inclusive).

3. Able to eat a high fat meal within a 30-minute period.

4. Male volunteers with sexual partners who are pregnant or who could become pregnant (ie, women of childbearing potential) should use barrier methods of contraception for at least 14 days after completing the study to avoid pregnancy and/or potential adverse effects on the developing embryo. Volunteers should avoid sperm donation during and for 14 days after study completion. Reliable methods of contraception should be used consistently and correctly.

Acceptable methods for volunteers' partners include:

- Implants, injectables, combined oral contraceptives (which must all be combined with barrier methods of contraception), some intrauterine devices, vasectomised partner (which must all be combined with barrier methods of contraception), and sexual abstinence.

Acceptable methods for volunteers include:

- Volunteers will be required to use reliable methods of contraception (condom and spermicide) for the duration of the study until 14 days after the investigational product administration.

5. Have a body mass index (BMI) between 18 and 30 kg/m^2 (inclusive) and weigh at least 50 kg and no more than 100 kg (inclusive).

6. Be a non-smoker (ie, has not smoked or used nicotine products within the previous 3 months).

7. Have a calculated creatinine clearance (CrCL) greater than 50 mL/min using the Cockcroft-Gault formula.

For inclusion in the genetic component of the study, healthy volunteers must fulfill the following additional criterion:

8. Provision of informed consent for genetic research. If a healthy volunteer declines to participate in the genetic component of the study, there will be no penalty or loss of benefit to the healthy volunteer. The healthy volunteer will not be excluded from other aspects of the study described in the protocol, as long as all the eligibility criteria are met.

4.2 Exclusion criteria

Healthy volunteers should not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study (applies to AstraZeneca staff and their close relatives regardless of their role in accordance with their internal procedures, 3rd party contractors, and/or staff at the study center).

2. Previous randomization and/or administration of the investigational product in the present study.

3. Has received another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment within at least 30 days of the first administration of the investigational product in this study. The period of exclusion begins 30 days after

the final dose or 1 month after the last visit whichever is the longest.
Note: volunteers consented and screened, but not randomized in this study or a previous Phase I study, are not excluded.

4. Current or past history of central serous retinopathy or retinal vein thrombosis, intra-ocular pressure greater than 21 mmHg or uncontrolled glaucoma.

5. Any clinically significant disease or disorder (eg, cardiovascular, pulmonary, gastrointestinal, liver, renal, neurological, musculoskeletal, endocrine, metabolic, malignant, psychiatric, major physical impairment) which, in the opinion of the principal investigator, may put the healthy volunteer at risk because of participation in the study, influence the results of the study, or influence the healthy volunteer's ability to participate in the study.

6. Any clinically relevant abnormal findings in physical examination, hematology, clinical chemistry, urinalysis, vital signs, or ECG at Visit 1 which, in the opinion of the principal investigator, may put the healthy volunteer at risk because of his participation in the study.

7. Use of any prescribed medicine or over-the-counter drugs (including herbal remedies, vitamins, and minerals) within 2 weeks/five times the half-life of the respective drug, whichever is the longer, prior to Visit 2, with the exception of occasional use of acetaminophen and over-the-counter adrenergic nasal spray for relief of nasal congestion. No medications known to prolong the QT/QTc interval are allowed.

8. Use of drugs with enzyme inducing properties such as St John's Wort within 4 weeks before the first administration of investigational product.

9. Any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges within 7 days of the first admission on Day -1.

10. Excessive intake of caffeine containing drinks or food, eg, coffee, tea, chocolate, Red Bull, or cola (more than 6 units of caffeine per day). One caffeine unit is contained in the following items: 1 (6 oz) cup of coffee, 2 (12 oz) cans of cola, 1 (12 oz) cup of tea, ½ (4 oz) cup of energy drink (eg, Red Bull), or 3 oz of chocolate.

11. Use of any prescribed medicine or over-the-counter drugs (including herbal remedies, vitamins, and minerals) within 2 weeks/five times the half-life of the respective drug, whichever is the longer, prior to Visit 2, with the exception of occasional use of acetaminophen and over-the-counter adrenergic nasal spray for relief of nasal congestion.

12. History of severe allergy/hypersensitivity or ongoing clinically important allergy/hypersensitivity, as judged by the investigator, or history of hypersensitivity to drugs with a similar chemical structure or class to selumetinib.

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

14. Involvement in the planning and/or conduct of the study of any third party contractor or AstraZeneca employee and their close relatives regardless of their role in accordance with their internal procedures.

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

16. History of, or current alcohol or drug abuse, as judged by the principal investigator, at screening or admission to the study center on Day -1.

17. A suspected or manifested infection according to the International Air Transport Association (IATA) Categories A and B infectious substances.

18. Positive results on screening tests for human immunodeficiency virus (HIV) and/or hepatitis B and/or hepatitis C.

19. Planned inpatient surgery, dental procedure, or hospitalization during the study.

20. Healthy volunteers who, in the opinion of the principal investigator, should not participate in the study.

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

21. Previous bone marrow transplant.

22. Whole blood transfusion within 120 days of the genetic sample collection.

For procedures for withdrawal of incorrectly enrolled healthy volunteers, see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

The following restrictions will be applied in this study:

- For Treatment A (fasted), healthy volunteers will be fasted overnight for at least 10 hours before receiving selumetinib and until 4 hours postdose. For Treatment B (fed), subjects will be fasted overnight for at least 9.5 hours before receiving a high fat breakfast which should be consumed within 30 minutes or less. Selumetinib will be administered 30 minutes after the start of the high fat breakfast. Following breakfast, healthy volunteers will be fasted for at least 4 hours postdose. For both Treatments A and B, no water will be allowed from 1 hour before selumetinib administration until 1 hour after selumetinib administration, except for water needed to swallow the selumetinib capsules. Standardized meals (lunch, dinner, and a snack) will be provided at the same time in each treatment period (Visits 2 and 3).

- Caffeine intake should be limited to 5 cups per day from enrolment and limited to 3 cups per day at meal times from admission to the study center and during the study visits.

- Abstain from consuming energy drinks (or other formulations) containing taurine or glucuronolactone from the day of enrolment until after the completion of the follow-up visit.

