Clinical Study Protocol

Drug Substance	Selumetinib
Study Code	D1532C00085
Edition Number	1

A Phase I Open-label, Single-center Study to Assess the Effect of the CYP3A4 inducer Rifampicin on the Pharmacokinetics of a 75 mg Single Oral Dose of Selumetinib (AZD6244; ARRY-142886) (Hyd-Sulfate) in Healthy Volunteers aged 18 to 45 years

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 Open-label, Single-center Study to Assess the Effect of the CYP3A4 inducer Rifampicin on the Pharmacokinetics of a 75 mg Single Oral Dose of Selumetinib (AZD6244; ARRY-142886) (Hyd-Sulfate) in Healthy Volunteers aged 18 to 45 years

Principal Investigator

Study center and number of subjects planned

This study will be conducted at a single study center, . Approximately 24 healthy volunteers will be enrolled in order to ensure at least 20 evaluable healthy volunteers complete the study. Withdrawn healthy volunteers will not be replaced; however, additional volunteers may be included in the study until such a time as 20 evaluable volunteers have completed all 3 treatments.

Study period		Phase of development
Estimated date of first healthy volunteer enrolled	Q1 2014	I
Estimated date of last healthy volunteer completed	Q2 2014	

Objectives

Primary objective

To investigate the effect of multiple 600 mg (2 x 300 mg) oral doses of rifampicin on the exposure of a single 75 mg oral dose of selumetinib in healthy volunteers.

Secondary Objectives

The secondary objectives of the study are:

- To investigate the pharmacokinetics (PK) of N-desmethyl selumetinib when selumetinib is administered with or without rifampicin.
- To determine the plasma concentration of rifampicin at 2 hours after administration during the rifampicin dosing period to monitor the exposure of the cytochrome P450 (CYP)3A4 inducer.

- To determine the 4β-hydroxycholesterol to cholesterol concentration ratios as a marker of CYP3A4 induction by rifampicin.

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

Exploratory Objective

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

The exploratory analysis will be reported separately.

Study design

This clinical study is designed as a Phase I, open-label, fixed sequence, single-center study to investigate the effect of rifampicin (a known CYP3A4 inducer) on the PK, safety and tolerability of a single 75 mg oral dose of selumetinib in healthy volunteers. Approximately 24 healthy male and female (of non-childbearing potential) volunteers aged between 18 to 45 years (inclusive), will be enrolled in the study. Withdrawn healthy volunteers will not be replaced; however, additional volunteers may be included in the study until such a time as 20 evaluable volunteers have completed both treatments. Screening procedures will only be performed for healthy volunteers who provide written informed consent.

The study will consist of 3 visits. Visit 1 will be a screening visit and will take place within 28 days of Visit 2. Visit 2 will be the treatment visit and the healthy volunteers will be resident at the study center from Day -1 up to Day 15. Visit 3 will be the follow-up visit and will take place 7 to 10 days after discharge on Day 15, Visit 2.

Healthy volunteers will be assigned to the following treatment schedule:

- Treatment A: Healthy volunteers will receive a single oral dose of 75 mg (3 x 25 mg) selumetinib on Day 1. Safety assessments will be performed and blood samples collected for PK analysis until Day 4.

- Treatment B: Following completion of assessments for Treatment A on Day 4, volunteers will receive single, daily, oral doses of 600 mg (2 x 300 mg) rifampicin on Days 4 to 11.

- Treatment C: On Day 12, volunteers will receive 600 mg (2 x 300 mg) rifampicin with a single oral dose of 75 mg (3 x 25 mg) selumetinib administered at the same time. Once daily rifampicin administrations will continue through to Day 14.

Safety assessments will be performed and blood samples collected for PK analysis until Day 15.

Target subject population

Healthy male and female (of non-childbearing potential) volunteers aged 18 to 45 years (inclusive) who are non-smokers, have a body mass index (BMI) between 18 and 30 kg/m^2 (inclusive) and weigh at least 50 kg and no more than 100 kg (inclusive), have a calculated creatinine clearance greater than 50 mL/min using the Cockcroft-Gault formula. Healthy volunteers with current or past history of central serous retinopathy or retinal vein thrombosis, intra-ocular pressure greater than 21 mmHg or uncontrolled glaucoma will be excluded.

Investigational product, dosage and mode of administration

A single administration of 75 mg selumetinib will be administered as 3 x 25 mg oral capsules (Treatment A).

Comparator, dosage and mode of administration

Healthy volunteers will receive single daily oral doses of 600 mg (2 x 300 mg) rifampicin on Days 4 to 11 and Days 13 to 14 (Treatment B). On Day 12, the volunteers will receive 600 mg (2 x 300 mg) rifampicin and 75 mg (3 x 25 mg) selumetinib at the same time (Treatment C).

Duration of treatment

Volunteers will participate in the study for approximately 8 weeks; including screening over 28 days. Volunteers will be resident in the study center from Day -1 until all study assessments are completed on Day 15, with a follow-up visit 7 to 10 days after discharge (Day 15).

Outcome variable(s):

- Pharmacokinetics

  The primary PK parameters will be: maximum observed plasma concentration (C_{max}), area under the plasma concentration-time curve from time zero to infinity (AUC), and area under plasma concentration-time curve to time of last measurable concentration ($AUC_{(0-t)}$).

  The secondary PK parameters will be: time to reach maximum observed concentration administration (t_{max}), area under the plasma concentration time curve from zero to 12 hours post-dose ($AUC_{(0-12)}$), terminal rate constant (λ_z), terminal elimination half-life ($t_{1/2}$), apparent oral clearance (CL/F), apparent volume of distribution at steady state (V_{ss}/F), apparent volume of distribution during the terminal phase (Vz/F), and mean residence time (MRT) for selumetinib, and AUC, C_{max}, t_{max}, $t_{1/2}$, λ_z, AUC_{0-12}, $AUC_{(0-t)}$, and the metabolite to parent AUC and C_{max} ratios (MR_{AUC} and MR_{Cmax}) for N-desmethyl selumetinib.

  Pharmacokinetic parameters will not be determined for rifampicin. Only the 2 hours post-dose plasma concentrations will be reported.

The following will be calculated for 4β-hydroxycholesterol and cholesterol: ratio of post-treatment (Day 12 or Day 14) to pre-treatment (Day 4 pre-dose) concentration.

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

Statistical methods

Pharmacokinetic parameters will be listed and summarized by analyte and treatment, as appropriate. Individual and geometric mean parameters will be presented graphically by treatment and analyte, as appropriate.

Following log-transformation, C_{max}, AUC, and $AUC_{(0-t)}$, of selumetinib will be separately analyzed by mixed effect analysis of variance model, fitting a fixed effect term for treatment (selumetinib + rifampicin [Treatment C] vs selumetinib alone [Treatment A]) and random effects for volunteer. Point estimates and adjusted 90% confidence intervals (CI) for the difference in treatment (selumetinib + rifampicin [Treatment C] or selumetinib alone [Treatment A]) will be constructed. The point estimate and adjusted 90% CIs will then be exponentially back transformed to provide point and CI estimates for the ratio of interest (ie, C_{max}, AUC, or $AUC_{(0-t)}$ of selumetinib contrasting with or without co-administration with rifampicin).

Analyses will be conducted separately for selumetinib and the metabolite N-desmethyl selumetinib.

