Clinical Study Protocol

Drug Substance	Selumetinib
Study Code	D1532C00077
Edition Number	1

A Phase I, Single-centre, Non-randomised, Open-label, Pharmacokinetic and Mass Balance Study of Orally Administered [^{14}C]-selumetinib in Healthy Male Volunteers

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

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

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

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

AstraZeneca

PROTOCOL SYNOPSIS

A Phase I, Single-centre, Non-randomised, Open-label, Pharmacokinetic and Mass Balance Study of Orally Administered [14C]-selumetinib in Healthy Male Volunteers

Principal Investigator

Study centre and number of subjects planned

The study will be performed at a single study centre,
Six healthy male volunteers will be enrolled in this study.

Study period		Phase of development
Estimated date of first healthy volunteer enrolled	Q3 2013	Clinical Pharmacology (Phase 1)
Estimated date of last healthy volunteer completed	Q4 2013	

Objectives

Primary objective

To determine the rates and routes of excretion of [^{14}C] radiolabeled selumetinib in healthy volunteers by assessment of concentrations of total [^{14}C] radioactivity of selumetinib and N-desmethyl selumetinib in plasma and percent recovery of radioactive dose in urine and faeces.

Secondary Objective(s)

1. To provide samples for subsequent studies to allow the characterisation of the metabolism of [^{14}C]-selumetinib through the assessment of metabolic profiles of selected plasma and excreta samples.

2. To calculate the pharmacokinetic parameters of selumetinib and N-desmethyl selumetinib in plasma and pharmacokinetic parameters of total plasma radioactivity.

3. To compare disposition of drug related total radioactivity in plasma to whole blood.

4. To evaluate the safety and tolerability of a single dose of selumetinib.

Study design

This is a phase 1, open label, single dose study to determine the rates and routes of elimination of a single dose of [^{14}C]-selumetinib and its metabolites by assessment of concentrations of total [^{14}C] radioactivity in blood and plasma, concentrations of selumetinib, and N-desmethyl selumetinib in plasma and percent recovery of the radioactive dose in urine and faeces. The study will be conducted at 1 study centre in 6 healthy male volunteers.

Target subject population

Healthy male volunteers, aged 50 to 65 years (inclusive) with regular daily bowel movements.

Investigational product, dosage and mode of administration

Each healthy volunteer will receive a single oral administration of 75 mg (3 x 25 mg) 22.57 MBq (610 μCi) [^{14}C]-selumetinib.

Comparator, dosage and mode of administration

None

Duration of treatment

Healthy volunteers will receive a single administration of [^{14}C]-selumetinib on Day 1.

A maximum of 28 days will be allowed for the screening period. Each healthy volunteer will be admitted to the study centre on Day -1 and remain in the study centre up to Day 7. Once the mass balance cumulative recovery >90% has been achieved or <1% of the dose administered has been collected in urine and faeces within 2 consecutive days, healthy volunteers will be permitted to leave the study centre. If emerging data indicates that adequate dose recovery has not been achieved after 7 days then some healthy volunteers may be asked to continue urine and/or faecal collections for a further 3 days either on an inpatient or an outpatient basis, and if adequate dose recovery is still not achieved, some healthy volunteers could be asked to return to the study centre approximately 7 days later, for a further 24 hour collection. For these healthy volunteers, a final follow-up visit will take place on the last day of urine and/or faecal collection.

Outcome variable(s):

- Pharmacokinetics (primary endpoints)

  If the data allow, the following parameters will be calculated:

  Amount of [^{14}C] radioactivity in plasma and whole blood and the resulting area under the concentration-time curve from zero to infinity (AUC), to the last measurable concentration [$AUC_{(0\text{-}t)}$], to 12 hours postdose [$AUC_{(0\text{-}12)}$], maximum concentration (C_{max}), time of C_{max} (t_{max}), elimination half-life ($t_{½}$), apparent oral clearance (CL/F), apparent volume of distribution (V_z/F) and apparent volume of distribution at equilibrium (V_{ss}/F) will be determined. Amount and percentage of radioactive dose recovered in both urine and faeces will be calculated along with whole blood to plasma radioactivity ratios for concentrations and selected pharmacokinetic parameters (AUC and C_{max}). Identification and quantification of metabolites in plasma and excreta will be reported separately.

- Plasma selumetinib and N-desmethyl selumetinib to [^{14}C] radioactivity ratios for concentrations and selected pharmacokinetic parameters (AUC and Cmax) will be determined.

- Selumetinib and N-desmethyl selumetinib plasma concentrations and the resulting AUC, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}12)}$, C_{max}, t_{max}, $t_{½}$, and selumetinib CL/F, V_z/F, and V_{ss}/F as well as plasma N-desmethyl selumetinib to selumetinib ratios for AUC and C_{max} will be determined.

- Safety

  Adverse events, vital signs, electrocardiogram, haematology, clinical chemistry, urinalysis, physical examination, left ventricular ejection fraction, and ophthalmology assessments.

Statistical methods

No formal statistical hypothesis testing will be performed in this study. The statistical analysis will be descriptive and consist of subject listings, graphs, and summary statistics comprising arithmetic mean, standard deviation, median, minimum, maximum, geometric mean, and/or geometric coefficient of variation as appropriate.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
λ_z	Terminal elimination rate constant
$\%AUC_{ex}$	Percentage of AUC obtained by extrapolation
AE	Adverse event (see definition in Section 6.4.1)
Ae_f	Amount recovered in faeces during each collection interval and overall
Ae_u	Amount recovered in urine during each collection interval and overall
ALT	Alanine aminotransferase
ARSAC	Administration of Radioactive Substances Advisory Committee
AST	Aspartate aminotransferase
AUC	Area under plasma concentration-time curve from zero extrapolated to infinity
$AUC_{(0-12)}$	Area under plasma concentration-time curve from zero to 12 hours postdose
$AUC_{(0-t)}$	Area under plasma concentration-time curve from zero to the last quantifiable concentration
AV	Atrioventricular
BLQ	Below the limit of quantification
BMI	Body mass index
CK	Creatine kinase
CL/F	Apparent plasma clearance
C_{max}	Maximum plasma (peak) drug concentration
C_p	Concentration in plasma
CPA	Clinical Pharmacology Alliance
CPK	Creatine phosphokinase
CRF	Case Report Form (paper)
CRCL	Creatinine clearance
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
Cum Ae_f	Cumulative radioactive amount recovered in faeces

Abbreviation or special term	Explanation
Cum Ae_u	Cumulative amount recovered in urine.
Cum fe_f	Cumulative percent (or fraction) of actually administered radioactivity recovered in faeces
Cum fe_u	Cumulative percent (or fraction) of actually administered dose/radioactivity recovered in urine
CV%	Coefficient of variation
C_{wb}	Concentration in whole blood
CYP	Cytochrome P450
DAE	Discontinuation of investigational product due to adverse event
EC	Ethics Committee
ECG	Electrocardiogram
ED	Effective dose
FBE	Free base equivalent
fe_f	Percent (or fraction) of actually administered radioactivity recovered in faeces during each collection interval and overall
fe_u	Percent (or fraction) of actually administered radioactivity recovered in urine during each collection interval and overall
GCP	Good Clinical Practice
GCV	Geometric coefficient of variation
GGT	Gamma glutamyl transpeptidase
GMP	Good Manufacturing Practice
HDPE	High density polyethylene
HIV	Human Immunodeficiency Virus
Ht	Haematocrit
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IP	Investigational product
LLOQ	Lower limit of quantification
LSC	Liquid scintillation counting
LSLV	Last Subject Last Visit
LVEF	Left ventricular ejection fraction
max	Maximum
MCH	Mean cell haemoglobin

Abbreviation or special term	Explanation
MCHC	Mean cell haemoglobin concentration
MCV	Mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen activated protein kinase
min	Minimum
MR_{AUC}	Metabolite to selumetinib AUC ratio
MR_{Cmax}	Metabolite to selumetinib C_{max} ratio
MRT	Mean residence time
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)
NA	Not applicable
ND	Not determined
OAE	Other significant adverse event (see definition in Section 11.2.1)
PCV	Packed cell volume
PK	Pharmacokinetic
PL	Plasma selumetinib or plasma N-desmethyl selumetinib
PR	Plasma radioactivity
QT	ECG interval measured from beginning of Q wave (or the R wave if Q is missing) to the end of the T wave; the time interval of ventricular depolorisation and repolarisation.
QTc	Corrected QT interval
QTcF	QT interval corrected according to Fridericia's formula
RBC	Red blood cells
Rsq	Goodness of fit statistic for calculation of λ_z (regression coefficient)
SAE	Serious adverse event (see definition in Section 6.4.2).
SD	Standard deviation
SI	Système International
SOP	Standard operating procedure
$t_{½}$	Half-life
t_{max}	Time to C_{max}
ULN	Upper limits of normal
V_{ss}/F	Volume of distribution at steady state
V_z/F	Apparent volume of distribution

Abbreviation or special term	Explanation
wb	Whole blood
WBC	White blood cell
WBR	Whole blood radioactivity

1. INTRODUCTION

1.1 Background

Selumetinib is a potent, selective, non-competitive inhibitor of mitogen-activated protein kinase (MEK), licensed for development by AstraZeneca Pharmaceuticals from Array BioPharma and is in phase 2 development for the treatment of solid tumours.