- Abstain from consumption of alcoholic beverages from within 48 hours before admission to the study center of each treatment period (Visits 2 and 3) until discharge from the study center, and should consume no more than 2 units of alcohol per day between treatment periods and after the final treatment period until after the follow-up visit.

- Abstain from any tobacco or nicotine containing products from the time of enrollment until after the follow-up visit.

- Blood donation will not be allowed at any time during the study and up to 3 months after the follow-up visit.

- Healthy volunteers should not start any new physical training activities or increase the intensity of their usual physical training from 5 days before the first investigational product administration until after the follow-up visit.

- Abstain from consuming grapefruit, grapefruit juice, cranberry juice, and other cranberry containing products or any products made with Seville oranges (eg, orange marmalade) from 1 week admission to the study center until after the follow-up visit.

- Healthy male volunteers with sexual partners who are pregnant or who could become pregnant (ie, women of childbearing potential) should use barrier methods of contraception from the time of the first administration until 14 days after completing the study to avoid pregnancy and/or potential adverse effects on the developing embryo. Healthy male volunteers should avoid sperm donation during and for 14 days after the study completion. Reliable methods of contraception should be used consistently and correctly.

  Acceptable methods for healthy male volunteers' partners include:

  – Implants, injectables, combined oral contraceptives (which must all be combined with barrier methods of contraception), some intrauterine devices, vasectomized partner (which must all be combined with barrier methods of contraception), and total sexual abstinence. When this is in line with the preferred and usual lifestyle of the healthy volunteer (periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent healthy volunteers have to agree to use one of the above mentioned contraceptive methods, if they start sexual activities 14 days after the last administration of the investigational product.

  Acceptable methods for healthy male volunteers include:

  – Healthy male volunteers will be required to use reliable methods of contraception (condom and spermicide) for the duration of the study until 14 days after the investigational product administration.

- Volunteers should avoid excessive sun exposure and use adequate sunscreen protection (greater than 30 sun protection factor [SPF]), if sun exposure is anticipated. Volunteers should use sunscreen for up to 14 days after the administration of [^{14}C]-selumetinib due to phototoxicity risk.

- Subjects should refrain from taking vitamin E supplements or multivitamin supplements from 2 weeks prior to administration of the investigational product and throughout the study until the follow-up visit (Visit 4).

- Abstain from using drugs of abuse during the entire study. In addition, poppy seeds (eg, on bread rolls) can give a positive signal for opiates and should not be ingested during the study.

For concomitant medication restrictions, see Section 5.6.

5.2 Subject enrolment and randomization and initiation of investigational product

The principal investigator will:

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

2. Determine healthy volunteer eligibility. See Sections 4.1 and 4.2.

3. Assign eligible healthy volunteers a unique randomization code (subject number), beginning with 1001.

If a healthy volunteer withdraws from participation in the study, then his randomization code cannot be reused.

5.2.1 Procedures for randomization

Up to 34 healthy male volunteers will be enrolled. The randomization scheme will be generated by using the global randomization system (GRand). Healthy volunteers will be randomized to one of the two sequences as shown in below:

Table 4 Randomization sequences

Sequence	Dosing Period 1	Dosing Period 2
1	A	B
2	B	A

Treatment A will consist of selumetinib 75 mg administered in the fasted state.
Treatment B will consist of selumetinib 75 mg administered in the fed state.

Randomization codes will be assigned strictly sequentially as healthy volunteers become eligible for randomization.

If a healthy volunteer withdraws from the study, they may be replaced. If the healthy volunteer is replaced, the replacement healthy volunteer will be given the same sequence as the healthy volunteer that withdrew and the same subject number plus 100. Eg, if healthy volunteer 1005 withdrew and was randomized to sequence 1, the replacement healthy volunteer will be given sequence 1 and their subject number will be 1105.

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

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

Where healthy volunteers that do not meet the inclusion and/or exclusion criteria, are enrolled in error, or incorrectly started on treatment, or where healthy volunteers subsequently fail to meet the study criteria post initiation, the investigator should inform the AstraZeneca Clinical Pharmacology Alliance physician immediately.

The AstraZeneca Clinical Pharmacology Alliance physician is to ensure all such contacts are appropriately documented.

5.4 Blinding and procedures for unblinding the study (not applicable)

5.5 Treatments

5.5.1 Identity of investigational product

Details of the investigational product are provided in Table 5.

Table 5 Identity of the investigational product

Investigational product	Dosage form and strength
Selumetinib	25 mg blue oral capsules (containing 25 mg free base equivalent of selumetinib hyd-sulfate)

Selumetinib capsules will be packaged in high-density polyethylene (HDPE) bottles containing 60 capsules per bottle.

5.5.2 Doses and treatment regimens

The dose level of 75 mg selumetinib (3 x 25 mg capsules) is considered to be in the therapeutic dose range and is the maximum dose permitted in healthy volunteers. A dose of 75 mg selumetinib twice daily is being investigated in ongoing efficacy studies of selumetinib.

For Treatment A, selumetinib in the fasted state, healthy volunteers will receive a single oral dose of 75 mg selumetinib (3 x 25 mg capsules) after fasting overnight for at least 10 hours and will remain fasted until 4 hours postdose. Water will not be allowed from 1 hour before administration until 1 hour after administration, except for water required to swallow the selumetinib capsules (240 mL). A standardized lunch will be provided 4 hours postdose, a standardized dinner will be provided 10 hours postdose, and a standardized snack will be provided 14 hours postdose.

For Treatment B, selumetinib in the fed state, healthy volunteers will received a high fat breakfast in accordance with the FDA guidance (Food and Drug Administration 2002) after fasting overnight for at least 9.5 hours. The entire high fat breakfast should be consumed within 30 minutes and a single oral dose of 75 mg selumetinib (3 x 25 mg capsules) will be administered 30 minutes after the start of the high fat breakfast. Healthy volunteers should consume the entire meal. Following breakfast, healthy volunteer will be fasted for at least 4 hours postdose. Start and stop date/time of the high fat breakfast will be recorded. If the healthy volunteer does not consume the full contents of the breakfast, this should be recorded.

In case of incomplete meal consumption, investigational product administration will be at the discretion of the investigator.