Rifampicin concentrations will be summarized by study day using appropriate descriptive statistics. Results for 4β-hydroxycholesterol and cholesterol post-treatment to pre-treatment concentration ratios will be listed and summarised by analyte and study day using descriptive statistics.

The AEs will be coded using the Medical Dictionary for Regulatory Activities for System Organ Class and Preferred Term. Adverse events will be summarized for each treatment group by System Organ Class and Preferred Term. Medications will be classified according to the AstraZeneca Drug Dictionary.

Tabulations and listing of data for frequency and severity of adverse events and results of clinical laboratory tests, vital signs, 12-lead electrocardiograms, and physical examinations will be presented by treatment. The safety data will be presented by treatment and will include all healthy volunteers who received at least one dose of investigational product. For clinical laboratory tests, listings of values for each healthy volunteer will be presented with abnormal or out of range values flagged.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
λ_z	Terminal rate constant
$\%AUC_{ex}$	Percentage of AUC obtained by extrapolation
AE	Adverse event (see definition in Section 6.3.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve from time zero to infinity
$AUC_{(0-12)}$	area under the plasma concentration time curve from zero to 12 hours post-dose
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from time zero to the last quantifiable concentration
BLQ	Below the lower limit of quantification
BMI	Body mass index
CI	Confidence interval
CL/F	Apparent oral plasma clearance
C_{max}	Maximum concentration in plasma
CPA	Clinical Pharmacology Alliance
CPK	Creatine phosphokinase test
CrCL	Creatinine clearance
CSA	Clinical Study Agreement
CSR	Clinical study report
CV	Coefficient of variation
CYP	Cytochrome P450
DAE	Discontinuation of investigational product due to adverse event
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture

Abbreviation or special term	Explanation
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GCV%	Geometric coefficient of variation
GMP	Good Manufacturing Practice
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
IATA	International Air Transport Association
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
λ_z	Terminal rate constant
LFT	Liver function test
LIMS	Laboratory Information Management System
LLOQ	Lower limit of quantification
LSLV	Last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase kinase
MRT	Mean residence time
MR_{AUC}	AUC metabolite to parent ratio, N-desmethyl selumetinib AUC/selumetinib AUC
MR_{Cmax}	C_{max} metabolite to parent ratio, N-desmethyl selumetinib C_{max}/selumetinib C_{max}
n	Number of observations
ND	Not Determined
NOEL	No observed effects level
NSCLC	Non-small cell lung cancer
OAE	Other significant adverse event (see definition in Section 11.1.2)
PICTS	Phase I Clinical Trial System
PK	Pharmacokinetic(s)
Rsq	Coefficient of determination
SAE	Serious adverse event (see definition in Section 6.3.2).

Abbreviation or special term	Explanation
SD	Standard deviation
SPF	Sun protection factor
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal elimination half-life
t_{max}	Time to reach maximum observed concentration administration
ULN	Upper limit of normal
V_{SS}/F	Apparent volume of distribution at steady state
V_Z/F	Apparent terminal phase volume of distribution

1. INTRODUCTION

1.1 Background

Selumetinib (AZD6244; ARRY-142886) (Hyd-Sulfate) is a potent, selective, uncompetitive inhibitor of mitogen-activated protein kinase kinase (MEK), licensed for development by AstraZeneca Pharmaceuticals (hereafter referred to as AstraZeneca or the sponsor) from and is in development for the treatment of solid tumours. was responsible for the first in man study. The remainder of the clinical development programme for oncology indications is the responsibility of AstraZeneca. Phase II studies are ongoing in patients with advanced non-small cell lung cancer (NSCLC) and patients receiving adjuvant treatment for differentiated thyroid cancer, and a Phase III study in advanced NSCLC is planned.

1.1.1 Summary of relevant preclinical and clinical information to date

Preclinical experience with selumetinib is described in the current version of the selumetinib Investigator's Brochure (IB).

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

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

To date (as of 15 November 2013) approximately 1930 patients with cancer and approximately 50 healthy male volunteers had received selumetinib in clinical studies. Clinical experience with selumetinib as monotherapy and in combination with other anti-cancer agents is described in the IB.

1.2 Rationale for conducting this study

As selumetinib is metabolized by cytochrome P450 (CYP)3A4, it is important to understand whether the inhibition or induction of CYP3A4 influences selumetinib exposure. This study is designed to investigate the effect of co-administration of the potent CYP3A4 inducer rifampicin with selumetinib, as significant induction of CYP3A4 could potentially reduce selumetinib exposure, thus reducing efficacy.

The primary objective of this study is to assess any differences in the pharmacokinetics (PK) of selumetinib at a dose of 75 mg when administered with or without rifampicin.

1.3 Clinical safety

1.3.1 Adverse events in healthy volunteers

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

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

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

A summary of AEs reported within 24 hours of a single dose of 75 mg selumetinib monotherapy treatment in advanced cancer patients is provided in (Table 1). Adverse event data are available from Study D1532C00005 and Study D1532C00020 (65 advanced cancer patients in total). The most frequently reported AEs were decreased blood potassium (3/65 patients [4.5%]), diarrhea, headache and nausea (each reported for 2/65 patients [3.0%]). The event of decreased blood potassium occurred in 3 patients. All 3 patients had a low potassium value at baseline. All events (further decrease or similar value/baseline) were considered unrelated to selumetinib by the investigator. Confounding factors included concomitant drugs such as diuretics and steroids. These events were not considered to be clinically significant findings. All other AEs were reported in only 1 patient each.

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

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

MedDRA: Medical Dictionary for Regulatory Activities
a Study D1532C00005 (A; 25, 50, 75, 100 mg twice daily Hyd-Sulfate) and (B; single dose 75 mg Hyd-Sulfate vs 100 mg free-base) are 75 mg selumetinib capsule formulation.

1.3.3 Potential adverse events

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

Section 5.4 of the IB acts as Reference Safety Information of the IB and lists those events that are to be regarded as expected for regulatory reporting purposes.

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

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

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

The following AEs have been reported in a small number of advanced cancer patients treated with selumetinib but a causal relationship with selumetinib has not been established:

- Central serous retinopathy
- Retinal vein occlusion
- Pneumonitis/ Interstitial lung disease
- Muscle weakness
- Increase in CPK

Further information on the investigational product can be found in the IB.

1.3.4 Summary of adverse events with rifampicin

Rifampicin is an antibiotic used in combination with other antibiotics to treat active tuberculosis (generally 6 months treatment) or for the prevention of tuberculosis in susceptible close contacts or those who have become tuberculin positive (generally 3 months treatment). It is generally well tolerated although it stains body fluids (including urine and tears) orange and can discolor soft contact lenses. Rifampicin can cause transient increases in liver transaminases and occasionally, especially in those with pre-existing liver disease, more

serious liver toxicity can occur necessitating discontinuation of treatment. Other AEs on continuous treatment are less common, but include, nausea, vomiting, diarrhea, hypersensitivity reactions, skin rashes and thrombocytopenia.

1.4 Benefit/risk and ethical assessment

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

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

2. STUDY OBJECTIVES

2.1 Primary objective

To investigate the effect of multiple 600 mg (2 x 300 mg) oral doses of rifampicin on the exposure of a single 75 mg oral dose of selumetinib in healthy volunteers.