Non-clinical experience with selumetinib is described in the current version of the selumetinib Investigator's Brochure.

Metabolism of selumetinib was investigated in vitro using hepatocytes from animals and humans. There was evidence of phase 1 and phase 2 metabolism, with the majority of metabolites detected as glucuronide conjugates. Phase 1 metabolism included N-demethylation, oxidative defluorination, and loss of the side chain to form amide and acid metabolites. Metabolite profiling in human plasma and urine showed direct glucuronide conjugation as a dominant metabolic route. Other metabolic routes apparent were loss of the side chain to form amide and acid metabolites, oxidative defluorination and N-demethylation.

Inhibition studies indicated that cytochrome P450 (CYP)1A2 was the enzyme primarily responsible for the formation of the N-desmethyl metabolite. Using expressed CYPs it was evident that, in addition to CYP1A2, both CYP2C19 and CYP3A4 also metabolised selumetinib. The in vitro metabolism of N-desmethyl selumetinib was also investigated in human hepatocytes and the metabolite was metabolised through the same routes as the selumetinib parent molecule. Direct glucuronide conjugation of the metabolite appeared to be the main metabolic route.

An excretion balance study was performed in intact and bile duct-cannulated rats. The predominant excretion route in intact rats was via faeces, with urinary excretion a minor route. Excretion via bile was confirmed following oral dosing to bile duct-cannulated rats. Excretion was fairly rapid, with the vast majority of the dose being recovered within 48 hours.

To date >1600 patients with cancer and 27 male healthy volunteers have received selumetinib in clinical studies. 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.

The following have been observed during administration of selumetinib in nonclinical toxicology studies: diarrhoea, dehydration, and electrolyte imbalance; gastrointestinal tract toxicity; inflammatory changes in the liver; tissue mineralisation (gastrointestinal mucosa, cornea, kidney, liver, myocardium, skeletal muscle, glandular tissue) associated with changes in plasma inorganic phosphate, calcium and/or albumin; haematopoietic atrophy, anaemia, and an associated reticulocytosis. There was evidence of reversibility of most changes, with the exception of tissue mineralisation. In vitro assays indicate a potential for phototoxicity (enhanced cytotoxicity in the presence of ultraviolet light).

Reproductive toxicology studies indicate that selumetinib can affect embryofetal development and survival at dose levels that do not induce maternal toxicity. Selumetinib showed no

evidence of mutagenic or clastogenic potential in vitro. Selumetinib produced an increase in micronucleated immature erythrocytes in mouse micronucleus studies, predominantly via an aneugenic mode of action.

AstraZeneca will immediately notify the Principal Investigator if any additional safety information becomes available during the study.

Further information on the investigational product (IP) can be found in the Investigator's Brochure.

1.2 Rationale for conducting this study

Human drug metabolism studies are essential in the support of drug development as they provide information related to major routes of drug absorption, distribution, disposition, and excretion as well as inter-subject variability and formation of metabolites.

Samples from this study will be used in subsequent studies in order to quantify and identify metabolites in plasma and excreta. This will provide a basis for the validation of the species used in toxicological studies and a comparison of the metabolism of selumetinib across species.

A single dose of 75 mg free base equivalent (FBE) selumetinib Hyd-Sulfate (91 mg Hyd-Sulfate salt) administered as 3 x 25 mg oral capsules will be used in this study. Each capsule contains 30.35 mg Hyd-Sulfate. The [^{14}C]-labeled selumetinib capsule is the same formulation as that used in clinical studies to date and therefore it is expected to provide representative exposure and information on the routes and rate of excretion of [^{14}C]-labeled selumetinib and/or its radiolabeled metabolites in whole blood, plasma, urine, and faeces.

1.3 Benefit/risk and ethical assessment

1.3.1 Adverse event profile

Adverse events potentially relevant to healthy volunteers include:

- Increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST).
- Diarrhoea, nausea, and vomiting.
- Dermatitis acneiform (rash).
- Blurred vision.
- Increases in blood pressure.
- Photosensitivity.
- Increase in blood phosphate levels.
- Decrease in blood calcium levels.

- Effects on embryos in pregnant women.
- Fatigue.
- Dyspnea/pneumonitis.
- Decreases in left ventricular ejection fraction.
- Peripheral edema.

For patient data refer to the Investigator's Brochure.

Adverse events within 24 hours of Selumetinib treatment

In a phase 1 study conducted in healthy volunteers to compare the pharmacokinetic (PK) profiles of selumetinib from different formulations (study D1532C00066), volunteers received single doses of 75 mg selumetinib as a capsule formulation on 3 occasions and a single dose of 35 mg selumetinib solution on 1 occasion. Selumetinib was well tolerated in this study with no clinically important trends in haematology, biochemistry, or urinalysis parameters or in vital signs, ECG parameters, or LVEF (measured by echocardiogram). The most common AEs reported were contact dermatitis (to ECG electrodes) (25.9%), headache (11.1%), raised CPK (due to physical exertion) (11.1%), and nasal congestion (7.4%).

A summary of AEs reported within 24 hours of a single dose of 75 mg selumetinib Hyd-Sulfate monotherapy treatment in advanced cancer patients is presented in (Table 1). Adverse event data are available from studies D1532C00005 and D1532C00020 (65 advanced cancer patients in total). The most frequent AEs were decreased blood potassium 3/65 (4.5%) patients, as well as diarrhoea, headache, and nausea (each reported from 2/65 [3.0%] patients). The event of decreased blood potassium occurred in 3 patients who each had blood potassium values below the lower limit of normal at the screening visit and therefore these events are not considered clinically important. All other AEs were reported in only 1 patient each. These AEs are commonly reported as background co-morbidities in advanced cancer patient studies.

Table 1 **Number and percentage of subjects with adverse events within 24 hours of selumetinib treatment ([A] and [B] are 75 mg selumetinib Hyd-Sulfate capsule formulation)**

MedDRA preferred term	Total n = 65		D1532C00005 (A) n = 7		D1532C00005 (B) n = 28		D1532C00020 n = 30	
	n	%	n	%	n	%	n	%
Blood potassium decreased	3	4.5	0	0	0	0	3	9.9
Diarrhoea	2	3.0	1	14.3	0	0	1	3.3
Headache	2	3.0	0	0	0	0	2	6.6

MedDRA preferred term	Total n = 65		D1532C00005 (A) n = 7		D1532C00005 (B) n = 28		D1532C00020 n = 30	
	n	%	n	%	n	%	n	%
Nausea	2	3.0	1	14.3	0	0	1	3.3
Abdominal pain	1	1.5	1	14.3	0	0	0	0
Anaemia	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
Dyspnoea 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

Healthy volunteers will be instructed to use sunscreen (>30 SPF) for up to 14 days after the last dose of selumetinib.

2. STUDY OBJECTIVES

2.1 Primary objective

To determine the rates and routes of excretion of [^{14}C] radiolabeled selumetinib in healthy volunteers by assessment of concentrations of total [^{14}C] radioactivity of selumetinib and N-desmethyl selumetinib in plasma and percent recovery of radioactive dose in urine and faeces.

2.2 Secondary objectives

1. To provide samples for subsequent studies to allow the characterisation of the metabolism of [^{14}C]-selumetinib through the assessment of metabolic profiles of selected plasma and excreta samples.

2. To calculate the PK parameters of selumetinib and N-desmethyl selumetinib in plasma and pharmacokinetic parameters of total plasma radioactivity.

