Clinical Study Protocol

Drug Substance	Selumetinib
Study Code	D1532C00071
Edition Number	1

A Phase I, Double-blind (Selumetinib [AZD6244; ARRY-142886] [Hyd-Sulfate]), Placebo-controlled, Open-Label (Moxifloxacin) Positive-controlled, Randomized, Three-period Crossover Study to Assess the Effects of Single Oral Dose of Selumetinib (75 mg) on QTc Interval Compared to Placebo, using AVELOX (Moxifloxacin) as a Positive Control, in Healthy Male Volunteers Aged 18 to 45 years

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

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

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

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PROTOCOL SYNOPSIS

A Phase I, Double-blind (Selumetinib [AZD6244; ARRY-142886] [Hyd-Sulfate]), Placebo-controlled, Open-Label (Moxifloxacin) Positive-controlled, Randomized, Three-period Crossover Study to Assess the Effects of Single Oral Dose of Selumetinib (75 mg) on QTc Interval Compared to Placebo, using AVELOX (Moxifloxacin) as a Positive Control, in Healthy Male Volunteers Aged 18 to 45 years

Principal Investigator

Study center and number of healthy volunteers planned

This study will be conducted at a single study center,
A total of approximately 54 healthy male volunteers will be randomized in order to ensure at least 47 evaluable healthy volunteers complete the study.

Study period		Phase of development
Estimated date of first healthy volunteers enrolled	Q1 2014	I
Estimated date of last healthy volunteers completed	Q3 2014	

Objectives

Primary Objective

The primary objective of this study is to assess the effect of a single dose of selumetinib (AZD6244; ARRY-142886) (Hyd-Sulfate) (75 mg) on the change in time-matched QT interval corrected according to Fridericia's formula (QTcF) interval compared to placebo.

Secondary Objectives

The secondary objectives of the study are:

To investigate the effect of selumetinib on additional electrocardiogram (ECG) variables (QT, HR, RR, QRS, PR) and QT interval corrected according to Bazett's formula (QTcB)

To assess the maximum of the mean changes in time-matched QTcF interval after moxifloxacin administration compared to placebo

To examine the pharmacokinetics (PK) of selumetinib, the N-desmethyl metabolite of selumetinib, and moxifloxacin

To explore the relationship between plasma concentration and cardiac ventricular repolarisation effect on the heart after a single oral dose of selumetinib or moxifloxacin by assessments of plasma concentrations of selumetinib, moxifloxacin and the QT/QTcF interval on digital electrocardiograms (dECGs)

To further assess the safety and tolerability of selumetinib by assessment of adverse events (AEs), laboratory variables and vital signs

Exploratory objective

To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to selumetinib (optional).

The exploratory analysis will be reported separately.

Study design

This is a double-blind (for selumetinib [AZD6244; ARRY-142886] [Hyd-Sulfate]), open-label (for moxifloxacin), positive-controlled, randomized, placebo-controlled, 3-way crossover study evaluating a single dose of oral selumetinib 75 mg with a single dose of oral moxifloxacin 400 mg as a positive control.

Approximately 54 healthy male volunteers randomized at 1 study center with at least 47 evaluable healthy volunteers to complete the study. Withdrawn healthy volunteers will not be replaced, however additional volunteers may be included in the study until such a time as 47 evaluable volunteers have completed all treatment periods.

The study will comprise 5 visits:

Visit 1: within 28 days of Visit 2. Screening procedures will only be performed for healthy volunteers who give voluntary written informed consent.

Visits 2 to 4: 3 randomized treatment periods with a duration of 3 days each in which healthy volunteers will receive each of the following on one occasion: selumetinib (blinded), placebo (blinded), and moxifloxacin (open-label). Healthy volunteers will be administered the investigational product on Day 1 and will be resident in the study center from the day before Day -1 until all study assessments are completed 48 hours post-dose (Day 3) for all 3 visits. Each investigational product administration will be separated by wash-out period of at least 3 days between investigational product administrations. Healthy volunteers may be asked

to return to the study center for further safety assessments, if deemed necessary by the principal investigator.

Visit 5: healthy volunteers will be required to return to the study center for follow-up assessments 7 to 10 days following discharge on Day 3, Visit 4.

Target healthy volunteers population

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

Investigational product, dosage and mode of administration

All healthy volunteers will receive all 3 treatments (Treatments A, B and C), blinded to selumetinib or placebo but open to moxifloxacin by using a double-dummy technique.

Treatment A: A single administration of a 75 mg dose of selumetinib which will be administered as 3x25 mg oral capsules

Treatment B: Moxifloxacin 400 mg (1 capsule)

Treatment C: Selumetinib placebo (3 x placebo capsules)

Comparator, dosage and mode of administration

Avelox® (moxifloxacin), a fluoroquinolone antibiotic, is administered to the healthy volunteers orally at a dose of 400 mg in the capsule formulation as the open-label positive control in the study.

Duration of treatment

Only a single dose of selumetinib will be administered during the study. The overall duration of participation in the study for each healthy volunteer is approximately 8 weeks.

Outcome variable(s):

Pharmacodynamics (PD)

The primary variable will be the time matched change from baseline QTcF. Secondary variables will include the digital electrocardiogram intervals including heart rate, RR, PR, QRS, QT, and QTcB

Pharmacokinetics

Where the data allow, the following pharmacokinetic parameters will be calculated for selumetinib and moxifloxacin: maximum concentration in the sampled matrix

(C_{max}), area under plasma concentration-time curve in the sampled matrix from time zero to infinity (AUC), area under plasma concentration-time curve in the sampled matrix from time zero to the last quantifiable concentration ($AUC_{(0-t)}$), time to C_{max} (t_{max}), terminal rate constant ($_z$), terminal half-life ($t_{½}$), apparent oral plasma clearance (CL/F), apparent volume of distribution at equilibrium (V_{ss}/F), apparent terminal phase volume of distribution (V_z/F), mean residence time (MRT). For the N-desmethyl metabolite of selumetinib AUC, C_{max}, t_{max} $_z$, $t_{½}$, $AUC_{(0-t)}$, and metabolite to parent exposure ratios: N-desmethyl selumetinib AUC/selumetinib AUC (MR_{AUC}), and N-desmethyl selumetinib C_{max}/selumetinib C_{max} (MR_{Cmax}) will be determined.

Safety

Safety endpoints will include adverse events, physical examinations, ophthalmologic assessments, vital signs, clinical laboratory assessments, and electrocardiogram parameters.

Statistical methods

Digital ECG variables (heart rate, RR, PR, QRS, QT, QTcF and QTcB) will be listed and summarized by treatment group using appropriate descriptive statistics (eg, n, arithmetic mean, standard deviation [SD], min, median, and max).

The primary analysis of change from baseline for QTcF will be carried out using a repeated measures linear mixed model with fixed effects for treatment, period, time, period-by-time interaction, treatment-by-time interaction, and the baseline value (pre-dose from each period) as a covariate. Healthy volunteers will be treated as a random effect. Time will be treated as repeated effect within healthy volunteer-period using an appropriate covariance. At each of the post-dose ECG nominal times, the least-squares means with corresponding 2-sided 90% confidence interval (CI) for selumetinib compared to placebo will be calculated. The upper bounds of the intervals will be compared against the 10 ms threshold under an intersection-union test.

To conclude that selumetinib shows no effect on the QTcF interval, all upper confidence bounds would need to be less than 10 ms.

In addition to this, a sensitivity analysis will be performed in which the treatment comparison (selumetinib vs placebo) will be performed at each time point, using an analysis of covariance (ANCOVA) with healthy volunteer, period and treatment as factors and baseline QTcF (pre-dose from each period) as a covariate. These intervals will be evaluated against the criteria above, and if there is conflicting conclusions from the two analyses the reason for this should be investigated to the level of detail necessary.

For QTcB, QT, HR, RR, QRS and PR the same statistical model as described for the primary analysis of QTcF will be used to assess the effect of treatment.

To test the assay sensitivity of the study, the treatment effect of moxifloxacin (from the model above) will be evaluated by estimating the mean difference to placebo for the mean of QTcF during the 1 to 4-hour period post-dose with a corresponding two-sided 90% CI. The lower bound of this two-sided interval will be evaluated against the 5 ms threshold, and assay sensitivity will be concluded if the lower bound of the CI is above this.

Descriptive statistics for both observed values and change from baseline for each treatment group will be presented over time for QTcF, QTcB, QT, HR, RR, QRS and PR. The number and percentage of healthy volunteers exceeding specified limits for QTcF will also be summarized.