Water will not be allowed from 1 hour before administration until 1 hour after administration, except for water required to swallow the selumetinib capsules (240 mL). The high fat breakfast will have a total of approximately 800 to 1000 calories with approximately 50% of the calorific content made up from fat. The meal will therefore derive approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat respectively. A standardized lunch will be provided 4 hours postdose, a standardized dinner will be provided 10 hours postdose, and a standardized snack will be provided 14 hours postdose.

A washout period of at least 7 days between dose administrations will be applied.

5.5.3 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling.

5.5.4 Storage

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

5.6 Concomitant and post-study treatment(s)

Any prescribed medicine and over-the-counter drugs (including herbal remedies, vitamins, and minerals) must be avoided from within 2 weeks/five times the half-life of the respective drug of the first investigational product administration until after the follow-up visit, with the exception of occasional use of acetaminophen for pain relief and over-the-counter adrenergic nasal spray for relief of nasal congestion, if needed. Use of 1 g paracetamol 6 hourly (to a maximum daily dose of 4 g) is permitted, however the investigator should be informed so it can be recorded.

No medications known to prolong the QT/QTc interval are allowed.

Use of drugs with enzyme inducing properties such as St John's Wort from within 4 weeks before the first investigational product administration until after the follow-up visit is not allowed.

If any forbidden medication is used, the principal investigator is to decide whether the healthy volunteer can remain in the study or should be withdrawn.

Other medication, which is considered necessary for the healthy volunteer's safety and well being, may be given at the discretion of the investigator during the residential period and recorded in the appropriate sections of the electronic case report form (eCRF).

5.7 Treatment compliance

Healthy volunteers will receive the investigational product at the study center under the supervision of the study personnel.

The date and time of administration of all investigational products should be recorded in the appropriate sections of the eCRF. Treatment compliance will be assured by supervised administration of the investigational product by the investigator or a delegate. The date and time of administration of the investigational product will be recorded and checked by the monitor at monitoring visits.

5.7.1 Accountability

The investigational product provided for this study will be used only as directed in the protocol.

The study personnel will account for the investigational product dispensed to the healthy volunteers.

Study personnel, if applicable, or the monitor will account for all investigational products received at the study center, unused investigational product, and for appropriate destruction/return. Certificates of delivery, destruction/return should be signed.

5.8 Discontinuation of investigational product and withdrawal from the study

Healthy volunteers may be discontinued from investigational product in the following situations:

- Healthy volunteer decision. The healthy volunteer is at any time free to discontinue treatment, without prejudice to further treatment.
- AE.
- Severe non-compliance to study protocol.
- Any significant and clinically relevant changes in the safety parameters (eg, ECG, blood pressure, pulse rate, laboratory assessments, and AEs) making the continuation of investigational product administration unjustified.

Withdrawn healthy volunteers may be replaced. Healthy volunteers who discontinue investigational product will be withdrawn from the study.

5.8.1 Procedures for discontinuation of a subject from investigational product

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

6. COLLECTION OF STUDY VARIABLES

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

- 12-Lead ECG.
- Vital signs.
- PK blood sampling.
- Safety laboratory assessments.

Predose assessments may be performed up to 60 minutes before the investigational product administration.

6.1 Recording of data

The investigator will ensure that data are recorded on the eCRF as specified in the protocol and in accordance with the instructions provided.

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

6.2 Data collection at enrolment and follow-up

6.2.1 Screening procedures

Each potential healthy volunteer will provide informed consent at screening before starting any study-related procedures. To participate in the optional pharmacogenetic part of the study, healthy volunteers will be required to sign a separate optional informed consent form.

The eligibility of healthy volunteers will be determined during the screening period. The following assessments will be performed at screening:

- Review of inclusion/exclusion criteria.
- Recording of demographic data (date of birth, gender, and race).
- Recording of medical/surgical history and smoking history.
- Ophthalmic examination (at screening or at Visit 2 Day -1).
- Urine sample for routine urinalysis and screening for drugs of abuse.

- Calculation of CrCL.
- Alcohol and cotinine screen.
- Recording of height and weight and calculation of BMI.
- A complete physical examination.
- Vital signs (supine blood pressure and pulse rate).
- Blood sampling for routine hematology, clinical chemistry, and screening for hepatitis B, C and HIV.
- 12-Lead ECG.
- Concomitant medication recording
- SAE recording.

6.2.2 Follow-up procedures

Follow-up assessments will be conducted 7 to 10 days after discharge from Visit 3 and will include recording of weight, a brief physical examination, vital signs (supine blood pressure and pulse rate), blood sampling for routine hematology and clinical chemistry, urine sampling for routine urinalysis, 12-lead ECG, recording of concomitant medication, and recording of AEs and SAEs.

6.3 Safety

The principal investigator is responsible for ensuring that all personnel involved in the study is familiar with the content of this section.

6.3.1 Definition of adverse events

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

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

6.3.2 Definitions of serious adverse event

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

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardize the healthy volunteer or may require medical intervention to prevent one of the outcomes listed above.

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

6.3.3 Recording of adverse events

Time period for collection of AEs

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

Serious AEs will be recorded from the time of informed consent.

Follow-up of unresolved AEs

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

Variables

The following variables will be collect for each AE:

- AE (verbatim).
- The date and time when the AE started and stopped.
- Maximum intensity.
  - Mild (awareness of sign or symptom, but easily tolerated).
  - Moderate (discomfort sufficient to cause interference with normal activities).

  - Severe (incapacitating, with inability to perform normal activities).

- Whether the AE is serious or not.
- Investigator causality rating against the investigational product (yes or no).
- Action taken with regard to the investigational product.
- AE caused healthy volunteer's withdrawal from study (yes or no).
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE.
- Date investigator became aware of SAE.
- AE is serious due to.
- Date of hospitalization.
- Date of discharge.
- Probable cause of death.
- Date of death.
- Autopsy performed.
- Causality assessment in relation to study procedure(s).
- Causality assessment in relation to other medication.
- Description of AE.

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

Causality collection

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

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

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

AEs based on signs and symptoms

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

AEs based on examinations and tests

The results from protocol-mandated safety assessments will be summarized in the clinical study report. Deterioration as compared to baseline in protocol-mandated safety assessments should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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

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

NB. Cases where a subject shows an AST **or** ALT ≥3 x upper limit of normal (ULN) **or** total bilirubin ≥2 x ULN may need to be reported as SAEs, please refer to Appendix D 'Actions required in cases of combined increase of aminotransferase and total bilirubin – Hy's Law', for further instructions.