3. To compare disposition of drug related total radioactivity in plasma to whole blood.

4. To evaluate the safety and tolerability of a single dose of selumetinib.

2.3 Safety objective (Not applicable)

2.4 Exploratory objectives (Not applicable)

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol (CSP) has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is a phase 1, open label, single dose study to determine the rates and routes of elimination of a single dose of [^{14}C]-selumetinib and its metabolites by assessment of concentrations of total [^{14}C] radioactivity in blood and plasma, concentrations of selumetinib and N-desmethyl selumetinib in plasma and percent recovery of the radioactive dose in urine and faeces.

Approximately 6 healthy male volunteers, aged 50 to 65 years (inclusive), will be recruited at 1 study centre.

Healthy volunteers will be screened over a period of maximum 28 days for eligibility. Screening assessments include evaluation of clinical chemistry, haematology, urinalysis, a physical examination, vital signs, an echocardiogram, a full ophthalmological examination and paper ECGs. Study-related procedures will only be performed after signing of the informed consent form (ICF).

Eligible healthy volunteers will be admitted to the study centre visit on Day -1 predose.

Healthy male volunteers will receive a single dose of [^{14}C]-selumetinib Hyd-Sulfate administered as 3 x 25 mg oral capsules on Day 1. Healthy volunteers will remain at the study centre up to 7 days following receipt of the IP when samples of blood, urine, and faeces will be collected. The length of the residential period may be reduced or extended if deemed appropriate based on emerging data. Once the mass balance cumulative recovery >90% has been achieved or <1% of the dose administered has been collected in urine and faeces within 2 consecutive days, healthy volunteers will be permitted to leave the study centre.

If emerging data indicates that adequate dose recovery has not been achieved after 7 days then these healthy volunteers may be asked to continue urine and/or faecal collections for a further 3 days either on an inpatient or an outpatient basis. If adequate dose recovery is still not achieved, these healthy volunteers could be asked to return to the study centre approximately 7 days later, for a further 24 hour collection. For these healthy volunteers, a final follow-up visit will take place on the last day of urine and/or faecal collection.

The healthy volunteer will fast for 4 hours prior to any clinical laboratory evaluations. Healthy volunteers should be fasted from 10 hours prior to the IP administration through 4 hours after administration. No fluids will be allowed from 1 hour prior to IP administration until 1 hour after IP administration, except the water needed (240 mL) to consume the IP. Thereafter, healthy volunteers will be allowed to have free access to water (see Section 5.1).

Table 2 Study Plan

Assessment		Residential period			
	Screening	Admission			Follow-up/ Discharge
Days	**-28 to -2**	**-1**	**1**	**2 to 6**	**7**
Informed Consent[a]	X				
Inclusion/Exclusion	X	X			
Demography	X				
Medical/Surgical & Smoking History	X				
Prior/Concomitant Medication	X	X	X	X	X
Complete Physical Examination[b]	X				X
Brief Physical Examination[c]		X			
Clinical Chemistry Haematology[d]	X	X			X
Serology (hepatitis B surface antigen, hepatitis C antibody, and HIV)	X				
Creatinine Clearance[e]	X				
Urinalysis[f]	X	X			X
Alcohol/Urine Drug Screen/Cotinine (nicotine)[g]	X	X			
Supine Blood Pressure/Pulse Rate	X	X	X[h]	X[h]	X[h]
Body Temperature	X	X			
Height/Weight and BMI Calculation[i]	X	X[i]			X[i]
Investigational Product Administration[j]			X		
PK Blood Collection[k]			X	X	X
Blood Sampling for Metabolite profiling[k]			X		
Urine Collection[k]			X	X	X
Faeces Collection[k]			X	X	X
Record AEs[l]	X	X	X	X	X
Record SAEs[l]	X	X	X	X	X
Paper Electrocardiogram[m]	X	X	X		X
Echocardiogram[n]	X				

Ophthalmic Examination[o]	X				

AE: adverse event; BMI: body mass index; HIV: human immunodeficiency virus; ICF: Informed Consent Form; IP: Investigational product; SAE: serious adverse event

[a] Informed consent will be collected prior to any study-related procedures being performed.

[b] A complete physical examination will be performed at screening and at discharge (Day 7). This examination will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities), and neurological systems.

[c] On Day -1 only a brief physical examination is required (including general appearance, skin, abdomen, cardiovascular system, and lungs).

[d] The healthy volunteer will fast for 4 hours prior to any clinical laboratory evaluations.

[e] Creatinine clearance will be calculated at screening using the Cockroft-Gault formula.

[f] Urine samples will be collected along with the other clinical laboratory evaluations. Urinalysis to be performed by standard dipstick analysis. Microscopy should only be performed if the urinalysis shows a positive result.

[g] Alcohol will be assessed by an alcohol breath test. Smoking will be assessed by performing a breath carbon monoxide test. A positive test will constitute a value of greater than 10 ppm.

[h] Supine blood pressure and pulse rate will be measured after the healthy volunteer has rested in a supine position for at least 10 minutes prior to the evaluation. If possible, the same arm and equipment should be used for each evaluation (refer to Table 3 for time points).

[i] Height and weight will be evaluated at screening. Only weight will be evaluated at Day -1 and on Day 7. The healthy volunteers will be required to remove their shoes and wear light indoor clothing for these measurements.

[j] Eligible healthy volunteers will receive a single administration of IP on Day 1.

[k] Blood, plasma, urine, and faeces samples will be collected as per Table 3 for time points.

[l] Only SAEs will be collected from the time the ICF is signed. AEs will be collected from Day 1 after the IP administration. For unresolved AEs/SAEs a follow-up phone call can be conducted 5 to 10 days following discharge to monitor unresolved AEs/SAEs. Unresolved AEs/SAEs will not be monitored following the follow-up phone call.

[m] Electrocardiograms will be recorded in the supine position after the healthy volunteer has rested in this position for at least 10 minutes.

[n] Echocardiogram (as early as 28 days prior to administration of the IP) will be conducted at screening (will be considered the baseline value; no need to repeat) and for cause (on occurrence of cardiac events only).

[o] Ophthalmic examination (best corrected visual acuity, intraocular pressure, slit-lamp fundoscopy) will be conducted at screening (will be considered the baseline value; no need to repeat) and for cause (on occurrence of AE only).

Table 3 Detailed Study Plan during residential period

t (hours)	PK Blood Collection[a]	[^{14}C] Whole Blood[b]	[^{14}C] plasma[c]	Urine Collection (20 mL aliquot)[d, f]	Faeces Collection[d, f]	Supine Blood Pressure	Blood sampling for metabolite ID[e]
0	X	X	X	X	X	X	X
0.5	X	X	X	X			
1	X	X	X				
1.5	X	X	X			X	
2	X	X	X				X
2.5	X	X	X				
3	X	X	X				
3.5	X	X	X				
4	X	X	X				X
6	X	X	X			X	
8	X	X	X	X			
12	X	X	X				X
24	X	X	X	X	X	X	X
48	X	X	X	X	X	X	X
72	X	X	X	X	X	X	X
96	X	X	X	X	X	X	
120	X	X	X	X	X	X	
144	X	X	X	X	X	X	
168	X	X	X	X	X	X	

[a] Blood (4 mL blood to produce 2 mL plasma for assessment of selumetinib and metabolite).

[b] Blood (4 mL for [^{14}C] radioactivity determination is whole blood). Collection for radioactivity assessment may cease if less than 1% of the radioactive dose is detected in 2 consecutive plasma or urine samples.

[c] Blood (4 mL to produce 2 mL for [^{14}C] radioactivity determination in plasma). Collection for radioactivity assessment may cease if less than 1% of the radioactive dose is detected in 2 consecutive plasma samples.

[d] Times indicated in the table present the stop-time of pooled collection. If emerging data indicates that adequate dose recovery has not been achieved after 7 days then some healthy volunteers may be asked to continue urine and/or faecal collections for a further 3 days either on an inpatient or an outpatient basis, and if adequate dose recovery is still not achieved, some healthy volunteers could be asked to return to the study centre approximately 7 days later, for a further 24 hour collection. Additional 24 hour collections of urine and/or faeces may continue until >90% mass balance cumulative recovery has been achieved or radioactivity counts are <1% on 2 consecutive samples (or recovery in urine/faeces in a 24 hour period is less than 1% of total administered dose of radioactivity on two consecutive collections).

[e] Plasma (3 x 9 mL blood to produce plasma) for metabolite profiling and identification .

[f] A portion of each sample will be sent to AstraZeneca Oncology iMed Alderley Park for metabolite identification, the remainder of the sample will be retained at for analysis of radioactivity.