Categorical analyses:

Frequency (number of healthy volunteers and number of events) of observed QTcF and QTcB interval prolongation:

maximum QTc interval >450 ms but ms

maximum QTc interval >480 ms but ms

maximum QTc interval >500 ms

Frequency (number of healthy volunteers and number of events) of QTcF and QTcB:

maximum QTc interval increases from baseline >30 ms but ms

maximum QTc interval increases from baseline >60 ms

Plasma concentrations and pharmacokinetic parameters for all analytes will be summarized using appropriate descriptive statistics and graphical presentations. Exploratory analyses may be performed to evaluate the relationship between selumetinib and plasma concentrations and corrected QT intervals.

Exploratory analyses may be performed to evaluate the relationship between selumetinib and plasma concentrations and corrected QT intervals.

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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
AE	Adverse event
ALP	Alkaline phophatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from time zero to the last quantifiable concentration
$AUC_{(0-48)}$	Area under the plasma concentration-time curve from time zero to 48 hours post-dose
AVblock	Atrioventricular block
BLQ	Below the lower limit of quantification
BMI	Body mass index
bpm	Beats per minute
CI	Confidence interval
C_{max}	Maximum plasma concentration
CL/F	Apparent clearance at steady state
CPA	Clinical Pharmacology Alliance
CPD	Clinical Pharmacology, Drug Metabolism and Pharmacokinetics
CrCL	Calculate creatinine clearance
CV	Coefficient of variation
DAE	Discontinuation of investigational product due to adverse event
DBP	Diastolic blood pressure
dECG	Digital electro cardiogram
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EClysis©	User-interactive computer-based system for analysis of digital ECGs and measurement of ECG intervals and wave amplitudes used by the AstraZeneca ECG center

Abbreviation or special term	Explanation
eCRF	Electronic Case Report Form
EDC	Electronic data capture
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
GRand	Global randomization system
hERG	Human ether-a-go-go related gene
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
HR	Heart rate
IATA	International Air Transport Association
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IOP	Intra-ocular pressure
IP	Investigational product
IRB	Institutional Review Board
LIMS	Laboratory Information Management System
LLOQ	Lower limit of quantification
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase
min	Minimum
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 data points included in the log-linear regression analysis used to determine $_z$ ^{z} determination)
NA	Not applicable
ND	Not determined
NOEL	No observed effects level
NSCLC	Non-small cell lung cancer

Abbreviation or special term	Explanation
OAE	Other significant adverse event
pECG	Paper print-out ECG
PD	Pharmacodynamics
PICTS	Phase I Clinical Trial System
PK	Pharmacokinetics
PR (PQ)	ECG interval measured from the onset of the P wave to the onset of the QRS complex
PRO	Patient reported outcomes
Rsq	Coefficient of determination for calculation of $_z$ ($_z$ and related parameters will be reported only if Rsq is 0.800 or more)
RR	The time between corresponding points on 2 consecutive R waves on ECG
QRS	ECG interval measured from the onset of the QRS complex to the J point
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTcB	QT interval corrected according to Bazett's formula
QTcF	QT interval corrected according to Fridericia's formula
SAE	Serious adverse event
SD	Standard deviation
SBP	Systolic blood pressure
SPF	Sun protection factor
SUSAR	Suspected unexpected serious adverse reactions
t_{max}	Time to reach maximum plasma concentration
$t_{1/2}$	Terminal elimination half-life
ULN	Upper limit of normal
V_{SS}/F	Apparent volume of distribution at equilibrium
V_Z/F	Apparent terminal phase volume of distribution
z	Terminal rate constant
%AUCex	Percentage of AUC obtained by extrapolation (if the extrapolated area is greater than 20% then AUC and related parameters for that specific profile will not be reported)
	Delta

1. INTRODUCTION

1.1 Background

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

1.1.1 Summary of relevant preclinical and clinical information to date

Preclinical experience with selumetinib is described in the 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 the disruption of the normal spindle function due to the known pharmacological action of selumetinib. With selumetinib, a no observed effects level (NOEL) of 24 mg/kg/day (for 2 days) was established for induction of micronuclei.

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

The human ether-a-go-go related gene (hERG) study showed no significant effect up to the maximum selumetinib concentration studied (10 [4.6]) and the maximum N-desmethyl metabolite concentration studied (100 [44]). In a minipig telemetry study no effects on QT/QTc were seen up to the maximum dose studied (30 mg/kg). From the preclinical safety evaluation, there was no evidence for QT/QTc prolongation after oral dosing selumetinib at dose levels of up to 30 mg/kg, in dogs given twice daily, with free plasma concentrations comparable with those achieved in humans following dosing of 75 mg twice daily.

To date (as of 15 November 2013), approximately 1930 patients with cancer and approximately 50 healthy volunteers have received selumetinib in clinical studies with no effect on QT/QTc interval observed. Clinical experience with selumetinib as monotherapy and in combination with other anti-cancer agents is described in the IB.

Following single oral doses of 75 mg (3x25 mg blue capsules) in healthy volunteers, exposures of maximum plasma concentration in the sampled matrix (C_{max}) 1150 ng/ml and area under the plasma concentration time curve (AUC) 3680 ng.h/ml were achieved. These exposures were slightly lower than those achieved in patients (Study D1532C00066) where single dose exposures of 1307 ng/ml (C_{max}) and 4736 ng.h/ml (AUC) and multiple dose exposures of 1439 ng/ml and 5448 ng.h/ml were achieved.

1.2 Rationale for conducting this study

The primary objective of the current study is to assess the effect of a single dose of selumetinib (75 mg) on the change in time-matched QT interval corrected according to Fridericia's formula (QTcF) interval compared to placebo, using moxifloxacin as a positive control. The study is also intended to assess the effect of selumetinib on other electrocardiogram (ECG) variables (QT, HR, RR, QRS, PR and QT interval corrected according to Bazett's formula [QTcB]). The study will be conducted in healthy male volunteers, in accordance with the International Conference on Harmonization (ICH) E14 guidelines. The ICH E14 guideline recommends the evaluation of the time interval of ventricular depolarization and repolarization in a dedicated placebo controlled trial utilizing the therapeutic dose and where tolerability considerations allow, a supratherapeutic dose at a substantial multiple of therapeutic exposure. For selumetinib, a 75 mg single dose is considered the highest acceptable dose to be administered in healthy volunteers. For this reason, the study does not include a supratherapeutic dose in the design.

The confidence in the ability of thorough QT/QTc study to detect QT/QTc prolongation can be enhanced by the use of a positive control to establish the assay sensitivity. For the current study, open label, moxifloxacin (fluoroquinolone antibiotic) is selected as the positive control because it is documented to cause a QT prolongation exceeding 5 ms at the therapeutic dose of 400 mg (Démolis et al 2000), (the selected positive control should have an effect on the mean QT/QTc interval of about 5 ms [ie, an effect that is close to the QT/QTc effect that represents the threshold of regulatory concern, around 5 ms]). Moxifloxacin is recommended as a positive control for thorough QT/QTc study by the ICH E14 Expert Working Group, due to its clear clinical signal of QT prolongation and consistent pharmacokinetics (PK) profile (Chen et al 2005). The current study is intended to assess the PK of selumetinib and moxifloxacin, to explore the relationship between plasma concentration and cardiac ventricular repolarisation effect on the heart after a single oral dose of selumetinib or moxifloxacin. The study is also considered to assess the safety and tolerability of selumetinib by the assessment of adverse events (AEs), laboratory variables and vital signs as the secondary objectives.

1.3 Clinical safety

1.3.1 Adverse events in healthy volunteers

In a phase 1 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 3 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, ECG parameters or left ventricular ejection fraction (measured by echogram). The most common AEs reported were contact dermatitis (to ECG electrodes) (25.9%), headache (11.1%), raised creatinine phosphokinase (due to physical exertion) (11.1%) and nasal congestion (7.4%). No serious adverse events (SAEs) were reported in this 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 hyd-sulfate monotherapy treatment in advanced cancer patients is included in Table 1. Adverse event data are available from Studies D1532C00005 and D1532C00020 (65 advanced cancer patients in total). The most frequent AEs were decreased blood potassium 3/65 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.

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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
Dyspnoea exertional	1	1.5	1	14.3	0	0	0	0
Dysuria	1	1.5	1	14.3	0	0	0	0
Fatigue	1	1.5	0	0	0	0	1	3.3
Frequent bowel movements	1	1.5	0	0	0	0	1	3.3
Pain in extremity	1	1.5	0	0	0	0	1	3.3
Somnolence	1	1.5	0	0	0	0	1	3.3
Syncope vasovagal	1	1.5	0	0	0	0	1	3.3
Tachycardia	1	1.5	1	14.3	0	0	0	0
Vision blurred	1	1.5	0	0	1	3.6	0	0
Vomiting	1	1.5	0	0	0	0	1	3.3
Wheezing	1	1.5	0	0	0	0	1	3.3

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, and paronychia

General: facial and/or peripheral oedema, fatigue/asthenia, pyrexia

Respiratory: dyspnea

Eye: blurred vision

Physical assessments: increased blood pressure reduced left ventricular ejection fraction

Laboratory changes: increases in serum aspartate transaminase or alanine transaminase, hypoalbuminemia, hyperphosphatemia, which may be associated with an increase in calcium x phosphate product requiring therapeutic intervention

Patients in previous studies with 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 some advanced cancer patients treated with selumetinib but a causal relationship with selumetinib had not been established:

Central serous retinopathy

Retinal vein occlusion

Pneumonitis/interstitial lung disease

Muscle weakness

Increase in creatine phosphokinase

Further information on selumetinib can be found in the IB.