2.2 Secondary objectives

The secondary objectives of the study are:

- To investigate the PK of N-desmethyl selumetinib when selumetinib is administered with or without rifampicin.
- To determine the plasma concentration of rifampicin at 2 hours after administration during the rifampicin dosing period to monitor the exposure of the CYP3A4 inducer.
- To determine the 4β-hydroxycholesterol to cholesterol concentration ratios as a marker of CYP3A4 induction by rifampicin.
- To further assess the safety and tolerability of selumetinib by the assessment of AEs, laboratory variables, and vital signs.

2.3 Exploratory objectives

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

The exploratory analysis will be reported separately.

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This clinical study is designed as a Phase I, open-label, fixed sequence, single-center study to investigate the effect of rifampicin (a known CYP3A4 inducer) on the PK, safety and tolerability of a single 75 mg oral dose of selumetinib in healthy male and female (of non-childbearing potential) volunteers. Approximately 24 healthy volunteers aged between 18 to 45 years (inclusive), will be enrolled in the study. Withdrawn healthy volunteers will not be replaced; however, additional volunteers may be included in the study until such a time as 20 evaluable volunteers have completed both treatments. Screening procedures will only be performed for healthy volunteers who provide written informed consent.

The study will consist of 3 visits. Visit 1 will be a screening visit and will take place within 28 days of Visit 2. Visit 2 will be the treatment visit and the healthy volunteers will be resident at the study center from Day -1 up to Day 15. Visit 3 will be the follow-up visit and will take place 7 to 10 days after discharge on Day 15, Visit 2.

Healthy volunteers will be assigned to the following treatment schedule:

- Treatment A: Healthy volunteers will receive a single oral dose of 75 mg (3 x 25 mg) selumetinib on Day 1. Safety assessments will be performed and blood samples collected for PK analysis until Day 4.

- Treatment B: Following completion of assessments for Treatment A on Day 4, volunteers will receive single, daily, oral doses of 600 mg (2 x 300 mg) rifampicin on Days 4 to 11.

- Treatment C: On Day 12, volunteers will receive 600 mg (2 x 300 mg) rifampicin with a single oral dose of 75 mg (3 x 25 mg) selumetinib administered at the same time. Once daily rifampicin administration will continue through Day 14.

Safety assessments will be performed and blood samples collected for PK analysis until Day 15.

The study flow chart is presented in Figure 1

Figure 1 Study flow chart

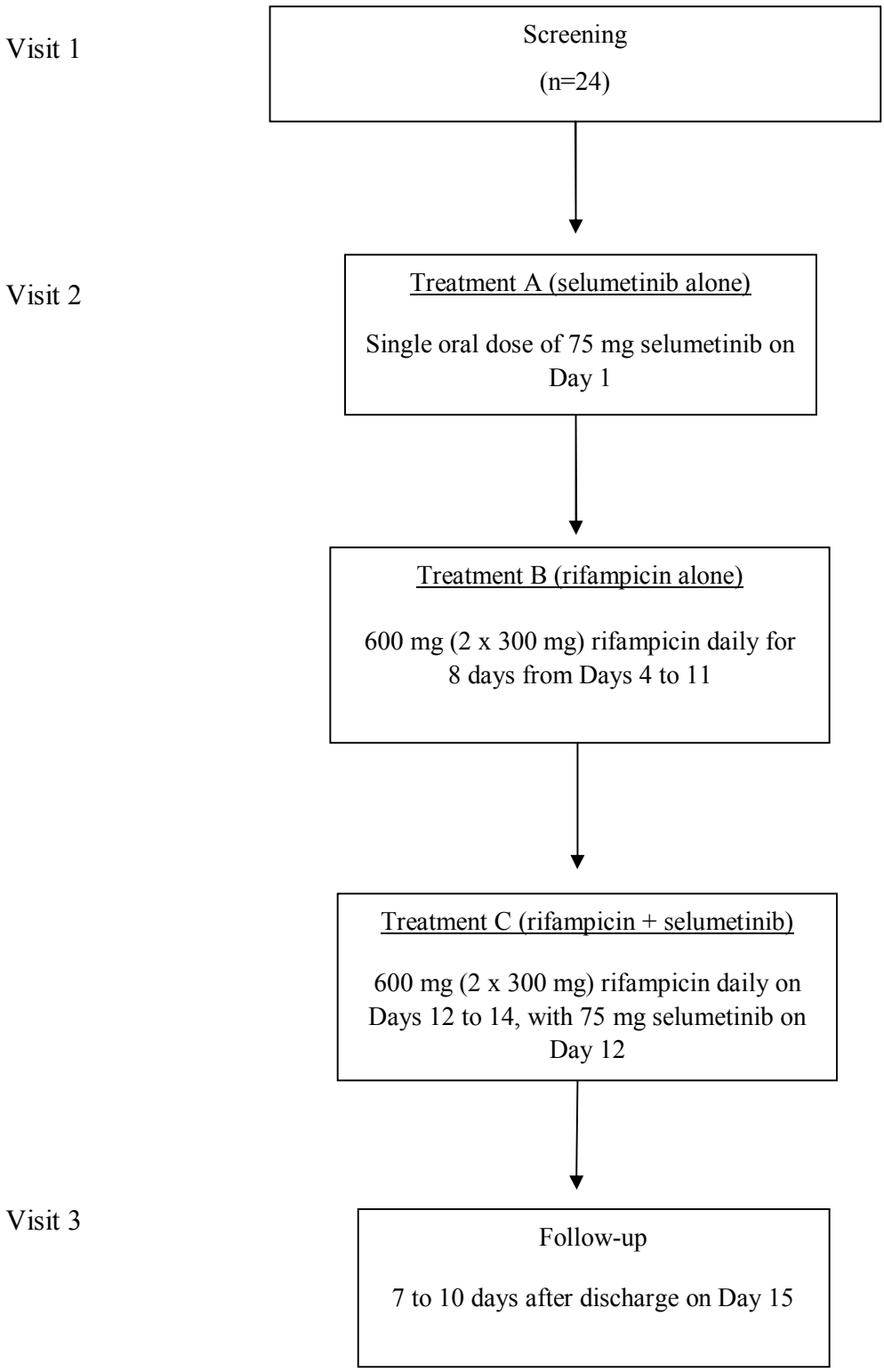

Table 2 Study plan

	Visit 1				Visit 2						Visit 3
	Screening	Treatment A (selumetinib only)			Treatment B (rifampicin only)			Treatment C (selumetinib +rifampicin)		Discharge	Follow-up visit
Days	**-28 to -2**	**-1**	**1**	**2 to 3**	**4**	**5 to 10**	**11**	**12**	**13 to 14**	**15**	**7 to 10 days after discharge**
Informed consent	X										
Optional informed consent for genotyping[j]		X[j]									
Demographic data	X										
Medical/surgical history	X										
Hepatitis B, C, and HIV screen	X										
Inclusion/exclusion criteria	X	X									
Weight	X	X									X
Height	X										
Residency period		X	X	X	X	X	X	X	X	X[b]	
Administration of selumetinib			X					X			
Administration of rifampicin					X	X	X	X	X		
Vital signs[c]	X		X[c]	X	X			X[c]	X		X
12-lead ECG	X[d]		X[e]					X[e]			X
Hematology, clinical chemistry, urinalysis[f]	X	X			X[f]	X		X[f]		X	X
Drugs of abuse screen[g]	X	X									