3.2 Rationale for study design, doses and control groups

Healthy male volunteers are considered appropriate because the PK data generated will not be influenced by any disease process or concomitant medication. It is expected that 6 healthy volunteers will be sufficient to provide a reliable estimate of rates and routes of excretion.

Selumetinib incorporating 22.57 MBq (610 μCi) of [^{14}C] will be administered as a single dose of 75 mg (3 x 25 mg). This gives an effective dose (ED) of 4.52 mSv which falls within the radiolabeled category II dose, World Health Organisation 1977 and category IIb, International Commission on Radiological Protection 1992 guidelines.

The dose level of 75 mg is considered to be in the therapeutic dose range and is high enough to fully characterise the single oral dose PK of the parent compound and to enable metabolite quantification and identification, as part of a separate study. A dose of 75 mg twice daily is being investigated in ongoing efficacy studies of selumetinib. A radioactive dose of 22.57 MBq is considered to be the minimum dose of radioactivity that will be sufficient to achieve the study objectives.

4. SUBJECT SELECTION CRITERIA

Investigator(s) should keep a record, the healthy volunteer screening log, of healthy volunteers who entered prestudy screening.

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

4.1 Inclusion criteria

For inclusion in the study healthy volunteers should fulfil the following criteria:

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

2. Regular bowel movements (ie, on average production of at least 1 stool per day).

3. Healthy male volunteers aged 50 to 65 years (inclusive) with suitable veins for cannulation or repeated venipunctures. (Healthy as determined by medical history, physical examination, laboratory parameters, ECG, echocardiogram, and eye examination performed predose.)

4. Have a body mass index (BMI) between 18 and 32 kg/m^2 inclusive and weigh at least 50 kg and no more than 100 kg, inclusive.

5. Calculated creatinine clearance (CRCL) greater than 50 mL/min using Cockcroft-Gault formula.

4.2 Exclusion criteria

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

1. Current or past history of central serous retinopathy or retinal vein thrombosis, intraocular pressure greater than 21 mmHg or uncontrolled glaucoma.

2. Radiation exposure from clinical studies, including that from the present study, excluding background radiation but including diagnostic X-rays and other medical exposures, exceeding 5 mSv in the last 12 months or 10 mSv in the last 5 years. No occupationally exposed worker, as defined in the Ionising Radiation Regulations 1999, shall participate in the study.

3. Left ventricular ejection fraction <55%.

4. Involvement in the planning and/or conduct of the study (applies to AstraZeneca, and staff).

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

6. History or presence of gastrointestinal, hepatic, or renal disease or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs.

7. Any clinically important illness, medical/surgical procedure, or trauma within 4 weeks of the IP administration.

8. Any clinically important abnormalities in clinical chemistry, haematology, or urinalysis results as judged by the Investigator.

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

10. Any healthy volunteer with a clinically important abnormality in vital signs as assessed by the Investigator.

11. Any healthy volunteer with any clinically important abnormalities in their 12-lead ECG as assessed by the Investigator.

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

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

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

15. Positive screen for drugs of abuse, cotinine (nicotine) or alcohol at screening or admission to the unit prior to the IP administration.

16. 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.

17. 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.

18. Use of drugs with enzyme inducing properties such as St John's Wort within 4 weeks prior to the IP administration.

19. Use of any prescribed or non-prescribed medication including antacids, analgesics other than paracetamol/acetaminophen, herbal remedies, vitamins or excluding routine vitamins but including megadose (intake of 20 to 600 times the recommended daily dose) and minerals during the 3 weeks prior to the IP administration or longer if the medication has a long half-life. Exceptions may apply if considered not to interfere with the objectives of the study on a case by case basis if agreed by both the Principal Investigator and the Sponsor's medical monitor.

20. Any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges within 7 days prior to admission on Day -1.

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

22. 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 3 months of the administration of IP in this study. The period of exclusion starts 3 months after the final dose or 1 month after the last visit whichever is the longest. Note: volunteers consented and screened, but not randomised in this study or a previous phase I study, are not excluded.

23. Judgment by the Investigator that the volunteers 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.

24. Volunteers who have previously received selumetinib.

25. Volunteers who are vegans or have medical dietary restrictions.

26. Volunteers who cannot communicate reliably with the Investigator.

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

Procedures for withdrawal of incorrectly enrolled volunteers see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

- Healthy volunteers will be fasted from 10 hours prior to the IP administration through 4 hours after administration. No fluids will be allowed from 1 hour prior to IP administration until 1 hour after IP administration, except the water needed (240 mL) to consume the IP. Thereafter, healthy volunteers will be allowed to have free access to water (see Section 5.5.2).
- The volunteer must be semi-supine (minimum of 30 degrees) for 4 hours following each IP administration unless specified for certain assessments eg, ECG.
- The healthy volunteers will be fasted for 4 hours prior to any clinical laboratory evaluations.
- Volunteers will be asked to abstain from grapefruit or grapefruit juice, Seville oranges, quinine (eg, tonic water) within 7 days prior to admission on Day -1.
- Volunteers will be asked to abstain from alcohol for 72 hours before admission on Day -1.
- During residency, volunteers will receive a standard high fibre diet and should abstain from consuming alcohol, high energy drinks (e.g. Red Bull), grapefruit-containing products, food containing poppy seeds, and any over the counter medication or herbal preparations until after their final follow-up visit on Day 7 has been completed. Volunteers should also limit their caffeine intake to equivalent of 3 cups of coffee per day (1 cup =12 oz soda, 6 oz coffee, or 8 oz tea). No additional food or beverages must be consumed whilst in the study centre.
- Volunteers will be required to abstain from blood or plasma donation until 3 months after the final medical examination on Day 7.
- If a volunteer does not comply with these restrictions or test positive to any laboratory tests (eg, drugs of abuse and/or alcohol) they may be excluded or withdrawn from the study.
- Male volunteers with sexual partners who are pregnant or who could become pregnant (ie, women of child-bearing 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 IP administration.

- Volunteers should not take vitamin E supplements or multivitamin supplements. Throughout the study, healthy volunteers should avoid the addition of any concomitant medications, in particular any that are likely to affect the metabolism of selumetinib (eg, CYP1A2 or 3A4 inhibitors or inducers), unless considered clinically essential for management of concurrent conditions as judged by the Investigator.
- Volunteers should avoid excessive sun exposure and use adequate sunscreen protection, if sun exposure is anticipated. Volunteers should use sunscreen for up to 14 days after the administration of [^{14}C]-selumetinib.
- Volunteers will be required to avoid excessive exercise during the study.

5.2 Subject enrolment and initiation of investigational product

The Principal Investigator will:

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

2. Assign potential volunteer a unique enrolment number, beginning with 'E#'.

3. Determine volunteer eligibility. See Sections 4.1 and 4.2.

If a volunteer withdraws from participation in the study, then his enrolment code cannot be reused. Enrolment codes will be assigned strictly sequentially as volunteers become eligible for enrolment.

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

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

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

The AstraZeneca CPA 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(s)

Table 4 Formulation of Investigational Product

Investigational product	Dosage form and strength	Manufacturer
Selumetinib	Oral capsules 25 mg (free base equivalent) selumetinib Hyd Sulfate capsule containing 7.52 MBq (203.3 μCi) [^{14}C]-selumetinib	

5.5.2 Doses and treatment regimens

Each healthy volunteer will receive 3 x 25 mg [^{14}C]-selumetinib Hyd-Sulfate oral capsules (FBE) as a single dose on Day 1. Healthy volunteers should be fasted from 10 hours prior to IP administration and remain fasted for 4 hours after administration. No fluids will be allowed from 1 hour prior to IP administration until 1 hour after IP administration, except the water needed (240 mL) to consume the IP. Thereafter, healthy volunteers will be allowed to have free access to water.

5.5.3 Labelling

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

5.5.4 Storage

Selumetinib capsules are supplied in 50 mL DUMA high density polypropylene (HDPE) bottles with DUMA polypropylene cap and integral desiccant.

The IP should be kept in a secure place under appropriate storage conditions. The IP label on the bottle specifies the appropriate storage.

5.6 Concomitant and post-study treatment(s)

Use of concomitant medications, herbal supplements, and/or ingestion of foods that significantly modulate CYP3A4 and/or CYP1A2 activity or which are significantly metabolised by CYP3A4 and/or CYP1A2 should be avoided. Any prescribed or non prescribed medication including drugs with hepatic enzyme-altering properties, such as St

John's wort, antacids, analgesics, herbal remedies, vitamins, and minerals should be avoided for 3 weeks (or longer depending on the medication's half-life) before administration of the IP until after the final follow-up visit (see Section 4.2).