1.4 Benefit/risk and ethical assessment

A single dose of selumetinib will be administered to healthy male volunteers purely for research and development purposes and those healthy volunteers receiving the investigational product (IP) 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 have been reported in metastatic cancer patients who received

previous treatment with chemotherapy and/or radiotherapy and took selumetinib for a long period of time. In a previous study D1532C00066 performed in healthy volunteers, selumetinib was well tolerated and AEs reported were managed in accordance with standard clinical practice. Moxifloxacin is known to induce well characterized and reproducible effects on the QT/QTc interval at a 400 mg dose without any clinically significant risk to the exposed healthy volunteers.

As for the safety consideration, the healthy male volunteers in the current study will be instructed to use sunscreen (greater than 30 Sun Protection Factor [SPF]) and to follow contraceptive measures for up to 14 days after last administration of selumetinib.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to assess the effect of a single dose of selumetinib (75 mg) on the change in time-matched QTcF interval compared to placebo.

2.2 Secondary objectives

The secondary objectives of the study are:

To investigate the effect of selumetinib on additional ECG variables (QT, HR, RR, QRS, PR) and QTcB

To assess the maximum of the mean changes in time-matched QTcF interval after moxifloxacin administration compared to placebo

To examine the pharmacokinetics of selumetinib, the N-desmethyl metabolite of selumetinib, and moxifloxacin

To explore the relationship between plasma concentration and cardiac ventricular repolarization effect on the heart after a single oral dose of selumetinib or moxifloxacin by assessments of plasma concentrations of selumetinib, moxifloxacin and the QT/QTcF interval on digital electrocardiograms (dECGs)

To further assess the safety and tolerability of selumetinib by assessment of AEs, laboratory variables and vital signs

2.3 Exploratory objective

To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to selumetinib (optional).

The exploratory analysis will be reported separately.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

This is a double-blind (for selumetinib), open-label (for moxifloxacin), positive-controlled, randomized, placebo-controlled, 3-way crossover study evaluating a single dose of oral selumetinib 75 mg with a single dose of oral moxifloxacin 400 mg as a positive control.

Approximately 54 healthy male volunteers randomized at 1 study center with at least 47 evaluable healthy volunteers to complete the study. Withdrawn healthy volunteers will not be replaced, however additional volunteers may be included in the study until such a time as 47 evaluable volunteers have completed all treatment periods.

The study will comprise 5 visits:

Visit 1: within 28 days of Visit 2. Screening procedures will only be performed for healthy volunteers who provide voluntary written informed consent.

Visits 2 to 4: 3 randomized treatment periods with a duration of 3 days each in which healthy volunteers will receive each of the following on one occasion: selumetinib (blinded), placebo (blinded), and moxifloxacin (open-label). Healthy volunteers will be administered the investigational product on Day 1 and will be resident in the study center from the day before dosing (Day -1) until all study assessments are completed 48 hours post-dose (Day 3) for all 3 visits. Each investigational product administration will be separated by wash-out period of at least 3 days between investigational product administrations. Healthy volunteers may be asked to return to the study center for further safety assessments, if deemed necessary by the principal investigator.

Visit 5: healthy volunteers will be required to return to the study center for follow-up assessments 7 to 10 days following discharge on Day 3, Visit 4.

Healthy volunteers will be randomized to one of 6 treatment sequences as presented in Figure 1. All healthy volunteers will receive all 3 treatments (Treatments A, B and C), blinded to selumetinib or placebo but open to moxifloxacin by using a double-dummy technique.

Figure 1 Schematic design of study

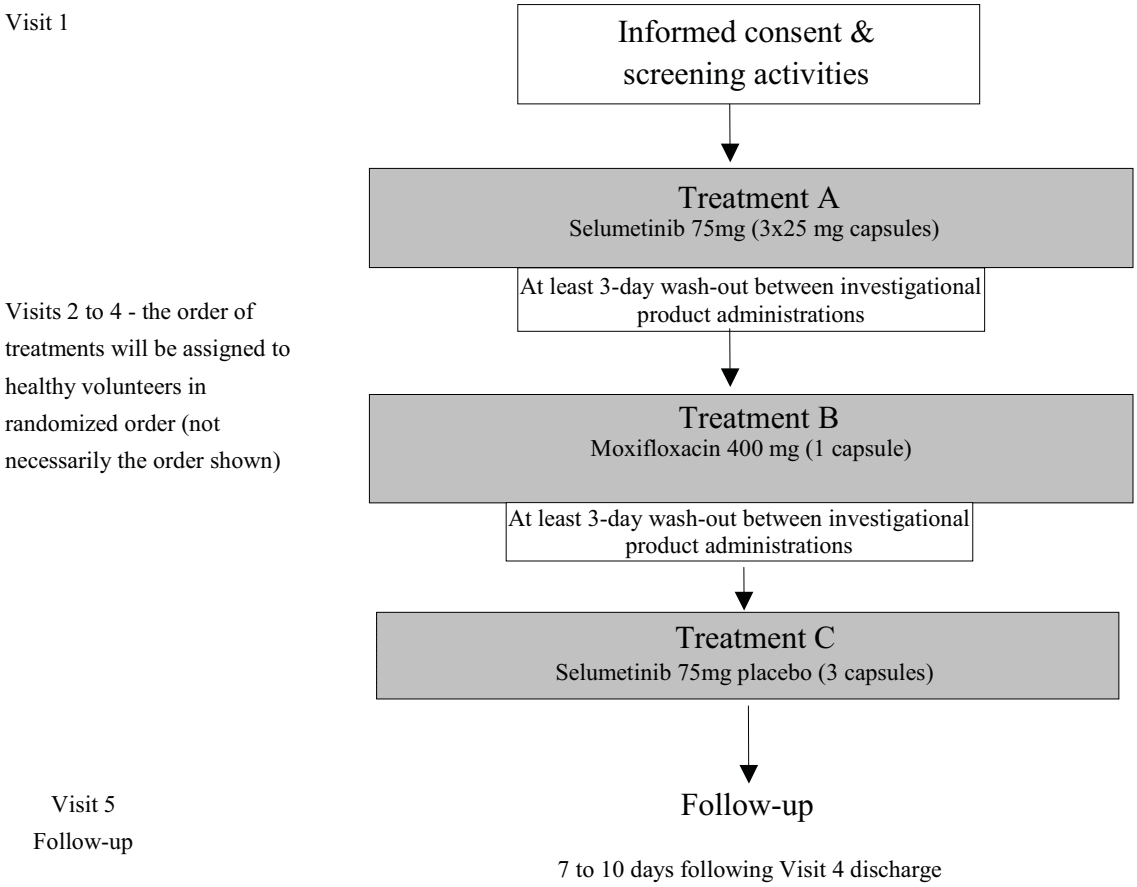

Table 2 Study assessments

Assessments	Visit 1 Screening	Visits 2 to 4 Residential period				Visit 5 Follow-up
	prior to Visit 2	Day -1 Admission	Day 1	Day 2	Day 3 Discharge	7 to 10 days after Visit 4
Informed consent/ allocation of enrollment code	X					
Informed consent for genotyping (optional)	X					
Demography	X					
Medical/surgical history	X					
Physical examination	X	X[a]			X[a]	X
Eligibility criteria	X	X[g]				
Weight and height	X					
Vital signs[j]	X	X	X	X	X	X
Hematology, clinical chemistry, urinalysis[j]	X	X		X	X	X
Drugs of abuse screen[c]	X	X				
HIV, hepatitis B and C	X					
Ophthalmic examination[d]	X[d]	X[d]				
Randomization		X[h]				
Investigational product administration			X			
Safety 12-lead ECG[b,e]	X	X	X	X	X	X
Digital ECG[b]			X	X		
Telemetry[b]		X	X	X		
Pharmacogenetic sampling (optional)[f]			X			
PK selumetinib blood sampling[j]			X	X	X	
PK moxifloxacin blood sampling[j]			X	X	X	
Concomitant medication	X	X	X	X	X	X
Adverse events questioning[i]		X	X	X	X	X

dECG: digital electrocardiogram; ECG: electrocardiogram; HIV: human immunodeficiency virus, IOP: intra-ocular pressure, PK: pharmacokinetics

a Brief physical examination at Day-1 for Visits 2, 3, and 4.
b Telemetry ends on Day 2 at 24 hours.
c Includes alcohol and cotinine.
d Ophthalmic examination (best corrected visual acuity, IOP, slit-lamp fundoscopy) will be conducted at screening or on Day-1 (will be considered the baseline value; no need to repeat) and for cause (on occurrence of AE only).
e Following dECG where appropriate.
f Sample can be collected at any time during the study.
g Eligibility assessment is performed at screening (Visit 1) and on Day-1 of Visit 2.
h Randomization will be performed only once for each volunteer in the study on Day 1, Visit 2.
i SAE collection will start after informed consent and information on AE will be collected from admission at Visit 2 until Visit 5.
j See Table 3 for details of assessments during Visits 2 through 4.