Table 2 Study plan

	Visit 1	Visit 2							Visit 3
	Screening	Treatment A (selumetinib only)			Treatment B (rifampicin only)			Treatment C (selumetinib +rifampicin)	Discharge	Follow-up visit
Days	**-28 to -2**	**-1**	**1**	**2 to 3**	**4**	**5 to 10**	**11**	**12**	**13 to 14**	**15**	**7 to 10 days after discharge**
Ophthalmic examination[a]	X	X									
Physical examination[h]	X	X								X	X
Selumetinib PK blood[i]			X	X	X[m]			X	X	X	
Rifampicin PK blood[l]						X[l]			X		
4β-hydroxycholesterol and cholesterol blood[k]					X			X	X		
Optional pharmacogenetic blood[j]		X									
Pregnancy test (female subjects only)	X	X									X
Follicle-stimulating hormone[n]	X										
AEs		X	X	X	X	X	X	X	X	X	X
SAE	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X

AE: Adverse event, ECG: Electrocardiogram, PK: Pharmacokinetic, IOP: Intra-ocular pressure, SAE: Serious adverse event

a Ophthalmic examination (best corrected visual acuity, IOP, slit-lamp fundoscopy) will be conducted at screening or Day -1 (considered as the baseline value; no need to repeat) and for cause (on occurrence of an AE only).

b Volunteers will be discharged from the study center on the morning of Day 15 following completion of all the study assessments scheduled for that day.

c Vital signs includes supine blood pressure and heart rate to be measured after the volunteer has been resting for 10 minutes and before any blood sampling. On the selumetinib administration days of each treatment period, blood pressure and pulse rate will be recorded at pre-dose, 1.5 hours (t_{max}), 4 hours, 8 hours, 12 hours, and 24 hours post-dose.

d 12-lead ECGs. Patients should be supine and resting for at least 10 minutes before the ECG recording. If the volunteer has QTcF ≥450 ms on baseline ECG, the ECG may be repeated (at least 24 hours apart). The average QTcF from the 2 screening ECGs must be less than ≥450 ms in order for the volunteer to be eligible for the study.

e 12-lead ECGs. Patients should be supine and resting for at least 10 minutes before the ECG recording. On the selumetinib administration days of each treatment period, ECGs will be recorded at pre-dose, 1.5 hours (t_{max}), 8 hours, and at follow-up.

f Clinical laboratory tests consist of hematology, clinical chemistry and urinalysis assessments, full test screens will be performed at screening, Days -1, 4 (prior to rifampicin administration), 15, and at follow-up. Additional liver function tests will be performed every 3 days while on rifampicin (Days 6, 9 and 12).

g Includes alcohol and cotinine .

h Full physical examinations will be performed at screening and follow-up and brief physical examinations on Day -1 and at discharge, Day 15.

i When PK and vital measurements are scheduled at the same time point, ECG and vital signs will precede PK, with the PK blood sample collected at the specified protocol scheduled time. Blood samples (2 mL) to measure selumetinib will be collected pre-dose, and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 36, 48 & 72 hours after selumetinib administration on Days 1 and 12.

j Pharmacogenetics blood sampling is optional and will be done if the volunteer provides additional informed consent on Day -1 (Visit 2).

k Blood samples (4 mL) to determine 4β-hydroxycholesterol and cholesterol plasma concentrations prior to administration of rifampicin or selumetinib on Day 12 and before the rifampicin administration on Days 4 and 14.

l Blood samples (2 mL) to measure plasma concentration of rifampicin at 2 hours after rifampicin administration on Days 7, 9, and 14.

m Selumetinib 72 hour blood sample (2 mL) to collected prior to first administration of rifampicin.

n Follicle-stimulating hormone will be tested at screening, only for post-menopausal females.

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3.2 Rationale for study design, doses and control groups

The primary objective of this study is to investigate the effect of multiple 600 mg (2 x 300 mg) oral doses of rifampicin on the exposure of a single 75 mg oral dose of selumetinib in healthy male and female (of non-childbearing potential) volunteers by comparing the AUC and C_{max} of selumetinib in the presence and absence of rifampicin. The dose level of 75 mg selumetinib (3 x 25 mg capsules) is considered to be in the therapeutic dose range and is the maximum dose permitted in healthy volunteers. A dose of 75 mg twice daily is being investigated in ongoing efficacy studies of selumetinib.

Daily dosing of 600 mg (2 x 300 mg) rifampicin for 9 days will maximize the induction effect on CYP3A4.

A sample size of 20 evaluable healthy volunteers has been selected based on the desire to gain adequate information while exposing as few healthy volunteers as possible to the study procedures. Statistical implications of this sample size are shown in Section 12.3.

Preliminary data suggest that Japanese and non-Japanese Asian healthy volunteers may experience higher systemic drug exposure compared to Western healthy volunteers who receive the same dose of selumetinib. Exclusion of Japanese and non-Japanese Asian healthy volunteers from these studies is to safeguard them from potentially higher systemic drug exposure. This exclusion criterion applies to all clinical pharmacology studies as the selumetinib dosage has been set based on a study design that recruits Western healthy volunteers.

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

These results will support labeling statements with regards to posology.

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

4. SUBJECT SELECTION CRITERIA

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

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

4.1 Inclusion criteria

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

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

2. Healthy male and female (of non-childbearing potential) volunteers aged 18 to 45 years (inclusive).

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

   - Post- menopausal defined as amenorrhea for at least 24 months following cessation of all exogenous hormonal treatments or if less than 24 months, follicle-stimulating hormone (FSH) levels in the laboratory defined post-menopausal range.

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

4. Healthy volunteers must be eligible to receive rifampicin in accordance with local prescribing rifampicin information.

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

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

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

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

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

4.2 Exclusion criteria

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

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

2. Previous administration of the investigational product in the present study.

3. 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.

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

5. Subjects of Japanese or non-Japanese Asian ethnicity.

6. Any one parent or grandparent (maternal or paternal) is Japanese or non-Japanese Asian (eg, China, Taiwan, Korea, Philippines, Thailand, Vietnam and Malaysia). Asian Indians are acceptable.

7. Has received another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment within at least 30 days of the first administration of the investigational product in this study. The period of exclusion begins 30 days after the final dose or 30 days after the last visit whichever is the longest.
   Note: volunteers consented and screened, but who did not receive investigational product in this study or a previous Phase I study, are not excluded.

8. Current or past history of central serous retinopathy or retinal vein thrombosis, intra-ocular pressure greater than 21 mmHg or uncontrolled glaucoma. Including, volunteers who wear soft contact lenses, unless the volunteer is prepared to refrain from wearing soft contact lenses throughout the rifampicin dosing days and until after the last PK sample in treatment period C.

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

10. Any clinically relevant abnormal findings in physical examination, hematology, clinical chemistry, urinalysis, vital signs or ECG at Visit 1, which in the opinion of the principal investigator, may put the volunteer at risk because of his participation in the study. Specific criteria regarding liver function tests (LFTs), any clinically significant abnormalities in clinical chemistry, hematology, or urinalysis results as judged by the Investigator (AST and ALT should be within the reference range of the study center).

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

12. 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.

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

14. A definite or suspected personal history of intolerance or hypersensitivity to drugs and/or their excipients, judged to be clinically relevant by the principal investigator.