Healthy volunteers should abstain from using any medication, over-the-counter remedies, herbal medications, high-dose or "mega" vitamins, or medicines purchased via the Internet from 3 weeks before dosing until after follow-up. 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.

Other medication, which is considered necessary for the healthy volunteer's safety and well being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the paper Case Report Form (CRF).

5.7 Treatment compliance

The date and time of administration of all study drugs (including IPs) should be recorded in the appropriate sections of the CRF.

5.7.1 Accountability

The IP provided for this study will be used only as directed in the study protocol. The IP will be administered under supervision.

5.8 Discontinuation of investigational product (Not applicable)

5.9 Withdrawal from study

Healthy volunteers are at any time free to withdraw from study (IP and assessments), without prejudice to further treatment (withdrawal of consent). These healthy volunteers 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 6.4.3 and 6.4.4).

Withdrawn healthy volunteers will not be replaced.

6. COLLECTION OF STUDY VARIABLES

It is important that PK sampling occurs as close as possible to the scheduled time (see Table 2 and Table 3). In order to achieve this, other assessments scheduled at the same time may be initiated prior to the time point. The sequence at a particular time point is:

1. 12-lead ECG.

2. Blood pressure and pulse rate (and body temperature).

3. Pharmacokinetic blood sample.

4. Safety laboratory assessment blood sample.

5. Pharmacokinetic urine sample.

Predose assessments may be performed up to 60 minutes prior to IP administration.

For occasions when more than 1 assessment is required at a particular time point, PK blood samples should be prioritised.

6.1 Recording of data

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

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

6.2 Data collection at enrolment and follow-up

Following a signed informed consent, healthy volunteers will be screened for eligibility to be enrolled in the study.

6.2.1 Enrolment procedures

At enrolment each potential volunteer will provide written informed consent prior to starting any study-specific procedures.

Demographic data and other characteristics will be recorded and will include date of birth, gender, race, ethnicity, alcohol consumption, and smoking history.

Each volunteer will undergo screening during the 28 days prior to Day -1 to confirm eligibility. This will consist of:

- Review of inclusion and exclusion criteria
- A standard medical, surgical, and smoking history of the volunteer inclusive of prior and concomitant medications
- A complete physical examination
- Eye examination
- Height and weight measurements and calculation of BMI
- Vital sign measurements (supine pulse rate and blood pressure)
- Recording of 12-lead ECG
- Echocardiogram

- Collection of blood sample for predose safety laboratory assessments (clinical chemistry and haematology), and screening for hepatitis B virus surface antigen, antibodies to hepatitis C virus, and HIV.
- Collection of urine sample for routine urinalysis and urine microscopy (if there is an abnormal urinalysis result), drugs of abuse, alcohol, and cotinine
- Serious adverse event (SAE) recording

6.2.2 Follow-up procedures

The final medical assessment on Day 7 or on the last day of urine/faecal collection (whichever is later) will include the assessment of concomitant medication, complete physical examination, clinical chemistry, haematology, PK blood collection, urinalysis, faeces collection, supine blood pressure and pulse rate, weight and record AEs/SAEs.

6.3 Efficacy (Not applicable)

6.4 Safety

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

6.4.1 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 IP has been administered.

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

6.4.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, screening, treatment, residency, and follow-up [Day 7]), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect

- Is an important medical event that may jeopardise the 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 to the CSP.

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse events will be collected from informed consent up to Day 7 or the last day of urine/faecal collection (whichever is later). Serious AEs will be recorded from the time of informed consent.

Follow-up of unresolved adverse events

Any AEs that are unresolved on Day 7 or the last day of urine/faecal collection (whichever is later), are to be followed up by the Investigator. A follow-up phone call can be conducted 5 to 10 days following discharge on Day 7 or the last day of PK blood sample collection (whichever is later), to monitor unresolved AEs. Adverse events will not be monitored following the follow-up phone call.

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

Variables

The following variables will be collected for each AE;

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- 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 serious AE
- Date Investigator became aware of serious AE

- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Description of AE

The following intensity ratings will be used:

1. Mild (awareness of sign or symptom, but easily tolerated)
2. Moderate (discomfort sufficient to cause interference with normal activities)
3. Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs.

Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2.

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 IP 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 IP?"

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

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

Adverse Events based on signs and symptoms

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

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the Clinical Study Report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, ECGs, and other safety assessments should therefore only be reported as AEs if they fulfil any of the SAE criteria.

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

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

NB. Cases where a healthy volunteer shows an AST or ALT ≥3 x upper limits 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.

6.4.4 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then Investigators or other study centre staff 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 is undertaken immediately. Investigators or other study centre staff 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.

Investigators or other study centre staff send relevant CRF modules by fax to the designated AstraZeneca representative.

The reference document for definition of expectedness/listedness is the Investigator's Brochure for the AstraZeneca drug.

6.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be collected at the time points indicated in the Study Plan (see Table 2 and Table 3).

The following laboratory variables will be measured:

Table 5 Laboratory safety variables

Haematology[a]	**Clinical Chemistry**[a]	**Virology**	**Urinalysis**[b]	**Drugs of Abuse**
Basophils	Alanine Aminotransferase (ALT)	Hepatitis B Surface Antigen	Bilirubin	Amphetamines
Eosinophils	Albumin	Hepatitis C Antibody	Blood	Barbiturates
Haematocrit (Packed Cell Volume- PCV)	Alkaline Phosphatase	Human Immunodeficiency Virus (HIV) Antibody	Glucose	Benzodiazepines
Haemoglobin	Aspartate Aminotransferase (AST)		Ketones	Cocaine
Lymphocytes	Bicarbonate		Leukocytes	Marijuana/Cannabis.
Mean Cell Haemoglobin (MCH)	Bilirubin (Total)		Nitrates	Methadone
Mean Cell Haemoglobin Concentration (MCHC)	Bilirubin (Direct) (only if Total is elevated)		pH	Methamphetamine
Mean Cell Volume (MCV)	Calcium		Protein	Ecstasy
Monocytes	Chloride		Specific gravity	Morphine/Opiates
Neutrophils	Creatinine		Urobilinogen	Phencyclidine

Haematology[a]	**Clinical Chemistry**[a]	**Virology**	**Urinalysis**[b]	**Drugs of Abuse**
Platelet Count	Gamma Glutamyl Transpeptidase (GGT)			Tricyclic Antidepressants
Red Blood Cell (RBC) Count	Glucose (Fasting)			
White Blood Cell (WBC) Count	Potassium			
	Phosphate (Inorganic)			
	Protein (Total)			
	Sodium			
	Urea			

[a] The healthy volunteers will be fasted for 4 hours prior to any clinical laboratory evaluations.
[b] Urinalysis to be performed by standard dipstick analysis. Microscopy should only be performed if the urinalysis shows a positive result.

Blood will be tested for hepatitis B surface antigen, antibodies to hepatitis C, and antibodies to HIV at screening. CRCL will be calculated at screening using the Cockcroft-Gault formula.

Urine will be tested at screening and on Day -1 for drugs of abuse. Urine will be collected at the study centre. Alcohol will be assessed by an alcohol breath test. Smoking will be assessed by performing a breath carbon monoxide test. If a volunteer tests positive for drugs of abuse, a retest may be performed and the volunteer may be excluded from entering the study, as judged by the Investigator.

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

The safety laboratory samples will be analysed using routine methods at

NB. 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.

6.4.6 Physical examination

Physical examinations will be performed at the time points indicated in Table 2.

A complete physical examination will be performed during screening and on Day 7. This examination will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities), and neurological systems. On Day -1 only a brief physical examination is required (including general appearance, skin, abdomen, cardiovascular system, and lungs).

6.4.7 ECG

The ECG assessments will be performed at the time points indicated in Table 2.

6.4.7.1 Resting 12-lead ECG

Electrocardiograms will be recorded in the supine position after the healthy volunteer has rested in this position for at least 10 minutes. Only the overall evaluation (normal/abnormal) will be captured in the CRF. Any abnormalities (including corrected QT interval [QTc] values) should be reviewed by a cardiologist or an appropriately qualified person.

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

6.4.8 Echocardiogram

Echocardiogram will be performed at screening to determine LVEF.

A complete high quality standardised 2-D with Doppler echocardiographic examinations should be performed by an experienced sonographer (preferably with the same sonographer performing all echocardiograms for a given volunteer) including evaluation of both systolic and diastolic function. Ejection fraction determinations should be determined quantitatively based on bi-plane measurements of end diastolic and end systolic left ventricular volumes.