Table 3 Assessments during residential period (Visits 2 to 4)

Assessment	Day -1	Pre-dose	0	0.5 h	1 h	1.5 h	2 h	2.5 h	3 h	3.5 h	4 h	6 h	8 h	12 h	24 h	36 h	48 h
Investigational product administration			X														
Safety 12-lead ECG		X		X	X	X	X				X	X	X	X	X		X
dECG[a]		X		X	X	X	X		X		X	X	X	X	X		
Telemetry[b]	[g]																
Supine pulse rate and blood pressure (after dECG)		X				X	X				X	X	X	X	X	X	X
Hematology, clinical chemistry, urinalysis	X														X		X
Urine screen for drugs of abuse[c]	X																
Blood sampling PK-selumetinib / moxifloxacin[d,e,f]		X		X	X	X	X	X	X	X	X	X	X	X	X		X
Adverse events questioning																	

dECG: digital electrocardiogram, ECG: electrocardiogram, h: hour/s, min: minutes, PK: pharmacokinetic

a Continuous 12-lead resting dECG recordings will be made for 20 minutes pre-dose and, as 5 minutes recordings post-dose for analysis in the EClysis© system on dosing days (Day 1 through 24 hour post-dose [Day 2] of each visit), at the time points specified in this table.

b During the treatments (Visits 2 to 4), telemetry will be monitored from 30 minutes pre-dose through 24 hours post-dose.

c Includes alcohol and cotinine.

d The 10 minutes rest + 5 minutes dECG should precede PK assessment at each dECG time point.

e Blood samples (2 mL) will be taken at the indicated time points to measure selumetinib and N-desmethly metabolite concentrations or moxifloxacin concentrations.

f Plasma will be collected and prepared from all PK blood samples; however only the samples from the healthy volunteers receiving selumetinib or moxifloxacin will be analyzed for plasma concentrations at the bioanalytical laboratory.

g A baseline telemetry will be performed on Day -1, Visit 2 from 0h to 4h.

Table 4 Time schedule for digital ECG (dECG) assessments during residential period (Visits 2 to 4)

Study Days	ECG Number	Time: Start hour: minute	Dose	Time: Stop hour: minute	dECG continuous[abc]	Other
1		-01:30		-01:00		Apply the electrodes[b]
1		-00:55		-00:40		Rest in bed
1	1	-00:40	Pre-dose	-00:20	20 minutes[c]	
1		-00:20		-00:05		Toilet use recommended
1		00:00	investigational product administration			
1	2	00:25		00:30	5 minutes[c]	
1	3	00:55		01:00	5 minutes[c]	
1	4	01:25		01:30	5 minutes[c]	
1	5	01:55		02:00	5 minutes[c]	
1	6	02:55		03:00	5 minutes[c]	
1	7	03:55		04:00	5 minutes[c]	
1	8	05:55		06:00	5 minutes[c]	
1	9	07:55		08:00	5 minutes[c]	
1	10	11:55		12:00	5 minutes[c]	
2	11	23:55		00:00	5 minutes[c]	

dECG: digital electrocardiogram, ECG: electrocardiogram;

a The healthy volunteer must be in the same supine body position (maximum 30 degrees flexion in the hip) at each time point and at all visits. The healthy volunteer's feet should not contact the footboard of the bed.

b Skin must be cleaned, and the electrode positions marked with an indelible pen. Electrodes should be applied at least 30 minutes before first recording.

c Healthy volunteer must rest in bed for at least 10 minutes prior to each ECG time point.

3.2 Rationale for study design, doses and control groups

This study is designed to evaluate the effect of a single dose of selumetinib 75 mg on the QT/QTc interval of healthy male volunteers in comparison to placebo and using moxifloxacin as open-label positive control. Healthy volunteers are considered appropriate because the data generated will not be influenced by any disease process or concomitant medication.

The eligibility to this study is restricted to healthy male volunteers. Female gender is generally regarded as associated with a greater inter- and intra-individual variability of QT interval assessments. The objective of this study is to confirm or refute a very small effect on the QT/QTc interval in a model situation, thus it is considered appropriate to exclude female volunteers to optimize precision. The magnitude of the presumed maximum mean effect in the power calculation for this study will also preclude any attempts to draw significant conclusions on possible small differences between subgroups within the study, such as by gender, and such hypotheses will be required to be investigated later in the clinical development should the outcome of the current study indicate any overall effect of a regulatory concern.

All of the healthy volunteers will receive each of the three treatments; selumetinib 75 mg (blinded), placebo (blinded), and moxifloxacin 400 mg (open-label). The order in which these treatments are received will be determined by randomization to one of six treatment sequences. Further details are given in Section 5.2.1.

The dose level of 75 mg of selumetinib 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. Since a 75 mg single dose of selumetinib is considered the highest acceptable dose to be administered in healthy volunteers, this study does not include a supratherapeutic dose in the design.

The healthy volunteers will receive moxifloxacin 400 mg in the unblinded treatment. Moxifloxacin is known to induce well characterized and reproducible effects on the QT/QTc interval at a 400 mg dose without any clinically significant risk to the exposed healthy volunteers.

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

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.

4. HEALTHY VOLUNTEERS SELECTION CRITERIA

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

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

4.1 Inclusion criteria

For inclusion in the study, 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 volunteers aged 18 to 45 years (inclusive).

3. Healthy volunteers willing to use barrier methods of contraception, unless their partners are post-menopausal, surgically sterile or are using accepted contraceptive methods (oral contraceptive, implant, long-term injectable, or intra-uterine device). In addition, healthy male volunteers with sexual partners who are pregnant or who could become pregnant (ie, women of childbearing potential) should use barrier methods of contraception for at least 14 days after completing the study to avoid pregnancy and/or potential adverse effects to the developing embryo.

   Acceptable methods for volunteers' partners include:

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

   Acceptable methods for volunteers include:

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

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

5. Be a non-smoker or have not smoked in the last 30 days prior to screening for this study.

6. 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:

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

4.2 Exclusion criteria

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

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

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

3. Has received another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment within at least 30 days of the first administration of the investigational product in this study. The period of exclusion begins 30 days after the final dose or 1 month after the last visit whichever is the longest.
Note: volunteers consented and screened, but not randomized in this study or a previous Phase I study, are not excluded.

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

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

6. Any clinically relevant abnormal findings in physical examination, hematology, clinical chemistry, urinalysis, vital signs or ECG at Visit 1, which in the opinion of

the principal investigator, may put the healthy volunteer at risk because of his participation in the study.

7. History of additional risk factors for Torsade de Pointes (eg, heart failure, hypokalemia, personal or family history of arrhythmia or long QT syndrome).

8. Abnormal vital signs, after 10 minutes supine rest, defined as any of the following:

   Systolic blood pressure (SBP) >140 mmHg

   Diastolic blood pressure (DBP) >90 mmHg

   Heart rate (HR) <40 or >85 beats per minute (bpm)

9. Any clinically important abnormalities in the rhythm, conduction or morphology of resting ECG that may interfere with the interpretation of the QTc interval changes. These include healthy volunteers with any of the following:

   PR (PQ) interval shortening <120 ms (healthy volunteers with PR>110 ms but <120 ms are acceptable if there is no evidence of ventricular pre-excitation and no other ECG findings that would exclude the healthy volunteer)

   PR(PQ) interval prolongation (>240 ms). Intermittent second or third degree atrioventricular (AV) block (ie, Mobitz type 1, Wenckebach; while asleep or at deep rest is not disqualifying)

   Incomplete, full or intermittent bundle branch block (QRS >110 ms but <115 ms with normal QRS and T wave morphology is acceptable if there is no evidence of ventricular hypertrophy)

   Abnormal T wave morphology, particularly in the protocol defined primary lead V2

   Prolonged QTcF >450 ms or shortened QTcF <340 ms, or having a family history of long QT syndrome

10. Use of any prescribed medicine and over-the-counter drugs (including herbal remedies, vitamins and minerals) within 2 weeks/5 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.

11. 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.

12. 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.

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

14. 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.

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, at screening or admission to the study center on Day -1.

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

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

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

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

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

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

23. Healthy volunteers of Japanese or non-Japanese Asian ethnicity.

24. Any healthy volunteer whose one parent or grandparent (maternal or paternal) is Japanese or non-Japanese Asian (e.g. China, Taiwan, Korea, Philippines, Thailand, Vietnam, and Malaysia). Asian Indians are acceptable.