6.3.4 Reporting of serious adverse events

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

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

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

6.3.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be collected at the times indicated in Table 2. The urine drugs of abuse screen will be performed by the laboratory at the study center and all other samples, including the cotinine and alcohol screens, will be analyzed by the Physician's Reference Laboratory, United States. The date and time of sample collection will be recorded in the eCRF.

The laboratory variables to be measured are provided in Table 6.

Table 6 Safety laboratory variables

Clinical chemistry (serum/plasma)	**Hematology**
Creatinine	Platelet count
Total bilirubin	Leukocyte differential count
Alkaline phosphatase	Leukocyte count
Alanine aminotransferase	Hemoglobin
Aspartate aminotransferase	Erythrocytes
Albumin	Erythrocyte volume fraction
Total calcium	Erythrocyte mean cellular volume
Sodium	Reticulocytes
Potassium	**Urinalysis**
C-reactive protein	Erythrocytes
Thyroxine free (only at screening)	Albumin
Thyroid-stimulating hormone (only at screening)	Glucose

At screening a blood sample will be collected to screen for hepatitis B, C, and HIV. Creatinine clearance will be calculated at screening using the Cockcroft-Gault formula:

$$Males: CrCL(mL/\min) = \frac{(140 - age) \times (kg\ body\ weight)}{(0.814 \times micromol/L\ serum\ creatinine)}$$

Where age is expressed in years, weight in kg, and serum creatinine in µmol/L.

A urine sample will be collected at screening and Day -1 of Visits 2 and 3 to screen for the following drugs of abuse: amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, methadone, methamphetamine, ecstasy, opiates, phencyclidine, oxycodone, and tricyclic antidepressants. Alcohol breathalyzer test and urine cotinine test will be performed at screening and Day -1 of Visits 2 and 3.

Additional and repeat testing may be performed at the discretion of the investigator. Laboratory values outside the reference limit suspected to be of any clinical significance will be repeated. Healthy volunteers in whom suspected clinical significance is confirmed will either not be included or if already enrolled will be followed until normalization or for as long as the investigator considers necessary.

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

For blood volume see Section 7.1.

6.3.6 Physical examination

Complete and brief physical examinations will be performed at the time points indicated in Table 2.

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

The brief physical examinations will include an assessment of the general appearance, skin, abdomen, cardiovascular system, and lungs.

6.3.7 ECG

The 12-lead ECGs will be performed at the time points indicated in Table 2 after the healthy volunteer has rested in the supine position for 10 minutes.

The investigator's overall interpretation (normal/abnormal) will be captured in the eCRF. If abnormal, the nature of the abnormality will be recorded and the clinical significance will be assessed by the investigator.

Additional 12-lead ECGs may be performed at the investigator's discretion.

The original ECG printouts with variables must be signed and dated and stored in the healthy volunteer's medical record as source data.

6.3.8 Vital signs

Vital signs will be measured at the time points indicated in Table 2.

6.3.8.1 Pulse and blood pressure

Supine blood pressure and pulse rate will be measured using a semi-automatic blood pressure recording device with an appropriate cuff size after the 12-lead ECG assessments after the healthy volunteers have rested for 10 minutes on a bed. If possible, the same arm and the same make and model of equipment should be used for each evaluation. Additional blood pressure/pulse rate assessments may be taken for safety at the discretion of the investigator or delegate.

6.3.8.2 Height and weight

Height (cm) and body weight (kg) will be measured at screening and BMI (kg/m^2) will be calculated. Healthy volunteers will be required to remove their shoes and wear light indoor clothing for these measurements.

6.3.9 Ophthalmology

A full ophthalmologic examination including a slit-lamp fundoscopy, best corrected visual acuity, and intra-ocular pressure measurement must be performed at screening for all healthy volunteers. If a healthy volunteer experiences visual disturbance he should undergo a full ophthalmological examination and optical coherence tomography scans must be done if a retinal event is suspected. Management of the ocular event will be guided by the ophthalmologist based on available results.

The same ophthalmic expert will perform ophthalmic assessments on each occasion where possible.

During the study the healthy volunteers will be asked to report if they experience any eye symptoms such as dry eyes, grittiness, or irritation. In case of clinically relevant ophthalmological abnormalities, an additional full examination will be performed.

Any corneal changes must be monitored frequently, with therapeutic intervention as appropriate until resolution. Any abnormalities elicited will be recorded as an AE.

6.4 Pharmacokinetics

6.4.1 Collection of samples

Blood samples (2 mL at each time point) for determination of selumetinib and N-desmethyl selumetinib concentrations in plasma will be taken at the times presented in Table 2. If

deemed appropriate, the amide metabolite may also be measured. Individual venipunctures for each time point may be performed or an in-dwelling catheter may be used. If the study center chooses to use an in-dwelling catheter, an additional 1 mL of blood will be collected to flush the catheter prior to each sampling. Following each sampling the catheter will be flushed with saline. Heparin may not be used to flush the catheter.

The date and time of collection of each sample will be recorded in the eCRF. Samples will be collected, labeled, stored, and shipped as detailed in Laboratory Manual.

For blood volume see Section 7.1.

6.4.2 Determination of drug concentration

Samples for determination of selumetinib and N-desmethyl selumetinib concentrations and amide metabolite, if appropriate, in plasma will be analyzed by , Inc. on behalf of , AstraZeneca Research & Development, using an appropriate bioanalytical method. All samples still within the known stability of the analytes of interest at time of receipt by the bioanalytical laboratory will be analyzed. Full details of the analytical method used will be described in a separate bioanalytical report.

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

6.5 Pharmacogenetics

6.5.1 Collection of pharmacogenetic samples

The blood sample for genetic research will be obtained from the healthy volunteers at Visit 2 after the optional informed consent has been signed. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding healthy volunteers who may withdraw due to an AE, such healthy volunteers would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per healthy volunteer for genetics during the study. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

For blood volume see Section 7.1.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each healthy volunteer in this study is provided in Table 7.

Table 7 Volume of blood to be drawn from each healthy volunteer

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	8.5	8	69
	Hematology	4	8	32
Hepatitis B, C, and HIV screen		8.5	1	8.5
Pharmacokinetics[a]		2	32	64
Pharmacogenetics (optional)		10	1	10
Total				183.5

HIV: human immunodeficiency virus
a If an in-dwelling catheter is used, an additional 1 mL of blood will be collected to flush the catheter prior to collecting each sample.