6.4.9 Vital signs

Vital signs assessments will be performed at the times indicated in Table 2.

6.4.9.1 Pulse and blood pressure

Supine blood pressure and pulse rate will be measured using standard equipment after 10 minutes rest on a bed. Additional blood pressure/pulse assessments may be taken for safety at the discretion of the Investigator or delegate.

6.4.9.2 Height and weight

Height (cm) and weight (kg) will be evaluated at screening and BMI (kg/m^2) will be calculated. Only weight will be evaluated at Day -1 and on Day 7. The healthy volunteers will be required to remove their shoes and wear light indoor clothing for these measurements. When requested or judged necessary for the program, body weight and/or BMI can be measured at additional time points.

6.4.9.3 Body temperature

Body temperature will be measured in degrees Celsius using an automated thermometer at the times indicated in the Study Plan (see Table 2).

6.4.10 Ophthalmology

A full ophthalmologic examination including a slit-lamp fundoscopy, best corrected visual acuity, and intraocular pressure measurement must be performed at screening for all volunteers. If a volunteer experiences visual disturbance the ophthalmological algorithm should be followed for diagnosis and management of these symptoms. Volunteers should undergo an ophthalmological examination and Optical Coherence Tomography scans should be considered.

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.

6.5 Patient reported outcomes (PRO) (Not applicable)

6.6 Pharmacokinetics

6.6.1 Collection of samples

Separate blood samples will be taken for the determination of total blood radioactivity, selumetinib (and N-desmethyl selumetinib), and [^{14}C] radioactivity in plasma and for metabolic profiling.

Venous blood samples for the determination of concentrations of total radioactivity in whole blood (approximately 4 mL) and plasma (approximately 4 mL) will be taken at the times presented in the Study Plans (Table 2 and Table 3). The actual date and time of collection will be recorded in the appropriate sections of the CRF.

Venous blood samples for the determination of concentrations of selumetinib and N desmethyl selumetinib (approximately 2 mL of whole blood) in plasma will be taken at the times presented in the Study Plans (Table 2 and Table 3). The actual date and time of collection will be recorded in the appropriate sections of the CRF.

Venous blood samples will be taken for use in an additional study in order to quantify and characterise metabolites in plasma. Approximately 3 x 9 mL of blood will be taken at the times presented in the Study Plans (Table 2 and Table 3). The actual date and time of collection will be recorded in the appropriate sections of the CRF.

Urine samples for determination of total radioactivity in urine will be taken at the time intervals presented in the Detailed Study Plan (Table 3). For the pooled urine collections, healthy volunteers will void all urine before dosing, and a predose urine sample will be retained for further metabolite identification studies. Following consumption of the radioactive dose, each healthy volunteer's urine will be collected as voided into screw top plastic containers, using separate containers for each collection period. The total urine volume of each urine collection will be recorded. The actual start and stop dates and times of the pooled collection will be recorded in the appropriate sections of the CRF. Samples collected must be kept refrigerated (approximately 4°C) during each collection period.

Following consumption of the radioactive dose, each healthy volunteer's faeces will be collected into pre-weighed rigid polypropylene containers (with lids), contained in bags. Individual containers will be used for each 24 hour collection period. All tissue wipes will be collected and put into the relevant faecal bag (tissue wipes are to be kept separate from the actual faecal samples). For hygiene purposes, more than 1 faecal sampling pot can be requested during each collection period. The weight of faeces collected will be recorded for each sample collection period and included in the database and listings. The actual start and stop dates and times of the pooled collection will be recorded in the appropriate sections of the CRF.

A portion of each urine and faecal sample will be sent to AstraZeneca Oncology iMed Alderley Park to characterise metabolites in urine and faeces.

Should a healthy volunteer vomit within 6 hours of IP administration, all vomitus will be collected into preweighed rigid polypropylene containers (with lids), contained in bags, including all tissue wipes used. Instances of vomiting will be recorded as an AE, and date and time of vomiting will be recorded on the appropriate AE CRF, in addition to on the container label.

Blood, urine, faeces, and any vomitus samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

For blood volume see Section 7.1.

6.6.2 Determination of drug concentration

Samples for determination of selumetinib and N-desmethyl selumetinib concentration in plasma will be analysed by on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report. All samples still within the known stability of the analytes of interest (ie, Selumetinib and N-desmethyl selumetinib) at time of receipt by the bioanalytical laboratory will be analysed.

The analysis of radioactivity in whole blood and plasma will be performed by using Liquid Scintillation Counting (LSC) methodology.

The analysis of radioactivity in the urine will be performed by Bioresearch, using LSC methodology.

The analysis of radioactivity in faeces will be performed by Bioresearch, using standard combustion followed by LSC methodology. Full details will be included in the CSR.

The analysis of radioactivity in vomitus will be performed by Bioresearch, using standard combustion followed by LSC methodology.

The mass balance output will be provided as a separate report which can be appended to the CSR.

As part of a further study performed by AstraZeneca Oncology iMed, Alderley Park, profiling and characterisation of the radioactive urinary and faecal components will be carried out using appropriate analytical techniques. These results will be reported separately from the CSR.

Full details of the analytical methods used will be detailed in the CSR.

6.7 Pharmacodynamics (Not applicable)

6.8 Pharmacogenetics (Not applicable)

6.9 Health economics (Not applicable)

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 as follows:

Table 6 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	5	4	20
	Haematology	2	4	8
Pharmacokinetic determination of selumetinib and N-desmethyl selumetinib concentrations in plasma		2	19	38
Pharmacokinetic determination of [^{14}C]-radioactivity in plasma		4	19	76
Pharmacokinetic determination of [^{14}C]-radioactivity in whole blood		4	19	76
Blood sampling for metabolite profiling		27	7	189
Total				**407**

The number of samples taken, as well as the volume required for each analysis, maybe changed during the study (ie, if additional samples are drawn for repeated safety assessments). However, the maximum volume to be drawn from each 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 15 years following the Last Subject Last Visit (LSLV) in the study. The samples should be protected from light to control or minimise the formation of amides. The results from future analysis will not be reported in the CSR but separately in a Scientific Report.

7.2.1 Pharmacokinetic and/or pharmacodynamic samples

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

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR. Anonymised samples will be retained for no more than 5 years after the CSR is finalised.

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

7.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures 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 collected from the healthy volunteer unless agreed with AstraZeneca and appropriate labelling, shipment, and containment provisions are approved.

7.4 Chain of custody of biological samples

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

The Principal Investigator will keep full traceability of collected biological samples from the healthy volunteers while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

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

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

If a 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 analysed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator:

- Ensures the healthy volunteer's 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 centre, are immediately identified, disposed of/destroyed, and the action documented.
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study centre.
- Ensures that the healthy volunteer and AstraZeneca are informed about the sample disposal.

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

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Subject data protection

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

8.3 Ethics and regulatory review

Approval to administer the chosen dose of radioactivity will be sought from the Department of health (United Kingdom) Administration of Radioactive Substances Advisory Committee (ARSAC) prior to commencing the study. As part of the CSP review process, the CSP will be reviewed and approved by the ARSAC certificate holder.

An Ethics Committee (EC) should approve the final CSP, including the final version of the ICF 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 EC, and to the study centre staff.

The opinion of the EC should be provided in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any healthy volunteer into the study.

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

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the CSP should be re-approved by the EC annually.

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

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

AstraZeneca will provide Regulatory Authorities, ECs and Principal Investigator with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions, where relevant.

The Principal Investigator is responsible for providing the EC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. 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 at the centre will:

- Ensure each healthy volunteer is provided 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 ICF will be provided for genotyping.

- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File.
- Ensure a copy of the signed ICF is given to the healthy volunteer.
- Ensure that any incentives for healthy volunteers who participate in the study as well as any provisions for healthy volunteer's harmed as a consequence of study participation are described in the ICF that is approved by an EC.

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 CSP (Revised CSP).

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

AstraZeneca will distribute any subsequent amendments and new versions of the CSP to the Principal Investigator(s). For distribution to EC see Section 8.3.

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

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

8.6 Audits and inspections

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

9. STUDY MANAGEMENT

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 centre to:

- Determine the adequacy of the facilities
- Determine availability of appropriate healthy volunteers for the study

- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities with regard to CSP adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a CSA 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 CSP and related documents with the study centre staff and also train them in any study specific procedures and system(s) utilised.