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

25. Previous bone marrow transplant.

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

Procedures for withdrawal of incorrectly enrolled healthy volunteers see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

The following restrictions will be applied in this study:

On Day 1 of each treatment period, healthy volunteers will be fasted from midnight on Day -1 up to 4 hours after dosing. No fluids will be allowed from 1 hour prior to investigational product administration until 1 hour after, except the water needed to swallow the investigational product.

Healthy volunteers should avoid the intake of high fatty meals during the study. Standardized meals will be provided at the same time during each visit while resident at the study center (Visits 2 to 4).

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

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

Abstain from consumption of alcoholic beverages from within 48 hours before admission to each of the treatment period until discharge from the study center during each treatment visit, and should consume no more than 2 units of alcohol per day between treatment periods and after the final treatment period until after the follow-up visit (Visit 5).

Abstain from any tobacco or nicotine containing products from the time of screening until after the follow-up visit (Visit 5).

Blood donation will not be allowed at any time during the study and up to 3 months after the follow-up visit (Visit 5).

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

Abstain from consuming grapefruit, grapefruit juice, cranberry juice and other cranberry-containing products or any products (eg, orange marmalade) made with Seville oranges from 1 week prior to Visit 2 until completing all assessments at Visit 4.

Healthy male volunteers with sexual partners who are pregnant or, who could become pregnant (ie, women of childbearing potential) and are not using accepted contraceptive methods, should use barrier methods of contraception from the time of the administration of IP until 14 days after completing the study to avoid pregnancy and/or potential adverse effects to the developing embryo. Healthy male volunteers should avoid sperm donation during and for 14 days after the study completion. Reliable methods of contraception should be used consistently and correctly.

Acceptable methods for healthy volunteer's partners include:

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

Acceptable methods for healthy male volunteers include:

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

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

Healthy volunteers should refrain from taking vitamin E supplements or multivitamin supplements from 2 weeks prior to administration of the investigational product and throughout the study until the follow-up visit (Visit 5).

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

For concomitant medication restrictions, see Section 5.6.

5.2 Subject enrollment and randomization and initiation of investigational product

The principal investigator will:

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

2. Assign potential volunteer a unique enrollment number, beginning with 'E0001001'.

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

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

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

5.2.1 Procedures for randomization

Approximately 54 healthy male volunteers (ages 18 to 45 years) will be randomized at one study center; out of which at least 47 healthy volunteers should complete the study. A randomization scheme will be produced by using the AstraZeneca global randomization system (GRand), under a 3-period, 3 treatment William's Latin square design. Randomization codes will be assigned strictly sequentially as healthy volunteers become eligible for randomization. Healthy volunteers will be randomized to one of 6 treatment sequences as shown in Table 5.

Table 5 Randomization sequences

Sequence	Dosing period 1	Dosing period 2	Dosing period 3
1	A	B	C
2	A	C	B
3	B	A	C
4	B	C	A
5	C	A	B
6	C	B	A

Treatment A = single 75 mg dose of selumetinib, administered as 3x25 mg oral capsules.
Treatment B = moxifloxacin 400 mg (1 capsule).
Treatment C = selumetinib placebo (3 capsules).

Withdrawn healthy volunteers will not be replaced, however additional volunteers may be included in the study until such a time as 47 evaluable volunteers have completed all treatment periods.

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

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

Where healthy volunteers who 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

5.4.1 Methods for ensuring blinding

Double dummy method is used for ensuring blinding of the selumetinib and placebo treatments in the study. Moxifloxacin will be administered in an open-label fashion.

Selumetinib and placebo will be matched for formulation, appearance, and number of capsules administered.

The randomization list should be kept in a secure location until the database is locked or equivalently, clean file is declared. The pharmacokineticist will remain blinded during the study conduct, unless otherwise required based on study findings. The pharmacokineticists will be unblinded to perform the final PK analyses after all volunteers have completed the study, final bioanalytical results are available, and all required study data are considered clean. This may occur prior to database lock.

The following personnel will have access to the randomization list:

The pharmacy personnel preparing the investigational product at the study center

The personnel performing the bioanalyses of the plasma samples

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomization for each randomized healthy volunteers, will be available to the pharmacists at the study center.

The treatment code should not be broken except in medical emergencies when the appropriate management of the healthy volunteers requires knowledge of the treatment randomization. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to healthy volunteers to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analysis of data until all decisions on the evaluability of the data from each individual healthy volunteer have been made and documented.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Details of the investigational product are provided in the Table 6.

Table 6 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)	
Placebo matching selumetinib	Placebo capsules matching 25 mg selumetinib	

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

In Treatment C, the healthy volunteers will be provided 25 mg placebo capsules which would be blue in color resembling selumetinib, to ensure the maintenance of the double-blind.

5.5.2 Doses and treatment regimens

Visit 2 to 4 in this study would comprise of 3 treatments:

Treatment A: A single administration of a 75 mg dose of selumetinib which will be administered as 3x25 mg oral capsules

Treatment B: Moxifloxacin 400 mg (1 capsule)

Treatment C: Selumetinib placebo (3 x placebo capsules)

The 3 treatment arms would form 6 treatment sequences; ABC, ACB, BAC, BCA, CAB, and CBA. Each of the healthy volunteers will receive all 3 treatments, one treatment at each visit (Visit 2, Visit 3 and Visit 4) according to the treatment sequence assigned by the randomization.

At each treatment visit, the healthy volunteers will be admitted to the study center the day prior to dosing (Day -1). The investigational product (treatment A/ B/ C) will be administered

on Day 1 and the healthy volunteers will remain resident in the study center until Day 3 after all study assessments are completed 48 hours post-dosing. Each investigational product administration will be separated by wash-out period of at least 3 days between investigational product administrations. The healthy volunteers will return to the study center for follow-up assessments at Visit 5, seven to ten days following discharge on Day 3 of Visit 4.

Investigational product will be administered to the healthy volunteers orally following a fast from midnight on Day -1 up to 4 hours after dosing on Day 1. The healthy volunteers will not be allowed any fluid intake from 1 hour prior to investigational product administration until 1 hour after dosing, except the water needed to swallow the investigational product.

Dietary and other restrictions to be followed by the healthy volunteers during the treatment period are explained in the Section 5.1.

5.5.3 Additional study drug

Avelox® (moxifloxacin), a fluoroquinolone antibiotic, is administered to the healthy volunteers orally at a dose of 400 mg in the capsule formulation as the open-label positive control in the study. Avelox® will be sourced locally by the 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 as per the relevant labeling instructions.

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/5 times the half-life of the respective drug of Visit 2 until Visit 5, with the exception of occasional use of acetaminophen for pain relief and over-the-counter adrenergic nasal spray for relief of nasal congestion, if needed. Use of 1 g acetaminophen 6 hourly (to a maximum daily dose of 4 g) is permitted, however the investigator should be informed so it can be recorded.

Healthy volunteers should refrain from taking vitamin E supplements or multivitamin supplements from 2 weeks prior to administration of the investigational product and throughout the study until the follow-up visit (Visit 5).

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

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

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

Other medication, which is considered necessary for the healthy volunteers' 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 checked by the monitor at monitoring visits.

5.7.1 Accountability

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

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

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

5.8 Discontinuation of investigational product

The healthy volunteers may be discontinued from the study in the following situations:

Healthy volunteer decision: The healthy volunteer is at any time free to discontinue treatment, without prejudice to further treatment

AEs

Severe non-compliance to study protocol

Documented tachyarrhythmia of concern after consultation with a cardiologist at the AstraZeneca ECG Center

Any significant and clinically relevant changes in the safety parameters (eg, ECG, blood pressure, pulse rate, laboratory assessments and AEs) making the continuation of dosing unjustified

Risk to volunteer as judged by the investigator and AstraZeneca

Healthy volunteer lost to follow-up

Healthy volunteers who discontinue investigational product administration will be withdrawn from the study, see section 5.2.1.

5.8.1 Procedures for discontinuation of a healthy volunteers 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).

5.9 Withdrawal from study

Healthy volunteers are at any time free to withdraw from the study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such healthy volunteers will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (See Sections 6.3.3 and 6.3.4).

Withdrawn healthy volunteers will not be replaced, see section 5.2.1.

6. COLLECTION OF STUDY VARIABLES

The study assessments are described in the sections below.

It is important that the dECG 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 after the scheduled time point. The sequence at a particular time point is:

dECG

Paper 12-lead ECG

Blood pressure and pulse rate

PK blood sampling

Safety laboratory assessments

For timing of pre-dose dECG assessment see Table 4.