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

16. History of, or current alcohol or drug abuse, as judged by the principal investigator.

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

18. History of hypersensitivity to rifampicin or any excipient of this agent.

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

20. Planned in-patient surgery, dental procedure or hospitalization during the study.

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

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

22. Previous bone marrow transplant.

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

Procedures for withdrawal of incorrectly enrolled volunteers are provided in Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

The following restrictions will be applied in this study:

- On Day 1 and Day 12, healthy volunteers will be fasted overnight for at least 10 hours before receiving selumetinib (or selumetinib plus rifampicin) and until 4 hours post-dose. Similarly, healthy volunteers will be fasted overnight for at least 10 hours before receiving rifampicin (alone) and until 1 hour post-dose (Days 4 to Day 11, and Days 13 and 14). No fluids will be allowed from 1 hour before investigational product administration until 1 hour after investigational product administration, except for water needed to swallow the investigational product. Standardized meals (lunch, dinner, and a snack) will be provided at the same time during Visit 2.

- The caffeine intake should be limited to 5 cups per day from screening and limited to 3 cups per day at meal times from admission (Day -1) to the study center and during residency.

- Healthy volunteers should abstain from consuming energy drinks (or other formulations) containing taurine or glucuronolactone from the day of enrollment until follow-up (Visit 3).

- Abstain from consumption of alcoholic beverages from within 48 hours before admission (Day -1) until discharge (Day 15) from the study center and should consume no more than 2 units of alcohol per day otherwise from discharge until after follow-up.

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

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

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

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

- Male volunteers with sexual partners who are pregnant or who could become pregnant (ie, women of childbearing potential) should use barrier methods of contraception from the time of the first administration until 12 weeks after completing the study to avoid pregnancy and/or potential adverse effects on the developing embryo. Male volunteers should avoid sperm donation during and for 12 weeks after the study completion. Reliable methods of contraception should be used consistently and correctly.

  Acceptable methods for male partners include:

  – Implants, injectables, combined oral contraceptives (which must all be combined with barrier methods of contraception), some intrauterine devices, vasectomized partner (which must all be combined with barrier methods of contraception), and total sexual abstinence. When this is in line with the preferred and usual lifestyle of the subject (periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent subjects have to agree to use one of the above mentioned contraceptive methods, if they start sexual activities 12 weeks after the last administration of the investigational product.

  Acceptable methods for healthy male volunteers include:

  – Male subjects will be required to use reliable methods of contraception (condom and spermicide) for the duration of the study until 12 weeks after the investigational product administration.

- Healthy volunteers should not take Vitamin E supplements or multivitamin supplements from 14 days prior to Day -1 and throughout the study until follow-up.

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

- Healthy volunteers should avoid excessive sun exposure and use adequate sunscreen protection (greater than 30 sun protection factor [SPF]), if sun exposure is anticipated. Volunteers should use sunscreen for up to 14 days after the last administration of selumetinib.

5.2 Subject enrollment and initiation of investigational product

The principal investigator will:

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

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

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

4. Assign eligible healthy volunteers a unique subject number, beginning with 1001.

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

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

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

Where healthy volunteers that do not meet the inclusion and/or exclusion criteria, are enrolled in error, or incorrectly started on treatment, or where healthy volunteers subsequently fail to meet the study criteria post initiation, the investigator should inform the AstraZeneca Clinical Pharmacology Alliance (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 3 Identity of the investigational product

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

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

5.5.2 Doses and treatment regimens

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

Daily administrations of 600 mg (2 x 300 mg) rifampicin oral capsules for 9 days will maximize the induction effect on CYP3A4.

Treatment A (selumetinib alone):

A single administration of 75 mg selumetinib will be administered as 3 x 25 mg oral capsules in the fasted state. Healthy volunteers will be fasted overnight for at least 10 hours before receiving selumetinib and until 4 hours post-dose. No fluids will be allowed from 1 hour before investigational product administration until 1 hour after investigational product administration, except for water needed to swallow the investigational product. Standardized meals (lunch, dinner, and a snack) will be provided at the same time during Visit 2.

Treatment B (rifampicin):

Healthy volunteers will receive single daily oral doses of 600 mg (2 x 300 mg) rifampicin as capsules on Days 4 to 11 under food restriction where they will be fasted overnight for at least 10 hours before receiving rifampicin and until 1 hour post-dose. Standardized meals (lunch, dinner, and a snack) will be provided at the same time during Visit 2. No fluids will be allowed from 1 hour before investigational product administration until 1 hour after investigational product administration, except for water needed to swallow the investigational product.

Treatment C (rifampicin + selumetinib):

On Day 12, healthy volunteers will receive 600 mg (2 x 300 mg) rifampicin oral capsules and 75 mg (3 x 25 mg) selumetinib oral capsules in the fasted state (fasted from midnight on Day 11 to 4 hours after investigational product administration) administered at the same time. Healthy volunteers will continue to receive single daily oral 600 mg (2 x 300 mg) doses of rifampicin on Days 13 to 14 under food restriction where they will be fasted overnight for at least 10 hours before receiving rifampicin and until 1 hour post-dose. Standardized meals (lunch, dinner, and a snack) will be provided at the same time during Visit 2. No fluids will be allowed from 1 hour before investigational product administration until 1 hour after investigational product administration, except for water needed to swallow the investigational product.

5.5.3 Additional study drug

Investigational product	Dosage form and strength	Manufacturer
Rifampicin	300 mg oral capsules	To be sourced by local study center

5.5.4 Labeling

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

5.5.5 Storage

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

5.6 Concomitant and post-study treatment(s)

Any prescribed medicine and over-the-counter drugs (including herbal remedies, vitamins, and minerals) must be avoided from within 2 weeks/five times the half-life of the respective drug of the first investigational product administration until after the follow-up visit, with the exception of occasional use of acetaminophen for pain relief and over-the-counter adrenergic nasal spray for relief of nasal congestion, if needed.

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

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

Healthy volunteers should not take Vitamin E supplements or multivitamin supplements from 2 weeks prior to Day -1 and throughout the study until follow-up.

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

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

5.7 Treatment compliance

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

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

5.7.1 Accountability

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

The study personnel will account for all investigational products administered to the healthy volunteers.

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

5.8 Discontinuation of investigational product and withdrawal from the study

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

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

Withdrawn healthy volunteers will not be replaced; however, additional volunteers may be included in the study until such a time as 20 evaluable volunteers have completed all 3 treatments treatments.

5.8.1 Procedures for discontinuation of a subject from investigational product

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

6. COLLECTION OF STUDY VARIABLES

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

- 12-Lead ECG.
- Vital signs.
- PK blood sampling.

- Safety laboratory assessments.

Pre-dose assessments may be performed up to 60 minutes before the investigational product administration.

6.1 Recording of data

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

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

6.2 Data collection at enrollment and follow-up

6.2.1 Screening procedures

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

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

- Review of inclusion/exclusion criteria.
- Recording of demographic data (date of birth, gender, and race).
- Recording of medical/surgical history and smoking history.
- Ophthalmic examination (at screening or at Visit 2 Day -1).
- Urine sample for routine urinalysis and screening for drugs of abuse.
- Calculation of CrCL.
- Alcohol and cotinine screen.
- Recording of height and weight and calculation of BMI.
- A complete physical examination.
- Vital signs (supine blood pressure and pulse rate).

- Blood sampling for routine hematology, clinical chemistry, and screening for hepatitis B, C and HIV.
- 12-Lead ECG.
- Concomitant medication recording
- SAE/AE recording.