The number of samples collected, as well as the volume required for each analysis, may be changed during the study (ie, if additional samples are drawn for repeated safety assessments). However, the maximum volume to be drawn from each healthy volunteer will not exceed 450 mL ie, the same volume as would be drawn during a regular blood donation.

7.2 Handling, storage and destruction of biological samples

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

Biological samples for future research can be retained on behalf of AstraZeneca for a maximum of 15years following the last healthy volunteer's last visit in the study. The results from future analysis will not be reported in the clinical study report but separately in a scientific report.

7.2.1 Pharmacokinetic samples

Pharmacokinetic samples received by the Bioanalysis group will be disposed of after the bioanalytical report finalization or 6 months after issuance of the draft bioanalytical report (whichever is earlier), unless requested for future analysis.

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

separately from the clinical study report. Anonymized samples will be retained for no more than 5 years after the clinical study report is finalized.

Selected PK samples may be used and/or pooled for metabolite identification and/or quantification, assessment of incurred sample storage stability or assessment of incurred sample reproducibility. These samples will be retained by on behalf of AstraZeneca, for a maximum of 1 year following the finalization of the clinical study report. The results from this additional work will not be reported in the clinical study report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the clinical study report but separately in a bioanalytical report.

7.2.2 Pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain healthy volunteer confidentiality. Samples will be stored for a maximum of 15 years, from the date of the last healthy volunteer's last visit, after which they will be destroyed. Deoxyribonucleic acid (DNA) is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

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

The samples and data for genetic analysis in this study will be single coded. The link between the healthy volunteer enrolment/randomization code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the healthy volunteer has requested disposal/destruction of collected samples not yet analyzed.

7.3 Labeling and shipment of biohazard samples

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

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

7.4 Chain of custody of biological samples

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

The principal investigator will keep full traceability of collected biological samples from the healthy volunteers while in storage at the study center until shipment or disposal (where appropriate) and will keep documentation of receipt of arrival.

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

AstraZeneca will keep oversight of the entire lifecycle through internal procedures, monitoring of study center and auditing of external laboratory providers.

Samples retained for further use will be registered in the AstraZeneca biobank system during the entire lifecycle.

7.5 Withdrawal of informed consent for donated biological samples

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

As collection of the biological samples is an integral part of the study, then the healthy volunteer will be withdrawn from further study participation. If a healthy volunteer withdraws consent for the genetic component of the study, then they may continue in the study.

The principal investigator:

- Ensures healthy volunteers' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca.
- Ensures that biological samples from that healthy volunteer, if stored at the study center, are immediately identified, disposed of/destroyed, and the action documented.
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study center.

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

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

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Subject data protection

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

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

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

8.3 Ethics and regulatory review

An Institutional Review Board (IRB) should approve the final study protocol, including the final version of the informed consent form and any other written information and/or materials to be provided to the healthy volunteers. The investigator will ensure the distribution of these documents to the applicable IRB, and to the study center personnel.

The opinion of the IRB should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any healthy volunteer into the study.

The IRB should approve all advertising used to recruit healthy volunteers for the study.

AstraZeneca should approve any modifications to the informed consent form that are needed to meet local requirements.

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

Before enrolment of any healthy volunteer into the study, the final study protocol, including the final version of the informed consent form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

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

AstraZeneca will provide regulatory authorities, IRB, and principal investigator with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions (SUSARs), where relevant.

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

8.4 Informed consent

The principal investigator will:

- Ensure each healthy volunteer is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study.
- Ensure each healthy volunteer is notified that they are free to discontinue from the study at any time.
- Ensure that each healthy volunteer is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each healthy volunteer provides signed and dated informed consent before conducting any procedure specifically for the study. A separate informed consent form will be provided for the optional genotyping.
- Ensure the original, signed informed consent forms are stored in the Investigator's Study File.
- Ensure a copy of the signed informed consent forms are given to the healthy volunteer.
- Ensure that any incentives for healthy volunteers who participate in the study as well as any provisions for healthy volunteers harmed as a consequence of study

participation are described in the informed consent form that is approved by an IRB.

8.5 Changes to the protocol and informed consent form

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

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

The amendment is to be approved by the relevant IRB and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to the principal investigator. For distribution to IRB see Section 8.3.

If a protocol amendment requires a change to the study center's informed consent form, AstraZeneca and the study center's IRB are to approve the revised informed consent form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by the IRB.

8.6 Audits and inspections

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

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first healthy volunteer is entered into the study, it is necessary for a representative of AstraZeneca to visit the study center to:

- Determine the adequacy of the facilities.
- Determine availability of appropriate healthy volunteer for the study.

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

9.2 Training of study site personnel

Before the first healthy volunteer is entered into the study, an AstraZeneca representative will review and discuss the requirements of the clinical study protocol and related documents with the investigational staff and also train them in any study specific procedures and system(s) utilized.

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

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

9.3 Monitoring of the study

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

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

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

9.3.1 Source data

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

9.4 Study agreements

The principal investigator at the study center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this clinical study protocol and the Clinical Study Agreement, the terms of clinical study protocol shall prevail with respect to the conduct of the study and the treatment of healthy volunteers and in all other respects, not relating to study conduct or treatment of healthy volunteers, the terms of the Clinical Study Agreement shall prevail.

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

9.4.1 Archiving of study documents

The investigator will follow the principles outlined in the Clinical Study Agreement.

9.5 Study timetable and end of study

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

The study is expected to start in Q4 2013 and to end by Q1 2014.

The study may be terminated at the study center if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with selumetinib.

10. DATA MANAGEMENT

Data management will be performed by

A 21 Code of Federal Regulations part 11 compliant electronic data capture (EDC) system, the Phase I Clinical Trial System (PICTS) will be used for this study. Electronic CRFs will be produced for each healthy volunteer. The majority of study data collected will be either directly entered by clinical research personnel or directly captured from devices onto the eCRF. Data will be available for AstraZeneca review via predefined reports extracted from the database at agreed intervals.

The eCRFs must be kept in order and up-to-date so that they reflect the latest observations on the enrolled healthy volunteers.