6.1 Recording of data

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

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

6.2 Data collection at 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.

Demographic data and other characteristics will be recorded and will include date of birth, gender, race, ethnicity, alcohol consumption, and smoking history. Each healthy volunteer will undergo screening during the 28 days prior to Day -1 to confirm eligibility. 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 height and weight and calculation of BMI

Recording of medical/surgical history

Ophthalmic examination (at screening or at Day -1, Visit 2)

Urine sample for routine urinalysis and screening for drugs of abuse

Alcohol and cotinine screen

Calculation of CrCL

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

AE recording

6.2.2 Follow-up procedures

Follow-up assessments will be conducted 7 to 10 days after discharge on Day 3, Visit 4, and will include a brief physical examination, vital signs (supine blood pressure and pulse rate), blood sampling for routine hematology and clinical chemistry, urine sampling for routine urinalysis, 12-lead ECG, recording of concomitant medication, and recording of AEs and SAEs.

6.3 Safety

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

6.3.1 Definition of adverse events

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

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

6.3.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, wash-out, 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 healthy volunteers 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 time of signature of informed consent, throughout the treatment period and including the follow-up visit, Visit 5.

All SAEs will be recorded from the time of informed consent.

Follow-up of unresolved adverse events

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 collected for each AE:

AE (verbatim)

The date and time when the AE started and stopped

Maximum intensity

Mild (awareness of sign or symptom, but easily tolerated)

Moderate (discomfort sufficient to cause interference with normal activities)

Severe (incapacitating, with inability to perform normal activities)

Whether the AE is serious or not

Investigator causality rating against the investigational product (yes or no)

Action taken with regard to the investigational product

AE caused healthy volunteer's withdrawal from study (yes or no)

Outcome

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

Date AE met criteria for SAE

Date investigator became aware of SAE

AE is serious due to

Date of hospitalization

Date of discharge

Probable cause of death

Date of death

Autopsy performed

Causality assessment in relation to study procedure(s)

Causality assessment in relation to other medication

Causality assessment in relation to additional study drug

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 an SAE.

Causality collection

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

For SAEs, causal relationship will also be assessed for other medication, study procedures, and additional study drug. 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 laboratory tests and vital signs will be summarized in the clinical study report. Deterioration as compared to baseline in the protocol-mandated laboratory values and vital signs 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 healthy volunteer shows an aspartate aminotransferase (AST) **or** alanine aminotransferase (ALT) x upper limit of normal (ULN) **or** total bilirubin 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 adverse events 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 7. The urine drugs of abuse screen as well as the alcohol screen will be performed by the laboratory at the study center while all other

samples, including the cotinine screen, will be analyzed by the Physician's Reference Laboratory, United States. The date and time of sample collection will be recorded in the eCRF.

The laboratory variables to be measured are provided in Table 7.

Table 7 Safety laboratory variables

Clinical chemistry (serum)	**Hematology**
Creatinine	Platelet count
Bilirubin total	Leukocyte differential count
Alkaline phosphatase (ALP)	Leukocytes count
Alanine aminotransferase (ALT)	Hemoglobin
Aspartate aminotransferase (AST)	Erythrocyte volume fraction
Albumin	Reticulocytes
Calcium total	Erythrocytes
Sodium	Erythrocyte mean cellular volume
Potassium	**Urinalysis**
Phosphate	Erythrocytes
C-reactive protein high sensitive	Albumin
Thyroxine free (only at screening)	Glucose
Thyroid-stimulating hormone (only at screening)	

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:

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

Where age is expressed

A urine sample will be collected at screening and Day -1 of Visits 2 to 4 to screen for the following drugs of abuse: amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, methadone, methamphetamine, ecstasy, opiates, phencyclidine, oxycodone, and tricyclic antidepressants. Alcohol breathalyzer test and urine cotinine test will be performed at screening and Day -1 of Visits 2 to 4.

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 screened will be followed until normalization or for as long as the investigator considers necessary.

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

For blood volume see Section 7.1.

6.3.6 Physical examination

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

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

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

6.3.7 ECG

For timing of assessments refer to Table 2, Table 3 and Table 4.

6.3.7.1 Resting 12-lead ECG

The 12-lead ECGs will be performed after the healthy volunteer has rested in the supine position for 10 minutes. Paper ECG for safety review by the investigator will be performed following dECG recordings and at additional intervals if required.

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.

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

6.3.7.2 Electronic capture of 12-lead continuous digital ECG

Twenty-minute pre-dose recordings followed by pre-scheduled post-dose 5-minute recordings will be made on the dosing day (Day 1) on each treatment visit (Visits 2 to 4) according to the schedule shown in Table 2, Table 3 and Table 4.

The AstraZeneca ECG Center will perform the dECG analysis in this study, using the EClysis© system, version 3.3, or higher.

At the protocol-indicated time points (Table 3) during the residential period, 12-lead continuous dECG will be recorded over at least 5 minutes with the Schiller Cardiovit CS-200 recorder ( ) and transmitted to the AstraZeneca central dECG repository, according to AstraZeneca ECG Center´s standard procedures for settings, recording, and transmission of dECGs.

The same recorder will be used for each healthy volunteer at all time points, when possible. Date and time settings must be checked at the start of each study day and aligned with an official timekeeper for all machines used in the study.

Skin preparation must be thorough and electrode positions must be according to standard 12-lead ECG placement. Electrode positions for dECG take precedence over real-time ECG display electrodes. Electrode positions will be marked with an indelible pen at the start of each study day to ensure exact reposition. Permanent electrodes will be applied at least 30 minutes before first study recording and left in place for the duration of each relevant study day.

Healthy volunteers will rest in a supine position for at least 10 minutes before the start of each recording. The healthy volunteer should be in the same supine body position (maximum 30 degrees flexion of the hip and feet not in contact with the footboard) at each recording time point during the study.

The metadata for all dECG files will be checked and approved by the responsible personnel at the study center to ensure that the files transferred to the AstraZeneca central dECG files repository are made accessible to the ECG Scientific Advisors for analysis.

As standard, 10-second ECGs are extracted by the EClysis© system twice per minute from the continuous recording and initially automatically analyzed by the software.

In this study lead V2 will be analyzed and reported as primary. Lead V5 will be analyzed, for all visits, as backup for the individual where analysis in lead V2 is not deemed possible for pre-dose, for significant parts of whole visits or for whole visits. The analysis is performed blinded to treatment.

The ECG Scientific Advisor will perform all required manual adjustments to the ECG annotations provided automatically by EClysis©. Finally, an external expert cardiologist will review the totality of data and perform all necessary adjustments before locking the EClysis© data into a read-only state.

The numerical values for ECG intervals and amplitudes will be exported and made accessible on the AstraZeneca central dECG repository to accredited data management specialists for conversion into SAS files.

The following variables will be reported by the AstraZeneca ECG Center: HR, RR, PR, QRS and QT intervals from the lead defined as primary in the protocol. Derived parameters (QTcF, and QTcB) will be calculated by the study statistician or delegate.

6.3.7.3 Real time display (telemetry)

At treatment visits (Visits 2 to 4), the healthy volunteers will be continuously monitored for safety by telemetry ECG (2-lead real-time ECG display). The study lead II real time display ECG will be displayed at the times shown in Table 2, Table 3 and Table 4. The real time display will be monitored by the investigator, research nurse or delegate.

6.3.8 Vital signs

Vital signs will be measured at the time points indicated in Table 2 and Table 3.

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.

6.3.8.3 Ophthalmology

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

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

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

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

6.4 Pharmacokinetics

6.4.1 Collection of samples

The blood samples will be drawn at the visits and times indicated in the study assessment tables (Table 2 and Table 3) to measure plasma concentrations of selumetinib, the N-desmethyl metabolite of selumetinib and moxifloxacin.

Blood samples (2 mL total at each time point) for determination of selumetinib and N-desmethyl selumetinib or moxifloxacin concentrations in plasma will be collected and prepared at the study center. If deemed appropriate, the amide metabolite may also be measured. Individual venipunctures for each time point may be performed or an in-dwelling catheter may be used. If the study center chooses to use an in dwelling catheter, 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.

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.

6.4.2 Determination of drug concentration

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

While plasma will be collected and prepared from all PK blood samples, only the samples from healthy volunteers receiving selumetinib or moxifloxacin will be analyzed for plasma concentrations at the bioanalytical laboratory. Placebo samples will not be analyzed unless there is a question related to correct treatment administration.

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 clinical study report.

6.5 Pharmacodynamics

Section 6.3.7 outlines the capture of digital ECG assessments with the derivation of ECG Parameters (heart rate, RR, PR, QRS, QT, and QTc intervals).

6.6 Pharmacogenetics

All healthy volunteers screened in the study will have the option to provide a blood sample for pharmacogenetic analysis. Healthy volunteers will not be excluded from participating in the study if they decline participation in the genetic analysis. Blood samples for these analyses will be collected only after the healthy volunteer has signed a separate genetic informed consent for sample collection. The analysis and results from these optional studies will be handled and reported separately from the main study.