6.2.2 Follow-up procedures

Follow-up assessments will be conducted 7 to 10 days after discharge from Visit 2 and will include recording of weight, a full physical examination, vital signs (supine blood pressure and pulse rate), blood sampling for routine hematology and clinical chemistry, urine sampling for routine urinalysis, 12-lead ECG, recording of concomitant medication, and recording of AEs and SAEs.

6.3 Safety

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

6.3.1 Definition of adverse events

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

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

6.3.2 Definitions of serious adverse event

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

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.

- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardize the volunteer or may require medical intervention to prevent one of the outcomes listed above.

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

6.3.3 Recording of adverse events

Time period for collection of adverse events

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

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

Follow-up of unresolved AEs

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

Variables

The following variables will be collect for each AE;

- AE (verbatim).
- The date and time when the AE started and stopped.
- Maximum intensity.
  - Mild (awareness of sign or symptom, but easily tolerated).
  - Moderate (discomfort sufficient to cause interference with normal activities).
  - Severe (incapacitating, with inability to perform normal activities).
- Whether the AE is serious or not.
- Investigator causality rating against the investigational product (yes or no).
- Action taken with regard to investigational product.
- AE caused healthy volunteer's withdrawal from study (yes or no).
- Outcome.

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

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

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

Causality collection

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

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

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

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 the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the

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

Adverse Events based on examinations and tests

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

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

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

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

6.3.4 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then investigators or other study center personnel 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 center personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

6.3.5 Laboratory safety assessment

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

The laboratory variables to be measured are provided in Table 4.

Table 4 Safety laboratory variables

Hematology (blood)	Clinical chemistry (serum)	Urinalysis (urine)
Platelet count	Creatinine	Erythrocytes
Leukocyte differential count[a]	Bilirubin total	Albumin
Leukocytes count	Alkaline phosphatase (ALP)	Glucose
Hemoglobin	Alanine aminotransferase (ALT)	
Erythrocyte volume fraction	Aspartate aminotransferase (AST)	
Reticulocytes	Albumin	
Erythrocytes	Calcium total	
Erythrocyte mean cellular volume	Sodium	
	Potassium	
	C-reactive protein	
	Thyroxine free[a]	
	Thyroid stimulating hormone[a]	
	Follicle-stimulating hormone[b]	

[a] These tests should be performed at screening only.
[b] Follicle-stimulating hormone will be tested only at screening and only for post-menopausal females.

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

$$\textbf{Estimated CrCL (mL/min)} = \frac{(140\text{-age [years]}) \times (\text{body weight [kg]}) \ (\times 0.85)^{a}}{\text{Serum creatinine (mg/dL)} \times 72}$$

a For females.

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

Alcohol breathalyzer test and urine cotinine test will be performed at screening and Day -1 of Visit 2.

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

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

For blood volume see Section 7.1.

6.3.6 Physical examination

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

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

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

6.3.7 Resting 12-lead ECG

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

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

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

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

6.3.8 Vital signs

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

6.3.8.1 Pulse and blood pressure

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

6.3.8.2 Height and weight

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

6.3.9 Ophthalmology

A full ophthalmologic examination including a slit-lamp fundoscopy, best corrected visual acuity, and intra-ocular pressure measurement must be performed at screening or Day -1 of visit 2 for all healthy volunteers. If a healthy volunteer experiences visual disturbance he should undergo a full ophthalmological examination and optical coherence tomography scans must be done if a retinal event is suspected. Management of the ocular event will be guided by the ophthalmologist based on available results.

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

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

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

6.4 Pharmacokinetics

6.4.1 Collection of samples

Blood samples will be collected at the visits and times indicated in Table 2 and as outlined below to measure plasma concentrations of selumetinib, the N-desmethyl metabolite of selumetinib, rifampicin, and 4β-hydroxycholesterol and cholesterol.

Individual venipunctures for each time point may be performed or an in-dwelling catheter may be used. If the study center chooses to use an in-dwelling catheter, the first 1 mL of blood will be discarded and the catheter will be flushed with saline following the sampling. Heparin may not be used to flush the catheter.

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

For blood volume see Section 7.1.

6.4.1.1 Selumetinib and metabolite

Blood samples (2 mL total at each timepoint) to measure selumetinib and N-desmethyl metabolite collected predose, and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 36, 48 & 72 hours after the selumetinib administration on Days 1 and 12. If deemed appropriate, the amide metabolite may also be measured. The number of blood samples collected is 16 per study period, for a total of 32.

The selumetinib PK blood sample collected 72 hours post-dose on Day 4 will be collected prior to the administration of rifampicin.

Rifampicin and selumetinib are administered at the same time on Day 12. The blood samples collected for selumetinib PK at the 24 and 48 hours post-dose timepoints will likely coincide with rifampicin administrations on Day 13 and Day 14. While selumetinib blood sample collections should be captured on time, relative to the time of selumetinib dose administration, should these collections and the time for rifampicin dose administration coincide, the selumetinib PK blood sample should be collected prior to the dose of rifampicin.

6.4.1.2 Rifampicin

Blood samples (2 mL) to measure plasma concentration of rifampicin will be collected 2 hours after administration on Days 7, 9 and 14, for a total of 3 samples.

6.4.1.3 4β-hydroxycholesterol and cholesterol

Blood samples (4 mL) to measure 4β-hydroxycholesterol and cholesterol prior to administration of rifampicin or selumetinib will be collected on Day 12 and before rifampicin administration on Days 4 and 14, for a total of 3 samples.

6.4.2 Determination of drug concentration

Samples for the determination of selumetinib, N-desmethyl selumetinib, rifampicin concentrations and amide metabolite, if appropriate, in plasma will be analyzed by on behalf of AstraZeneca Research and Development using an appropriate bioanalytical method.

All samples still within the known stability of the analytes of interest at the time of receipt by the bioanalytical laboratory will be analyzed. Full details of the analytical method used will be described in a separate bioanalytical report.

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

The 4β-hydroxycholesterol and cholesterol concentrations will be reported by a clinical laboratory using standard validated methods.

6.5 Pharmacogenetics

6.5.1 Collection of pharmacogenetic samples

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

For blood volume see Section 7.1.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each healthy volunteer in this study is provided in Table 5

Table 5 Volume of blood to be drawn from each healthy volunteer

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	8.5	5	42.5
	Liver function tests only	5	3	15
	Hematology	4	5	20
Hepatitis B, C, and HIV screen		8.5	1	8.5
Pregnancy test/follicle-stimulating hormone (females)[a]		3.5	3	10.5
Pharmacokinetics[a]				
Selumetinib and metabolite		2	32	64
Rifampicin		2	3	6

Table 5 Volume of blood to be drawn from each healthy volunteer

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	8.5	5	42.5
	Liver function tests only	5	3	15
	Hematology	4	5	20
Hepatitis B, C, and HIV screen		8.5	1	8.5
Pregnancy test/follicle-stimulating hormone (females)[a]		3.5	3	10.5
Pharmacokinetics[a]				
4β-hydroxycholesterol and cholesterol		4	3	12
Pharmacogenetics (optional)		10	1	10
Total				188.5

HIV: human immunodeficiency virus
a If an in-dwelling catheter is used, an additional 1 mL of blood will be collected to flush the catheter prior to collecting each sample.
b Follicle-stimulating hormone will be tested only at screening, and only for post-menopausal females.

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

7.2 Handling, storage and destruction of biological samples

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

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

7.2.1 Pharmacokinetic samples

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

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

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

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

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.