When direct data entry into the eCRF is inappropriate or impractical, data will be collected on paper source documents and subsequently transcribed, where necessary, into the eCRFs by the Clinical Research Personnel/ All source documents will be retained by Photocopies of completed source documents will be provided only if essential (ie, for regulatory purposes) at the request of the AstraZeneca.

Safety laboratory data are managed and stored within the LIMS system and only the date and time of sampling are recorded in the eCRF. Safety laboratory data will be integrated with the consolidated clinical data before database lock.

The informed consent form will be kept with a copy of the completed source documents in the appropriate file folder provided, or a note to indicate where the records can be located. All records should be kept in conformance to applicable national laws and regulations.

Validity and consistency of data will be checked by employing pre-programmed data validation rules that will be applied to the data extracted from the EDC system during the course of the study. The data management team will raise queries in the EDC system to resolve discrepancies. The principal investigator must verify that all data entries in the eCRFs are accurate and correct. After completion of the study and when all collected data is validated, the database will be locked. Final data will be extracted from the EDC and delivered to the AstraZeneca in form of datasets.

All eCRF entries, corrections, and alterations must be made by the principal investigator or other authorized study center personnel and only by individuals who have received training on the EDC system. The study center personnel may be allowed access to the system only after training is completed. Training must be documented and a log of all EDC users and their rights within the system be maintained.

Adverse events and medical history will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA) vocabulary and concomitant medication will be coded using the AstraZeneca Drug Dictionary as appropriate.

The EDC system will keep track of all data entry, alterations, and query resolution in an audit trail. The audit trail will form an integral part of the database and will be archived alongside with the data.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of safety variable(s)

11.1.1 Calculation of change-from-baseline

Change-from-baseline variables will be calculated for the safety variables listed below, as the posttreatment value minus the value at baseline. The baseline values will be as follows:

- Clinical laboratory tests: last measureable value taken prior to dose in corresponding treatment period.
- Vital signs: last measureable value taken prior to dose in corresponding treatment period.
- Digital ECG: last measureable value taken prior to dose in corresponding treatment period.

If a healthy volunteer is missing the baseline collection, the previous nonmissing evaluation will become the baseline value. If no baseline or previous-to-baseline evaluations exist, then the baseline value will be treated as missing and no change-from-baseline value will be calculated.

11.1.2 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and discontinuations of the investigational product due to an AE (DAEs). Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the AstraZeneca Clinical Pharmacology Alliance Physician, be considered as other significant AEs (OAEs) and reported as such in the clinical study report. A similar review of laboratory/vital signs data will be performed for identification of OAEs.

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

Any asymtomatic deviation in ECG/telemetry intervals, amplitudes, or morphology that is deemed not to constitute a safety concern for the individual healthy volunteer, nor to require a change in healthy volunteer care, surveillance, or study participation is to be reported qualitatively as an outlier value or with a narrative in the clinical study report. This includes also eg, short, asymptomatic, accidentally found paroxysmal supraventricular tachycardia or nonsustained ventricular tachycardia with characteristics that are normally not associated with investigational product exposure:

Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics, but will be included in data listings. All AEs, ECG outliers for QTcF

(ie, greater than 450, greater than 480, greater than 500 ms, or change-from-baseline greater than 30 and greater than 60 ms) and clinical laboratory outliers that occur following the first dose of investigational product will be included in the tabulations of AEs and outlier events, including episodes that occur at unscheduled evaluations or during the washout period between treatments.

11.2 Calculation or derivation of pharmacokinetic variables

The PK analyses of the plasma concentration data for selumetinib and N-desmethvl selumetinib will be performed at
Pharmacokinetic analyses will be conducted according to Standard Operating Procedures unless otherwise specified.

Actual sampling times will be used in the plasma PK parameter calculations.
Pharmacokinetic parameters will be determined using standard noncompartmental methods

Pharmacokinetic parameter units will be consistent with the plasma
fied in the bioanalytical data. No conversion of units will be made.

The following PK parameters will be determined for both plasma selumetinib and N-desmethyl selumetinib from fed and fasted plasma concentration data as appropriate:

AUC	Area under the plasma concentration-time curve from time zero to infinity, calculated by linear up/log down trapezoidal summation.
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration, calculated by linear up/log down trapezoidal summation.
$AUC_{(0-12)}$	Area under the plasma concentration-time curve from time zero to 12 hours postdose, calculated by linear up/log down trapezoidal summation.
C_{max}	Maximum concentration in plasma, obtained directly from the observed concentration versus time data.
t_{max}	Time to C_{max}.
CL/F	Apparent systemic plasma clearance (selumetinib only).
V_{ss}/F	Apparent volume at distribution equilibrium, mean residence time (MRT)*CL/F (selumetinib only).
V_z/F	Apparent volume at distribution (selumetinib only).

$t_{½}$	Terminal half-life.
λ_z	Terminal rate constant.
MRT	Mean residence time.
MR_{AUC}	AUC metabolite to parent ratio, N-desmethyl selumetinib AUC/selumetinib AUC.
MR_{Cmax}	C_{max} metabolite to parent ratio, N-desmethyl selumetinib C_{max}/selumetinib C_{max}.

No dose adjustment is required for PK parameters which require selumetinib dose for calculation since the selumetinib dose being administered is based on the free base equivalent.

The following PK parameters for plasma selumetinib and N-desmethyl selumetinib will be calculated for diagnostic purposes and listed, but will not be summarized:

$t_{½}$, Interval	The time interval of the log-linear regression to determine λ_z.
N	Number of data points included in the log-linear regression analysis used to determine λ_z (a minimum of 3 data points will be used for λ_z determination).
Rsq	Coefficient of determination for calculation of λ_z (λ_z and related parameters will be reported only if Rsq is 0.800 or more).
$\%AUC_{ex}$	Percentage of AUC obtained by extrapolation (if the extrapolated area is greater than 20% then AUC and related parameters for that specific profile will not be reported).

Pharmacokinetic parameters will be computed and reported if the anomalous predose concentration value is not greater than 5% of the C_{max} in the profile. If the anomalous predose concentration value is greater than 5% of C_{max} in the profile, PK parameters for the profile will not be reported. If an anomalous concentration value is observed at the terminal phase and is judged as physiologically unreasonable, it will be excluded from computing parameter estimates.