6.6.1 Collection of pharmacogenetic samples

The blood sample for genetic research will be obtained from the healthy volunteers at Visit 2, only from the healthy volunteers who consent to provide samples for genetic research. 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 volunteers 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 8.

Table 8 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	14	119
	Hematology	4	14	56
	Serology	8.5	1	8.5
Pharmacokinetic[a]-selumetinib		2	28	56
Pharmacokinetic[a]-moxifloxacin		2	14	28
Pharmacogenetic (optional)		10	1	10
Total				**277.5**

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

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

7.2 Handling, storage and destruction of biological samples

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

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

7.2.1 Pharmacokinetic samples

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

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

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

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

7.2.2 Pharmacogenetic samples

The exploratory genetic research component of the study is optional.

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

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

The samples and data for genetic analysis in this study will be single coded. The link between the healthy volunteer screening/randomization 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 ensures that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be 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 is maintained for all samples throughout their lifecycle.

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

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

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

Samples retained for further use are 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 volunteer's withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca

Ensures that biological samples from that healthy volunteer, if stored at the study 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

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

8.1 Subject data protection

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

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

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

8.2 Ethics and regulatory review

An Institutional Review Board (IRB) should approve the final study protocol, including the final version of the informed consent forms 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 screening of any healthy volunteer into the study.

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

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

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

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

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

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

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

8.3 Informed consent

The principal investigator will:

Ensure each healthy volunteer is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study

Ensure each healthy volunteer is notified that they are free to discontinue from the study at any time

Ensure that each healthy volunteer is given the opportunity to ask questions and allowed time to consider the information provided

Ensure each healthy volunteer provides signed and dated informed consent before conducting any procedure specifically for the study. A separate informed consent form will be provided for the optional genotyping

Ensure the original, signed informed consent forms are stored in the investigator's Study File

Ensure a copy of the signed informed consent form is given to the healthy volunteer

Ensure that any incentives for healthy volunteers who participate in the study as well as any provisions for healthy volunteers harmed as a consequence of study participation are described in the informed consent form that is approved by an IRB

8.4 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 each principal investigator. For distribution to IRB see Section 8.2.

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

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

8.5 Audits and inspections

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

9. STUDY MANAGEMENT

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 Clinical Study Agreement between AstraZeneca and the investigator

9.2 Training of study site personnel

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

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

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

9.3 Monitoring of the study

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

Provide information and support to the investigator

Confirm that facilities remain acceptable

Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed

Perform source data verification (a comparison of the data in the eCRFs with the healthy volunteers' 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 volunteers

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

9.3.1 Source data

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

9.4 Study agreements

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

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

9.4.1 Archiving of study documents

The investigator follows the principles outlined in the Clinical Study Agreement.

9.5 Study timetable and end of study

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

The study is expected to start in Q1 2014 and to end by Q3 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 screened 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 informed consent form will be kept with a copy of the completed source documents in the appropriate file folder provided, or a note to indicate where the records can be located. All records should be kept in conformance to applicable national laws and regulations.

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

Vital signs: last measureable value taken prior to the first IP administration

Paper ECG: last measureable value taken prior to the first IP administration

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

11.1.2 Other significant adverse events (OAE)

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

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

11.2 Calculation or derivation of pharmacokinetic variables

The PK analysis of plasma concentration data will be performed at Pharmacokinetic analysis will be conducted according to Standard Operating Procedures unless otherwise specified.

Actual sampling times will be used in the plasma PK parameter calculations. Pharmacokinetic parameters will be determined using standard non-compartmental methods with Phoenix® WinNonlin® 6.3 or higher (or SAS® Version 9.2 or higher . Pharmacokinetic parameter units will be consistent with the plasma concentration units specified in the bioanalytical data. No conversion of units will be made.

The following PK parameters will be determined for plasma selumetinib, N-desmethyl selumetinib, and moxifloxacin as appropriate.

AUC	Area under the plasma concentration-time from time zero to infinity, calculated by linear up/log down trapezoidal summation.
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration, calculated by linear up/log down trapezoidal summation.
C_{max}	Maximum concentration in plasma, obtained directly from the observed concentration versus time data.
t_{max}	Time to C_{max}.
CL/F	Apparent systemic plasma clearance (selumetinib and moxifloxacin only).
V_{ss}/F	Apparent volume of distribution at equilibrium, mean residence time (MRT)*CL/F (selumetinib and moxifloxacin only).
V_z/F	Apparent terminal phase of volume at distribution (selumetinib and moxifloxacin only).
$t_{1/2}$	Terminal half-life.
z	Terminal rate constant.
MRT	Mean residence time
MR_{AUC}	AUC metabolite to parent ratio, N-desmethyl selumetinib AUC/selumetinib AUC.
MR_{Cmax}	C_{max} metabolite to parent ratio, N-desmethyl selumetinib C_{max}/selumetinib C_{max}.

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

No dose adjustment is required for PK parameters which require moxifloxacin dose for calculation since the moxifloxacin dose being administered is based on the free base equivalent where Avelox® tablets contain 400 mg moxifloxacin.

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

Additional PK parameters may be calculated if deemed appropriate.

11.3 Calculation or derivation of pharmacodynamic variable(s)

The PD variables to be reported or derived from the continuous dECG measurements are heart rate, RR, PR, QRS, QTcB, and QTcF.

The QT interval will be corrected for RR (the duration of a heart beat) to obtain corrected (QTc) variables. The general formula for QTc that will be used is: $QTc=QT/RR^b$, with QT intervals expressed in milliseconds and the RR interval in seconds.

The 'b' in the above formula will be:

For QTcF (Fredericia's correction), b=1/3

For QTcB (Bazett's correction), b=1/2

For the analysis of PD variables, the baseline value is defined as per the pre-dose value on Day 1 within each treatment period.

The change from baseline in PD variables (PR, QRS, QT, QTcF and QTcB) and placebo-corrected change from baseline in PD variables (QTcF and QTcB) will be calculated for each healthy volunteer at each post-dose time for each treatment period. Additional parameters may be determined if deemed appropriate.

11.4 Calculation or derivation of the relationship between pharmacokinetic and pharmacodynamic variables

See Section 12.2.6.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

There will be three analysis sets included in the study:

Safety analysis set

Pharmacokinetic analysis set

Pharmacodynamic (PD) analysis set

12.1.1 Safety analysis set

All healthy volunteers who received at least one dose of treatment (selumetinib, placebo or moxifloxacin) will be included in the safety population. Throughout the safety results sections, erroneously treated healthy volunteers (eg, those randomized to treatment A but actually given treatment B) will be accounted for in the actual treatment group.

12.1.2 PK analysis set

The PK analysis set will include all healthy volunteers who receive at least one dose of selumetinib or moxifloxacin and have at least one post-dose PK measurement without important events or protocol deviations thought to significantly affect the PK of the drug (eg, healthy volunteer vomited at or before 2 times median, t_{max}; wrong dose administered; prohibited concomitant medication; etc). Healthy volunteers will be analyzed according to the treatment they actually received. The PK scientist will evaluate the strategy for dealing with data affected by protocol deviations before any formal statistical analysis is performed.

12.1.3 PD analysis set

The PD analysis set will include all healthy volunteers who receive at least one dose of treatment (selumetinib, placebo, or moxifloxacin) and that have at least one post-dose QT measurement without important events or protocol deviations thought to significantly affect the QT. Healthy volunteers will be analyzed according to the treatment they actually received. A strategy for dealing with data affected by such protocol violations and deviations will be agreed by the PK scientist and the Study Statistician prior to the final analysis.

12.2 Methods of statistical analyses

12.2.1 General Principles

Statistical analyses will be performed per Standard Operating Procedures using 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 and not that assigned by randomization.

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

12.2.2 Subject characteristics

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

12.2.3 Safety and tolerability

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

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

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

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

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

volunteer from Day -1, Visit 2 until the follow-up visit. Adverse events that occur before dosing will be reported separately.

Adverse events will be listed for all healthy volunteers with AEs that occur before dosing indicated on the listing. The number of AEs experienced following administration of the investigational product will be summarized in tables using the MedDRA (Version 13.0 or higher) system organ class and preferred term. These summary tables will also be produced with severity and causality of AEs added as additional classification factors. The number of AEs overall, SAEs, other significant AEs, AEs that lead to withdrawal, AEs of severe intensity, and causally related AEs will be summarized. Any AE occurring post-dose will be considered associated with the last dose of investigational product taken. Adverse events occurring during the wash-out period and before the subsequent dose of the investigational product in Visit 3 or Visit 4 will be associated with the last dose. Any AE occurring on Day -1, Visit 2 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 observed value at each scheduled assessment and for the corresponding change-from-baseline.