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 centre, including visits to:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the CSP, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that IP accountability checks are being performed.
- Perform source data verification (a comparison of the data in the CRFs with the healthy volunteer's medical records at the study centre 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, study centre 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 or destroyed accordingly, and the action is documented, and reported to the healthy volunteer.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the study centre needs information and advice about the study conduct.

9.3.1 Source data

Refer to the CSA for location of source data.

9.4 Study agreements

The Principal Investigator at the study centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP 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 CSA 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 follows the principles outlined in the CSA.

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 Q3 2013 and to end by Q4 2013.

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

10. DATA MANAGEMENT

Data management will be performed by

When the completed CRFs have been scanned and indexed, the data are entered into the study database and proofread.

The data collected through third party sources will be obtained and reconciled against study data.

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

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, signed, and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

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

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of efficacy variable(s) (Not applicable)

11.2 Calculation or derivation of safety variable(s)

11.2.1 Other significant adverse events (OAE)

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 discontinuation of IP due to AE (DAEs). Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered OAEs and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

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

11.3 Calculation or derivation of patient reported outcome variables (Not applicable)

11.4 Calculation or derivation of pharmacokinetic variables

The PK analyses of [^{14}C] radioactivity concentration data in whole blood, plasma, urine, and faeces and selumetinib and N-desmethyl selumetinib concentration data in plasma will be performed at . Pharmacokinetic analyses will be conducted according to Standard Operating Procedures unless otherwise specified.

Total [^{14}C] radioactivity in whole blood and plasma will be converted to concentration equivalents of selumetinib based on the actual specific activity of the dose.

Pharmacokinetic parameters will be determined using standard noncompartmental methods with WinNonlin® Professional Version 5.2 or higher
or SAS® Version 9.2 or higher
Actual elapsed time from dosing will be used for final blood-based

PK parameter calculations. Pharmacokinetic parameter units will be consistent with the concentration units specified in the bioanalytical data.

The following PK parameters will be determined for plasma selumetinib and N-desmethyl selumetinib and whole blood and plasma [^{14}C] radioactivity:

AUC	Area under the concentration-time curve in the sampled matrix from time zero to infinity, calculated by linear up/log down trapezoidal summation
$AUC_{(0-t)}$	Area under the concentration-time curve in the sampled matrix 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 concentration-time curve in the sampled matrix from time zero to the time of 12 hours, calculated by linear up/log down trapezoidal summation
C_{max}	Maximum concentration in the sampled matrix, obtained directly from the observed concentration versus time data
t_{max}	Time to C_{max}
CL/F	Apparent oral plasma clearance (selumetinib only, whole blood and plasma radioactivity only)
V_{ss}/F	Apparent volume at distribution equilibrium, mean residence time (MRT)*CL/F (selumetinib only, whole blood and plasma radioactivity only)
V_z/F	Apparent volume at distribution (selumetinib only, whole blood and plasma radioactivity only)
$t_{1/2}$	Terminal half-life
λ_z	Terminal rate constant
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}
$C_{max}(PL)/C_{max}(PR)$	C_{max} ratio of plasma selumetinib or N-desmethyl selumetinib (PL) to plasma radioactivity (PR)
$C_{max}(WBR)/C_{max}(PR)$	C_{max} ratio of whole blood radioactivity (WBR) to PR
AUC(PL)/AUC(PR)	AUC ratio of PL to (PR)
AUC(WBR)/AUC(PR)	AUC ratio of WBR to PR

The following PK parameters for plasma selumetinib and N-desmethyl selumetinib and whole blood and plasma [^{14}C] radioactivity will be calculated for diagnostic purposes and listed, but will not be summarised:

$t_{1/2}$, Interval	The time interval of the log-linear regress to determine $t_{1/2}$
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 for that specific profile will not be reported)

The ratio of plasma selumetinib to plasma radioactivity concentrations, N-desmethyl selumetinib concentrations to plasma radioactivity concentrations, and whole blood to plasma [^{14}C] radioactivity concentrations and the distribution of radioactivity in blood cells (expressed as percentage) will be reported for each sampling time to assess the radioactivity distribution in blood based matrices over time. The distribution of radioactivity in red blood cells will be calculated by the following equation:

$$\frac{Cwb-(1-Ht)\times Cp}{Cwb}\times 100\%$$

where Cwb is concentration in whole blood, Cp is concentration in plasma and Ht is haematocrit [Ht will be the mean value of the laboratory Ht data obtained from Day -1 and follow-up].

The following PK parameters will be computed from the urine total radioactivity:

Ae_u	Amount recovered in urine during each collection interval (t1 to t2), calculated as urine concentration or concentration equivalent x urine volume
Cum Ae_u	Cumulative amount recovered in urine
fe_u	Percent (or fraction) of actually administered dose/radioactivity recovered in urine during each collection interval and overall
Cum fe_u	Cumulative percent (or fraction) of actually administered dose/radioactivity recovered in urine

The following parameters will be computed from the faecal total radioactivity versus time data:

Ae_f	Radioactive amount recovered in faeces during each collection interval (t1 to t2), calculated as [faecal radioactive concentration equivalent x faeces weight]
Cum Ae_f	Cumulative radioactive amount recovered in faeces
fe_f	Percent (or fraction) of actually administered radioactivity recovered in faeces during each collection interval and overall
Cum fe_f	Cumulative percent (or fraction) of actually administered radioactivity recovered in faeces

For all calculations, the faecal weights reported by the bioanalytical laboratory (the weight on which subsequent sample processing is based) will be used in calculation of the faecal radioactivity recovery.

The total recovery of radioactivity (fe_{tot}; percent of administered radioactive dose recovered in urine and faeces overall) will be computed as the sum of the cumulative excretion in urine and faeces. If a healthy volunteer vomits, the emesis product will be collected during the 0 to 6 hour postdose period only for potential analysis of [^{14}C] radioactivity, and if appropriate, included in calculation of the total radioactivity excreted for this healthy volunteer.

Determination of metabolic profiling and metabolite identification will be performed on relevant plasma/urine/faeces samples. The relative systemic exposure of any major

metabolites will be calculated, if appropriate. This may be summarised in a separate study report.

11.5 Calculation or derivation of pharmacodynamic variable(s) (Not applicable)

11.6 Calculation or derivation of pharmacogenetic variables (Not applicable)

11.7 Calculation or derivation of health economic variables (Not applicable)

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

Statistical analyses will be performed by using SAS® version 9.2 or higher and, where appropriate, additional validated software.

12.1 Description of analysis sets

12.1.1 Safety analysis set

All healthy volunteers who received at least 1 dose of [^{14}C]-selumetinib IP and for whom any postdose data are available will be included in the safety population.

12.1.2 Pharmacokinetic analysis set

The PK analysis set will include all healthy volunteers who receive at least 1 dose of [^{14}C]-selumetinib and have at least 1 postdose PK measurement without important protocol deviations/violations or events thought to significantly affect the PK of the IP.

12.2 Methods of statistical analyses

Statistical analysis will be performed by Global Phase 1 Services using Standard Operating Procedures and Work Instructions, unless otherwise specified. Statistical analysis will be carried out by using the SAS® software. Other analyses than those stated below might be performed to gain information needed for the planning and analyses of future studies.

12.2.1 General principles

Given the exploratory nature, no formal statistical hypothesis testing will be performed in this study.

The statistical analysis will be descriptive and consist of subject listings, graphs, and summary statistics comprising geometric mean, coefficient of variation (CV%), arithmetic mean, standard deviation (SD), median, minimum (min), and maximum (max) values as appropriate.

Missing data will be assumed to be missing completely at random, causing a reduced sample size. Since the descriptive statistics will be presented in tables and individual data listings, no action will be taken to handle missing data.

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

12.2.2 Pharmacokinetics

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. A listing of individual urine sample collection start and stop dates/times as well as urine volumes will be provided for each urine collection. A listing of individual faecal sample collection start and stop dates/times as well as sample weights will be provided. Faecal weight will be reported by both the study centre (collected) and the bioanalytical laboratory (re-weighed for processing).

Pharmacokinetic variables will be summarised using appropriate descriptive statistics (eg, n, arithmetic mean, CV%, SD, geometric mean, geometric coefficient of variation [GCV%], min, median, and max). The geometric mean is calculated as the exponential of the arithmetic mean calculated from individual observations on a log scale. The GCV% is calculated as $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where s is the SD of the data on a log scale. Mean, SD, CV%, geometric mean, and GCV% will not be calculated for t_{max}.

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 max value will be reported from the individual data, and the min 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, min, median, and max.