Additional PK parameters may be calculated if deemed appropriate.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 Safety analysis set

All healthy volunteers who received at least one dose of selumetinib will be included in the safety analysis set.

12.1.2 Pharmacokinetic analysis set

All PK analyses will be performed using the PK analysis set. The PK analysis set will consists of all healthy volunteers who receive a dose of selumetinib and provide evaluable PK profiles in at least one study period, without important events or protocol deviations or events thought to significantly affect the PK of the drug (eg, healthy volunteer vomited at or before 2 times median t_{max}; wrong dose administered; prohibited concomitant medication; etc).

A strategy for dealing with data affected by such protocol violations and deviations will be agreed by the Study Pharmacokineticist and the Study Statistician prior to the final analysis.

12.2 Methods of statistical analyses

12.2.1 General principles

Statistical analyses will be performed per Standard Operating Procedures using or higher and, where appropriate, additional validated software.

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

Data from non-valid healthy volunteers (healthy volunteers excluded from the analysis set[s]), which are recorded in the database, will only be presented in listings.

The analysis of data will be based on different subsets according to the purpose of analysis, ie, for safety and PK, respectively. The as-treated principle will be applied to all evaluations; ie, healthy volunteers who receive another treatment than the one assigned in the randomization list will be analyzed as belonging to the actual treatment group and not that assigned by randomization.

All derived variables/parameters will be rounded for reporting purposes in the summary tables and healthy volunteer listings, as per Standard Operating Procedures.

12.2.2 Subject characteristics

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation [SD], minimum, median, maximum) by treatment.

Categorical variables will be summarized in frequency tables (frequency and proportion) by treatment group.

12.2.3 Safety and tolerability

All safety data (scheduled and unscheduled) will be presented in the data listings. Continuous variables will be summarized using descriptive statistics (n, mean, SD, minimum, median, maximum) by treatment. Categorical variables will be summarized in frequency tables (frequency and proportion) by treatment.

Safety variables (eg, clinical laboratory values and vital signs) will be reported to the same precision as the source data. Derived variables will be reported using similar precision to those from which they were derived (eg, QTc derived from QT interval).

Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics by scheduled time point, but will be included in data listings. All AEs and clinical laboratory outliers that occur following the first dose of investigational product will be included in the analyses of AEs and outlier events, including episodes that occur at unscheduled evaluations, evaluations, or during the washout period.

All available data from healthy volunteers in the safety analysis set will be included in the safety analyses. No adjustment or imputation will be utilized for missing values or for healthy volunteers who withdraw prior to completing the study, nor will analyses be restricted to healthy volunteers with complete data.

All AEs will be collected for each healthy volunteer from Visit 2 Day -1 until the follow-up visit. All SAEs will be collected for each healthy volunteer from the time when informed consent is obtained until the follow-up visit.

Adverse events will be listed for all healthy volunteers with AEs that occur before dosing indicated on the listing. The number of AEs experienced following administration of the investigational product will be summarized in tables using the MedDRA (Version 13.0 or higher) system organ class and preferred term. These summary tables will also be produced with severity and causality of AEs added as additional classification factors. The number of AEs overall, SAEs, other significant AEs, AEs that lead to withdrawal, AEs of severe intensity, and causally-related AEs will be summarized. Any AE occurring postdose will be considered associated with the last dose of investigational product taken. Adverse events occurring during the washout period and before the second dose of investigational product in Visit 3 will be associated with the last dose. Any AE occurring on Visit 2 Day -1 will not be included in the summaries.

Tabulations and listings of data for vital signs, ECGs, and clinical laboratory tests will be presented, as appropriate. Results from physical examinations will be presented separately in listings only. All continuous safety data will be summarized across all treatments for the absolute value at each scheduled assessment and for the corresponding change-from-baseline. For clinical laboratory tests, listings of values for each healthy volunteer will be presented

with abnormal or out-of-range values flagged. Clinical laboratory data will be reported in Système International units in the clinical study report. Additional graphical presentations of the data eg, shift plots comparing baseline to on treatment values will be generated as appropriate to aid the interpretation of safety data.

12.2.4 Pharmacokinetics

For qualitative variables, the population size (sample size and available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarized using descriptive statistics, including available data, arithmetic mean, SD, coefficient of variation (CV), median, minimum, and maximum values. Additionally, geometric means and geometric CV will be reported for PK variables, except for t_{max}. The geometric mean is calculated as the exponential of the arithmetic mean calculated from data on a log scale. The geometric CV is calculated as $100*[\exp(s^2)-1]^{1/2}$; where s is the SD of the data on a log scale. Mean, SD, CV, geometric mean, and geometric CV will not be calculated for t_{max}; t_{max} will be summarized using median and range.

Plasma concentrations that are below the lower limit of quantification (LLOQ) will be handled as follows:

- At a time point where less than or equal to 50% of the values are below the LLOQ (BLQ), all BLQ values will be set to LLOQ, and all descriptive statistics will be calculated.

- At a time point where more than half of the values are BLQ, the mean, SD, geometric mean, and CV will be set to Not determined (ND). The maximum value will be reported from the individual data, and the minimum and median will be set to BLQ.

- If all values are BLQ at a time point, no descriptive statistics will be calculated for that time point. Not applicable (NA) will be written in the field for SD and CV and BLQ will be written in fields for mean, geometric mean, minimum, median, and maximum.

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

No imputations will be made for any missing data.

The PK data will be presented by treatment (fed/fasted) in order to estimate the effect of food on the PK of selumetinib.

A healthy volunteer listing and descriptive statistics of all concentration-time data (for selumetinib and N-desmethyl) will be presented by treatment. Data from healthy volunteers excluded from an analysis set will be included in the data listings, but not in the summaries. A listing of PK blood sample collection times as well as derived sampling time deviations will be provided.

Figures of geometric mean and ±geometric SD concentration-time data for each treatment will be presented for plasma selumetinib and N-desmethyl selumetinib concentrations separately, on linear and semi-logarithmic scales. Individual healthy volunteer concentration-time data for each analyte will be graphically presented separately on linear and semi-logarithmic scales. Scatterplots of the individual parameter data (C_{max}, AUC, and $AUC_{(0-t)}$) and geometric means will be presented by analyte, treatment, and parameter, with lines connecting the individual parameters and geometric means across the two treatments. Graphical presentations of other PK data may be added at the discretion of the pharmacokineticist.