7.2.2 Pharmacogenetic samples

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

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

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

7.3 Labeling and shipment of biohazard samples

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

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

7.4 Chain of custody of biological samples

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

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

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

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

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

7.5 Withdrawal of informed consent for donated biological samples

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

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

The principal investigator:

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

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

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

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Subject data protection

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

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

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

8.3 Ethics and regulatory review

An Institutional Review Board (IRB) should approve the final study protocol, including the final version of the 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 IRB, and to the study center personnel.

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

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

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

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

Before enrollment of any healthy volunteer into the study, the final study protocol, 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, IRB, and principal investigator with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions (SUSARs), where relevant.

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

8.4 Informed consent

The principal investigator will:

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

8.5 Changes to the protocol and informed consent form

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

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

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

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

If a protocol amendment requires a change to the study center's ICF, AstraZeneca and the study center's IRB 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 the IRB.

8.6 Audits and inspections

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

9. STUDY MANAGEMENT

9.1 Pre-study activities

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

- Determine the adequacy of the facilities
- Determine availability of appropriate healthy volunteers for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of

AstraZeneca or its representatives. 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 clinical study protocol and related documents with the investigational personnel and also train them in any study specific procedures and system(s) utilized.

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

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

9.3 Monitoring of the study

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

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

The AstraZeneca representative will be available between visits if the investigator or other personnel at the study center 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 center 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 clinical study protocol and the CSA, the terms of clinical study protocol shall prevail with respect to the conduct of the study and the treatment of healthy volunteers and in all other respects, not relating to study conduct or treatment of healthy volunteers, the terms of the 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 Q1 2014 and to end by Q2 2014.

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

10. DATA MANAGEMENT

Data management will be performed by

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

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

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

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

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

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

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

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

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

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of safety variable(s)

11.1.1 Calculation of change-from-baseline

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

- Clinical laboratory tests: last measureable value taken prior to the first investigational product administration.
- Vital signs: last measureable value taken prior to the first investigational product administration.

- Paper ECG: last measureable value taken prior to the first investigational product administration.

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

11.1.2 Other significant adverse events

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

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

11.2 Calculation or derivation of pharmacokinetic variables

11.2.1 Selumetinib and metabolites

Pharmacokinetic parameters will be determined by using standard non-compartmental methods with Phoenix® WinNonlin Professional Version 6.3 or higher) or SAS® Version 9.2 or higher). Standard Operation Procedures and Work Instructions will be used as the default methodology, unless otherwise specified. Actual elapsed time from investigational product administration will be used for final 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 the amide metabolite, if deemed appropriate):

AUC	Area under the plasma concentration-time curve from time zero to infinity, calculated by linear up/log down trapezoidal summation.
$AUC_{(0-t)}$	Area under the plasma concentration-time from time zero to the time of the last quantifiable concentration, calculated by linear up/log down trapezoidal summation.

$AUC_{(0-12)}$	Area under the plasma concentration-time curve from time zero to 12 hours post-dose, calculated by linear up/log down trapezoidal summation.
C_{max}	Maximum concentration, obtained directly from the observed concentration versus time data.
t_{max}	Time to C_{max}.
CL/F	Apparent systemic plasma clearance (selumetinib only).
V_{ss}/F	Apparent volume at distribution equilibrium, mean residence time (MRT)*CL/F (selumetinib only).
V_z/F	Apparent volume at distribution (selumetinib only).
$t_{1/2}$	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}.
MRT	Mean residence time.

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

The following PK parameters for plasma selumetinib and N-desmethyl selumetinib (and the amide metabolite, if deemed appropriate) will be calculated for diagnostic purposes and listed, but will not be summarized:

$t_{1/2}$, Interval	The time interval of the log-linear regression to determine λ_z.
N	Number of data points included in the log-linear regression analysis used to determine λ_z (a minimum of 3 data points will be used for λ_z determination).
Rsq	Coefficient of determination for calculation of λ_z (λ_z and related

	parameters will be reported only if Rsq is 0.800 or more).
$\%AUC_{ex}$	Percentage of AUC obtained by extrapolation (if the extrapolated area is greater than 20% then AUC for that specific profile will not be reported).

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

11.2.2 Rifampicin

Pharmacokinetic parameters will not be derived for rifampicin. Only the 2 hours post-dose plasma concentrations will be reported and assessed.

11.2.3 4β-hydroxycholesterol and cholesterol

The following will be calculated using 4β-hydroxycholesterol and cholesterol assesments:

4β-hydroxycholesterol ratio Day x	The post-treatment 4β-hydroxycholesterol ratio (4β-hydroxycholesterol/cholesterol) on Day 12 or Day 14 compared to the pre-treatment (Day 4 pre-dose) ratio (ie, Day 12 or Day 14/ Day 4).

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 Safety analysis set

All healthy volunteers who received at least 1 administration of investigational product (selumetinib or rifampicin) will be included in the safety population.

12.1.2 Pharmacokinetic analyses set

The PK analysis set will include all healthy volunteers who receive at least 1 administration of selumetinib and have at least 1 post-dose PK measurement without important protocol deviations/violations or events thought to significantly affect the PK of the investigational product (eg, healthy volunteer vomited at or before 2 times median t_{max}; wrong dose administered; prohibited concomitant medication; etc). The PK scientist will evaluate the

strategy for dealing with data affected by protocol deviations before any formal statistical analysis is performed.

12.2 Methods of statistical analyses

Statistical analyses will be performed per Standard Operating Procedures using SAS® Version 9.2 or higher and, where appropriate, additional validated software.

A healthy volunteer who withdraws prior to the last planned observation in the study period will be included in the analyses up to the time of discontinuation. No adjustment or imputation will be utilized for missing values or for healthy volunteers who withdraw prior to completing the study, nor will analyses be restricted to healthy volunteers with complete data.

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

The analysis of data will be based on different subsets according to the purpose of analysis, ie, for safety and PK, respectively. The as-treated principle will be applied to all evaluations; ie, healthy volunteers who receive another treatment than the one assigned in the randomization list will be analyzed as belonging to the actual treatment group.

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

12.2.1 Subject characteristics

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation [SD], minimum, median, maximum) by treatment. Categorical variables will be summarized in frequency tables (frequency and proportion) by treatment group.

12.2.2 Safety and tolerability

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

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

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

All available data from healthy volunteers in the safety analysis set will be included in the safety analyses.

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

Adverse events will be listed for all healthy volunteers with AEs that occur before investigational product administration indicated on the listing. The number of AEs experienced following administration of the investigational product will be summarized in tables using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 13.0 or higher) System Organ Class and Preferred Term. These summary tables will also be produced with severity and causality of AEs added as additional classification factors. The number of AEs overall, SAEs, OAEs, AEs that lead to withdrawal, AEs of severe intensity, and causally-related AEs will be summarized. Any AE occurring post-dose will be considered associated with the last administration of investigational product taken. Any AE occurring on Visit 2 Day -1 will not be included in the summaries.

Tabulations and listings of data for vital signs, ECGs, and clinical laboratory tests will be presented, as appropriate. Results from physical examinations will be presented separately in listings only. All continuous safety data will be summarized across all treatments for the absolute value at each scheduled assessment and for the corresponding change-from-baseline. For clinical laboratory tests, listings of values for each healthy volunteer will be presented with abnormal or out-of-range values flagged. Clinical laboratory data will be reported in Système International units in the CSR. Additional graphical presentations of the data eg, shift plots comparing baseline to on treatment values will be generated as appropriate to aid the interpretation of safety data.