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

12.2.4 Pharmacokinetics

The PK analysis and the PK summaries, figures, and data listings will be the responsibility of the All data received will be presented in data listings. Pharmacokinetic summaries will be presented for volunteers in the PK analysis set as defined in Section 12.1.2. Data from healthy volunteers excluded from the PD analysis set will be included in the data listings, but not in the summaries. Extra measurements (such as unscheduled or repeat assessments) will also not be included in summary tables, but will be included in the listings.

For quantitative variables, the population size (sample size and available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarized using descriptive statistics, including available data, arithmetic mean, SD, coefficient of variation (CV), median, minimum, and maximum values. Additionally, geometric means and geometric CV will be reported for PK variables, except for t_{max}. The geometric mean is calculated as the exponential of arithmetic mean calculated from the data on a log scale. The geometric CV 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. The mean SD, CV, geometric mean, and geometric CV will not be calculated for t_{max}; t_{max} will be summarized using median and range.

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

- At a time point where less than or equal to 50% of the values are below the LLOQ (BLQ), all BLQ values will be set to LLOQ, and all descriptive statistics will be calculated
- At a time point where more than half of the values are BLQ, the mean, SD, geometric mean, and CV will be set to Not determined (ND). The maximum value will be reported from the individual data, and the minimum and median will be set to BLQ
- If all values are BLQ at a time point, no descriptive statistics will be calculated for that time point. Not applicable (NA) will be written in the field for SD and CV and BLQ will be written in the fields for mean, geometric mean, minimum, median, and maximum
- The number of BLQ values (n below LLOQ) will be reported for each time point

The PK data will be presented by treatment group and analyte, as appropriate.

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

Figures of geometric mean and +/- geo SD concentration-time data for each treatment will be presented for each analyte separately, on linear and semi-logarithmic scales. Individual healthy volunteer concentration-time data for each analyte will be graphically presented separately on linear and semi-logarithmic scales. Graphical presentations of other PK data may be added at the discretion of the pharmacokineticist.

12.2.5 Pharmacodynamics

The PD analysis and the PD summaries, figures, and data listings will be the responsibility of the biostatistition. All data received will be presented in data listings. Pharmacodynamic summaries will be presented for healthy volunteers in the PD analysis set as defined in Section 12.1.3. Data from healthy volunteers excluded from the PD analysis set will be included in the data listings, but not in the summaries. Extra measurements (such as unscheduled or repeat assessments) will also not be included in summary tables, but will be included in the listings.

The primary analysis of change from baseline for QTcF will be carried out using a repeated measures linear mixed model with fixed effects for treatment, period, time, period-by-time interaction, treatment-by-time interaction and the baseline value (pre-dose from each period) as a covariate. Healthy volunteer will be treated as a random effect. Time will be treated as

repeated effect within healthy volunteer-period using an appropriate covariance. At each of the post-dose ECG nominal times, the least-squares means with corresponding two-sided 90% confidence intervals (CI) for selumetinib compared to placebo will be calculated. The upper bounds of the intervals will be compared against the 10 ms threshold under an intersection-union test.

To conclude that selumetinib shows no effect on the QTcF interval, all upper confidence bounds would need to be less than 10 ms.

In addition to this, a sensitivity analysis will be performed in which the treatment comparison (selumetinib vs placebo) will be performed at each time point, using an analysis of covariance (ANCOVA) with healthy volunteer, period and treatment as factors and baseline QTcF (pre-dose from each period) as a covariate. These intervals will be evaluated against the criteria above, and if there is conflicting conclusions from the two analyses the reason for this should be investigated to the level of detail necessary.

For QTcB, QT, HR, RR, QRS and PR the same statistical model as described for the primary analysis of QTcF will be used to assess the effect of treatment.

To test the assay sensitivity of the study, the treatment effect of moxifloxacin (from the model above) will be evaluated by estimating the mean difference to placebo for the mean of QTcF during the 1 to 4 hour period post-dose with a corresponding two-sided 90% CI. The lower bound of this two-sided interval will be evaluated against the 5 ms threshold, and assay sensitivity concluded if the lower bound of the CI is above this.

Digital ECG intervals (QTcF, QTcB, QT, HR, RR, QRS and PR) for both observed values and change from baseline will be listed and summarized by treatment and/or study day using descriptive statistics (n, mean, SD, %CV, median, minimum, and maximum). The number and percentage of healthy volunteers exceeding specified limits for QTcF and QTcB will also be summarized by treatment and/or study day. QTcF and QTcB outliers are defined as QTcF and QTcB values following dosing that are greater than 450 ms or are increases from baseline greater than 30 ms. QTcF and QTcB outliers will be summarized using the following categories:

Frequency (number of healthy volunteers and number of events) of observed QTcF and QTcB interval prolongation:

maximum QTc interval >450 ms but ms

maximum QTc interval >480 ms but ms

maximum QTc interval >500 ms

Frequency (number of healthy volunteers and number of events) of QTcF and QTcB:

maximum QTc interval increases from baseline >30 ms but ms

maximum QTc interval increases from baseline >60 ms

Additionally digital ECG data from this study may be pooled with data from another study(ies) and analyzed by AstraZeneca using statistical methods and PK/PD modeling. The methodology for these analyses will be described separately from this protocol.

12.2.6 Pharmacodynamics/pharmacokinetics

The relationship between plasma concentrations of selumetinib or moxifloxacin and changes in QTcF will be explored. Graphical displays will be presented for the individual observed and change from baseline values for QTcF and QTcB will be plotted against the corresponding selumetinib and metabolite plasma concentration. If the data suggest a relationship, the area under the plasma concentration-time curve from time zero to 48 hours post-dose ($AUC_{(0-48)}$) for the QTc intervals may be determined for further graphical exploration versus selumetinib exposure (C_{max} and AUC).

If a concentration–QTc relationship is believed to exist, regression models may be used to attempt to model the relationship between parameters.

If clinically relevant changes in QTc are observed in the study then a PK-PD analysis may be performed to investigate the relationship of QTc change with PK exposure. This will be performed as a separate analysis and reported separately from the clinical study report.

12.3 Determination of sample size

The primary comparison will be a test of non-inferiority of selumetinib compared to placebo for the mean time-matched differences in change from baseline in QTcF. The null hypothesis is:

H_0: $M_{Sel,\,t} - M_{plac,\,t} >= 10$ ms for at least one t

Versus the alternative hypothesis:

H_a: $M_{Sel,\,t} - M_{plac,\,t} < 10$ ms for all t

where $M_{Sel,\,t}$ and $M_{plac,\,t}$ are the mean changes in QTcF for selumetinib and placebo, respectively, at time point t.

The 10 ms non-inferiority limit is used, where the upper bounds of all one-sided 95% confidence intervals should be less than 10 ms. Assuming that there is a drug effect of 3 ms, the delta is 7 ms. The within-healthy volunteer between-period standard deviation of change from baseline (ms. When there are 10 post-dose time points, a one-sided 0.05 level paired t-test with 90% power requires n=47 evaluable healthy volunteers. This controls for multiplicity of tests at time points. Hence, 54 healthy volunteers will be randomized into this study in order to have at least 47 evaluable healthy volunteers.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

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

In the case of a medical emergency the investigator may contact the AstraZeneca Clinical Pharmacology Alliance (CPA) Program Director. 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 study drug 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 relevant information is provided to the AstraZeneca Patient Safety data entry site.

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

13.3 Pregnancy

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

13.3.1 Paternal exposure

Healthy male volunteers should refrain from fathering a child or donating sperm during the study and for 14 days after Visit 4 (last administration of investigational product).

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

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

14. LIST OF REFERENCES

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Démolis J-L, Kubitza D, Tennezé L, Funck-Brenton C. Effect of a single oral dose of moxifloxacin (400 mg and 800 mg) on ventricular repolarization in healthy subjects. Clin Pharmacol Ther. 2000;68:658-666.

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use 2005
ICH Harmonized Tripartite Guideline: The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs E14, 12 May 2005.

Clinical Study Protocol Appendix A

Drug Substance	Selumetinib
Study Code	D1532C00071
Edition Number	1

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Phase I, Double-blind (Selumetinib), Placebo-controlled, Open-Label (Moxifloxacin) Positive-controlled, Randomized, Three-period Crossover Study to Assess the Effects of Single Oral Dose of Selumetinib (75 mg) on QTc Interval Compared to Placebo, using AVELOX (Moxifloxacin) as a Positive Control, in Healthy Male 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 Developme
site representative

Medical Science Director,

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

ASTRAZENECA SIGNATURE(S)

A Phase I, Double-blind (Selumetinib), Placebo-controlled, Open-Label (Moxifloxacin) Positive-controlled, Randomized, Three-period Crossover Study to Assess the Effects of Single Oral Dose of Selumetinib (75 mg) on QTc Interval Compared to Placebo, using AVELOX (Moxifloxacin) as a Positive Control, in Healthy Male Volunteers Aged 18 to 45 years

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I agree to the terms of this study protocol.

AstraZeneca Research and Development site representativ

Global Product Statistician,

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