For statistical evaluation of food effect, log-transformed, C_{max}, AUC, and $AUC_{(0-t)}$ of selumetinib and N-desmethyl selumetinib will be separately analysed using a linear mixed-effects analysis of variance model with sequence, period, and treatment as fixed effects, and healthy volunteer nested within sequence as a random effect. Transformed back from the logarithmic scale, geometric least-squares means together with confidence intervals (CIs) (2-sided 95%) for C_{max}, AUC, and $AUC_{(0-t)}$ will be estimated and presented. Also, ratios of geometric least squares means (fed/fasted) together with CI (2-sided 90%) will be estimated and presented.

An analysis of selumetinib and N-desmehtyl selumetinib t_{max} using the Wilcoxon Signed Rank Test, and the Lehman median estimator of difference (fed-fasted) and 90% CIs will also be presented.

Analyses will be conducted separately for selumetinib and the metabolite N-desmethyl selumetinib, however, it should be noted that sample size was determined according to the precision of the food effect of selumetinib, rather than the metabolite.

These analyses of food effect will require healthy volunteers to have evaluable PK data in both study periods.

12.2.5 Interim analyses

Not applicable.

12.3 Determination of sample size

The primary objective of this study is to investigate the effect of food, in comparison to fasting conditions, on the exposure of selumetinib after a single 75 mg dose in healthy volunteers.

Data from a previous food effect study (Study D1532C00020) indicated a significant effect of food on the exposure of selumetinib, the geometric least squares means C_{max} and AUC were reduced by 62% and 19% respectively under fed conditions compared to fasted conditions. Consequently, this study has been sized to be able to estimate the fed/fasted effect on exposure with a good degree of precision.

A sample size of 30 evaluable healthy volunteers has been selected based on the desire to gain adequate information while exposing as few healthy volunteers as possible to study

procedures. Thirty-four healthy volunteers (17 per sequence group) will be randomized into the study in order to have at least 30 evaluable healthy volunteers complete the study (allowing for an approximate 10% dropout rate).

Table 8 displays expected 90% and 95% CIs for a range of possible fed/fasted ratios at the selected sample size of 30 evaluable healthy volunteers. Within-subject estimates of CV (16.9% for AUC and 34.0% for C_{max}) observed in a prior clinical study (D1532C00066) were used in these calculations. These CIs demonstrate that good precision of the food effect will be achieved from a sample size of 30 evaluable healthy volunteers.

Table 8 90% and 95% confidence intervals for C_{max} and AUC, varying fed/fasted ratios and using a sample size of 30

		Reduction of C_{max}, food effect, fed versus fasted (geometric least squares means ratio)				
Para-meter	**Confidence Interval**	**62% (0.38)**	**70% (0.3)**	**60% (0.4)**	**50% (0.5)**	**40% (0.6)**
C_{max}	90%	0.33, 0.44	0.26, 0.35	0.35, 0.46	0.43, 0.58	0.52, 0.69
C_{max}	95%	0.32, 0.45	0.25, 0.35	0.34, 0.47	0.42, 0.59	0.51, 0.71
AUC	90%	0.75, 0.87	0.65, 0.75	0.74, 0.86	0.84, 0.97	0.88, 1.02
AUC	95%	0.74, 0.88	0.64, 0.76	0.73, 0.87	0.83, 0.98	0.87, 1.03

AUC: area under the concentration-time curve in the sampled matrix from time zero to infinity; C_{max}: maximum concentration in the sampled matrix

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

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

In the case of a medical emergency the investigator may contact the AstraZeneca Clinical Pharmacology Alliance Program Director. If the AstraZeneca Clinical Pharmacology Alliance Program Director is not available, contact the AstraZeneca Clinical Pharmacology Alliance Physician.

13.2 Overdose

For the purposes of this study, exceeding the dosage requirements specified in this clinical study protocol represents an overdose. There is no known antidote for selumetinib. In case of suspected overdose, the healthy volunteer should be treated according to standard medical practice based on the investigator's judgment. Cases of overdose will be recorded as follows:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca investigational product occurs in the course of the study, then investigators or other study center personnel will inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

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

For overdoses associated with an SAE, standard reporting timelines apply, see Section 6.3.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy in partners of the healthy male volunteers should be reported to AstraZeneca.

13.3.1 Paternal exposure

Healthy volunteers should refrain from fathering a child or donating sperm during the study and for 14 days after Visit 4.

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

The outcome of any conception occurring from the date of the first administration until 1 month after the last investigational product administration should be followed up and documented.

14. LIST OF REFERENCES

Food and Drug Administration 2002
Guidance for Industry. Food-effect Bioavailability and Fed Bioequivalence Studies. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Dec 2002.

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Phase I, Randomized, Open-label, Single-center, Crossover Study to Assess the Effect of Food on the Pharmacokinetics of a 75 mg Single Oral Dose of Selumetinib in Healthy Male Volunteers Aged 18 to 45 Years

---

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

I agree to the terms of this study protocol.

ASTRAZENECA SIGNATURE(S)

A Phase I, Randomized, Open-label, Single-center, Crossover Study to Assess the Effect of Food on the Pharmacokinetics of a 75 mg Single Oral Dose of Selumetinib in Healthy Male Volunteers Aged 18 to 45 Years

---

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

I agree to the terms of this study protocol.

SIGNATURE OF PRINCIPAL INVESTIGATOR

A Phase I, Randomized, Open-label, Single-center, Crossover Study to Assess the Effect of Food on the Pharmacokinetics of a 75 mg Single Oral Dose of Selumetinib in Healthy Male Volunteers Aged 18 to 45 Years

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

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

Centre No.:

Clinical Study Protocol Appendix B

Drug Substance	Selumetinib
Study Code	D1532C00069
Edition Number	1

Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

Clinical Study Protocol Appendix C

Drug Substance	Selumetinib
Study Code	D1532C00069
Edition Number	1

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

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

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

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1. INTRODUCTION

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

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

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

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

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

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

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

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

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

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

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

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

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

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

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

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

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

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

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

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

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

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

  - The 'Medically Important' serious criterion should be used if no other serious criteria apply

  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

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

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to

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

6. REFERENCES

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

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