12.2.3 Pharmacokinetics

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided for each analyte, as appropriate.

12.2.3.1 Selumetinib and metabolites

Pharmacokinetic variables will be summarized using appropriate descriptive statistics (eg, number, arithmetic mean, CV%, SD, geometric mean, geometric coefficient of variation [GCV%], minimum, median, and maximum). 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 maximum value will be reported from the individual data, and the minimum and median will be set to BLQ.

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

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

A subject listing of all concentration-time data will be presented along with the descriptive statistics for all healthy volunteers. Data from healthy volunteers excluded from an analysis set will be included in the data listings, but not in the summaries. A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. Figures of geometric mean (± geometric SD) concentration-time data will be graphically presented on linear and semi-logarithmic scales.

Pharmacokinetic parameters will be summarized and presented graphically, as appropriate, using descriptive statistics by treatment and analyte. Scatter plots of the individual parameter data (C_{max}, AUC, and $AUC_{(0-t)}$) and geometric means will be presented by analyte, treatment, and parameter, with lines connecting the individual parameters and geometric means across the two treatments under comparison. Graphical presentations of other PK data may be added at the discretion the pharmacokineticist.

Following log-transformation of selumetinib C_{max}, AUC and AUC_{0-t} will be separately analyzed by mixed effect analysis of variance, fitting a fixed effect term for treatment (selumetinib + rifampicin vs selumetinib alone) and random effects for volunteer. Point estimates and adjusted 90% confidence interval (CI) for the difference in treatment (selumetinib + rifampicin or selumetinib alone) will be constructed. The point estimate and adjusted 90% CIs will then be exponentially back transformed to provide point and CI estimates for the ratio of interest (ie, C_{max} or AUC of selumetinib contrasting with or without co-administration with rifampicin).

Analyses will be conducted for selumetinib and separately for the metabolite N-desmethyl selumetinib. However, note that sample size was determined according to the precision of the drug-drug interactions effect on selumetinib, rather than the metabolite.

Although descriptive CIs will be presented for some outcomes, this study has not been powered to perform any formal hypothesis testing.

12.2.3.2 Rifampicin

Rifampicin concentrations will be summarized by study day using appropriate descriptive statistics.

12.2.3.3 4β-hydroxycholesterol and cholesterol

Results for 4β-hydroxycholesterol and cholesterol along with the ratio of post-treatment to pre-treatment concentration will be listed for individual volunteers and summarised by analyte and study day. Descriptive statistics (n, mean, SD, CV, minimum, median and maximum) will include the ratio of post-treatment to pre-treatment concentrations. These ratios with 90% CIs calculated on log-transformed data may also be determined with results back-transformed for presentation.

12.2.4 Interim analyses

Not applicable.

12.3 Determination of sample size

The primary objective of this study is to investigate the effect of multiple 600 mg (2 x 300 mg) oral doses of rifampicin on the exposure of a single 75 mg oral dose of selumetinib in healthy volunteers by comparing AUC and C_{max} of selumetinib in the presence and absence of rifampicin.

A sample size of 20 evaluable healthy volunteers has been selected based on the desire to gain adequate information while exposing as few healthy volunteers as possible to study procedures. Twenty-four healthy volunteers will be enrolled into the study in order to have at least 20 evaluable healthy volunteers complete the study (allowing for an approximate 20% dropout rate).

Table 6 displays expected 90% CI for a range of possible drug-drug interaction effects at the selected sample size of 20 evaluable volunteers. Within-volunteer estimates of coefficient of variation (CV) (16.9% for AUC and 34.0% for C_{max}) observed in a prior clinical study (Study D1532C00066) were used in these calculations. These 90% CIs demonstrate that good precision of the drug-drug interaction effect will be achieved from a sample size of 20 evaluable healthy volunteers.

Table 6 90% Confidence intervals for C_{max} and AUC varying drug-drug interaction effects given an evaluable sample size of 20

	Drug-drug interaction effect: Relative reduction of C_{max} or AUC (geometric least squares means ratio)						
Parameter	**70% (0.3)**	**60% (0.4)**	**50% (0.5)**	**40% (0.6)**	**30% (0.7)**	**20% (0.8)**	**10% (0.9)**
C_{max}	0.25, 0.36	0.34, 0.48	0.42, 0.59	0.51, 0.71	0.59, 0.83	0.67, 0.95	0.76, 1.07
AUC	0.27, 0.33	0.37, 0.44	0.46, 0.55	0.55, 0.65	0.64, 0.76	0.73, 0.87	0.82, 0.98

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

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

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

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

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	
	Project Manager	

13.2 Overdose

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

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

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

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

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

13.3 Pregnancy

All outcomes of pregnancies in female volunteers or pregnancies in partners of healthy male volunteers should be reported to AstraZeneca.

13.3.1 Maternal exposure

Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur, the investigational product should be discontinued immediately and the pregnancy reported to AstraZeneca.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

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

The designated AstraZeneca representative works with the principal investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.3.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the pCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

13.3.2 Paternal exposure

Healthy volunteers should refrain from fathering a child or donating sperm during the study and for 12 weeks after the last investigational product administration.

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

The outcome of any conception occurring from the date of the first administration until 30 days after the last investigational product administration should be followed up and documented.

14. LIST OF REFERENCES (Not applicable)

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Phase I Open-label, Single-center Study to Assess the Effect of the CYP3A4 inducer Rifampicin on the Pharmacokinetics of a 75 mg single oral dose of Selumetinib (AZD6244; ARRY-142886) (Hyd-Sulfate) in Healthy Volunteers aged 18 to 45 years

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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.

AstraZeneca Research and Developmen
site representative

Medical Science Director

ASTRAZENECA SIGNATURE(S)

A Phase I Open-label, Single-center Study to Assess the Effect of the CYP3A4 inducer Rifampicin on the Pharmacokinetics of a 75 mg single oral dose of Selumetinib (AZD6244; ARRY-142886) (Hyd-Sulfate) in Healthy Volunteers aged 18 to 45 years

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

I agree to the terms of this study protocol.

AstraZeneca Research and Development site representative

Global Product Statistician

SIGNATURE OF PRINCIPAL INVESTIGATOR

A Phase I Open-label, Single-center Study to Assess the Effect of the CYP3A4 inducer Rifampicin on the Pharmacokinetics of a 75 mg single oral dose of Selumetinib (AZD6244; ARRY-142886) (Hyd-Sulfate) in Healthy Volunteers aged 18 to 45 years

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

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

Centre No.:

Signature:

AstraZeneca

Clinical Study Protocol Appendix B

Drug Substance	Selumetinib
Study Code	D1532C00085
Edition Number	1

Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

Clinical Study Protocol Appendix C

Drug Substance	Selumetinib
Study Code	D1532C00085
Edition Number	1

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

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

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

TABLE OF CONTENTS PAGE

1. INTRODUCTION

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

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

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

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 x upper limit of normal (ULN) at any point during the study irrespective of an increase in alkaline phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

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

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

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

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

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

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

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

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment in the presence of liver metastases

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

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

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated

- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician

- Complete the three Liver CRF Modules as information becomes available

- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

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

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

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

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

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

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

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

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

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

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

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. REFERENCES

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

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