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

A subject listing of all concentration-time data will be presented along with the descriptive statistics for all healthy volunteers. Figures of geometric mean concentration-time data will

be presented for plasma and whole blood [^{14}C] radioactivity concentrations and plasma selumetinib and N-desmethyl selumetinib concentrations combined, as appropriate. Individual subject concentration-time data for the respective blood-based analyte combination will be graphically presented on linear and semi-logarithmic scales.

The ratio of plasma selumetinib to plasma [^{14}C] radioactivity concentrations (expressed as a percentage) as well as the ratio of plasma N-desmethyl selumetinib to plasma [^{14}C] radioactivity concentrations (expressed as a percentage) for each sampling time will be listed by healthy volunteer and summarised using descriptive statistics, to assess the contribution of unchanged drug to the total radioactivity in plasma over time.

A subject listing of whole blood/plasma [^{14}C] radioactivity concentration-time ratios (expressed as a percentage) and percent distribution of radioactivity in blood cells will be presented and the data will be summarised by scheduled time using descriptive statistics.

Blood-based PK parameters will be summarised using descriptive statistics. Individual PK parameters will be presented along with descriptive statistics for all healthy volunteers.

Urine [^{14}C] radioactivity data will be summarised by scheduled collection intervals using descriptive statistics. Individual urine recovery data will be presented along with the descriptive statistics for all healthy volunteers.

Faecal [^{14}C] radioactivity data will be summarised using descriptive statistics. Individual faecal recovery data will be presented along with the descriptive statistics for all healthy volunteers.

The total recovery of radioactivity over the study duration will be computed as the sum of the cumulative excretion (as % of dose) in urine, faeces, and emesis (if any). Cumulative mean recovery of radioactivity-time profiles will be graphically presented for urine, faeces, and total (sum of urine plus faeces, plus emesis, if applicable). Individual cumulative recovery data (urine, faeces, and total) will be presented graphically and in tables along with the descriptive statistics for all healthy volunteers.

12.2.2.1 Interim analysis

The bioanalytical laboratory will calculate percent of radioactive dose recovered in urine and faeces in support of healthy volunteer release criteria. These values will be used for interim reporting purposes only to track radioactive dose recovered on an ongoing basis. These results will be part of the radioactivity report which will be included as an appendix to the CSR. Following database lock, the percent of radioactive dose recovered in urine, faeces, and overall, and related parameters will be calculated following Standard Operating Procedures (SOPs) and rounding procedures as described above and in Section 11.4. The values calculated by will be considered the final study results and presented in the body of the CSR.

12.2.3 Safety and tolerability measurements

All safety data (scheduled and unscheduled) will be presented in the data listings. Continuous variables will be summarised using descriptive statistics (n, mean, SD, min, median, max). Categorical variables will be summarised in frequency tables (frequency and proportion). Graphical presentations may be used as appropriate. Examples may include line graphs showing individual or mean development over time, and shift plots showing pre-treatment values on horizontal axis and post-treatment values on vertical axis.

All AEs will be collected for each healthy volunteer from the time of informed consent until Day 7 or the last day of urine/faecal collection (whichever is later). Adverse events that occur before administration will be reported separately.

Adverse events will be summarised by Preferred Term and System Organ Class using MedDRA vocabulary. Furthermore, listings of SAEs and AEs that led to withdrawal will be made and the number of healthy volunteers who had any AEs, SAEs, AEs that led to withdrawal, and AEs with severe intensity will be summarised.

Tabulations and listings of data for vital signs (blood pressure, pulse rate, and body temperature), and clinical laboratory tests will be presented. Where applicable, data will be summarised 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 (SI) units (where available) in the CSR.

Results from the physical examinations, ECGs, echocardiograms, and eye examinations will be presented in listings only.

Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics, but will be included in subject listings.

12.3 Determination of sample size

The number of healthy volunteers is based on the desire to gain adequate information on the primary endpoints of PK, metabolism, and safety profile whilst exposing as few healthy volunteers as possible to study procedures. Based on previous similar studies, 6 healthy volunteers are considered to be adequate for this purpose.

12.4 Data monitoring committee (Not applicable)

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 6.4.4.**

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

Name	Role in the study	Address & telephone number
	AstraZeneca CPA Program Director	
	AstraZeneca CPA Physician	
Serious adverse event reporting	24-hour emergency cover at central R&D site	
	Principal Investigator	

Name	Role in the study	Address & telephone number
	Project Manager (	
	Project Manager (	

13.2 Overdose

For the purposes of this study, exceeding the dosage requirements specified in this CSP represents an overdose. There is no known antidote for selumetinib. In case of suspected overdose, the 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 CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca IP occurs in the course of the study, then the Investigator or other study centre staff must inform the 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 relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.4.4. 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

It is not known whether selumetinib or its metabolites are excreted in human semen. Therefore, conception while on treatment must be avoided.

Healthy male volunteers with sexual partners who are pregnant or who could become pregnant (ie, women of child-bearing potential) should use barrier methods of contraception during the study and up to 14 days after completing the study to avoid pregnancy and/or potential adverse effects on the developing embryo. Healthy volunteers should avoid sperm donation during the study and up to 14 days after study completion.

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) occurring from the date of IP administration until 1 month after IP administration should, if possible, be followed up and documented.

14. LIST OF REFERENCES

Investigator's Brochure
Investigator's Brochure for Selumetinib (AZD6244) Edition 12. 25 February 2013

Clinical Study Protocol Appendix A

Drug Substance	Selumetinib
Study Code	D1532C00077
Edition Number	1

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Phase I, Single-centre, Non-randomised, Open-label, Pharmacokinetic and Mass Balance Study of Orally Administered [^{14}C]-selumetinib in Healthy Male Volunteers

---

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

I agree to the terms of this study protocol/amendment

AstraZeneca Research and Developn
site representative

Principal Research Physician

Signing on behalf of:

Medical Science Director

ASTRAZENECA SIGNATURE(S)

A Phase I, Single-centre, Non-randomised, Open-label, Pharmacokinetic and Mass Balance Study of Orally Administered [14C]-selumetinib in Healthy Male Volunteers

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

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

AstraZeneca Research and Development site representa

Global Product Statistician

SIGNATURE OF PRINCIPAL INVESTIGATOR

A Phase I, Single-centre, Non-randomised, Open-label, Pharmacokinetic and Mass Balance Study of Orally Administered [14C]-selumetinib in Healthy Male Volunteers

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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.:

Signature:

Clinical Study Protocol Appendix B

Drug Substance	Selumetinib
Study Code	D1532C00077
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 healthy volunteer was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the healthy volunteer's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

Clinical Study Protocol Appendix C

Drug Substance	Selumetinib
Study Code	D1532C00077
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.

AstraZeneca

Clinical Study Protocol Appendix D

Drug Substance	Selumetinib
Study Code	D1532C00077
Edition Number	1

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 healthy volunteer meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. 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 healthy volunteer who meets any of the following identification criteria in isolation or in combination:

- ALT 3 or more times the ULN
- AST 3 or more times the ULN
- TBL 2 or more times the ULN

When a healthy volunteer meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory paper CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the healthy volunteer meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

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 healthy volunteer meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory paper CRF

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

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

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

4.2 Potential Hy's Law Criteria met

If the healthy volunteer does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment in the presence of liver metastases (See Section 6)
- 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 healthy volunteers' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the healthy volunteer until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the three liver paper 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. ACTIONS REQUIRED WHEN POTENTIAL HY'S LAW CRITERIA ARE MET BEFORE AND AFTER STARTING STUDY TREATMENT

This section is applicable to healthy volunteers who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the healthy volunteers' condition compared with the last visit where PHL criteria were met
  - If there is no significant change no action is required
  - If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described is Section 4.2 of this Appendix

A 'significant' change in the healthy volunteer's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

At the first on study treatment occurrence of PHL criteria being, even if there has been no significant change the healthy volunteer's condition[#] compared with pre-study treatment visits, the Investigator will:

- Notify the AstraZeneca representative who will inform the central Study Team.
- Follow the subsequent process described is Section 4.2 of this Appendix.

A 'significant' change in the healthy volunteer's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

7. ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a healthy volunteer meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met chronic or progressing malignant disease or did the healthy volunteer meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Section 6?

If No: follow the process described in Section 4.2 of this Appendix

If Yes:

Determine if there has been a significant change in the healthy volunteers' condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required

- If there is a significant change follow the process described in Section 4.2 of this Appendix

A 'significant' change in the healthy volunteer's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

8. REFERENCES

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

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