Revised Clinical Study Protocol

Drug Substance	Selumetinib
Study Code	D1532C00081
Edition Number	1

An Open-label Comparative Study of the Pharmacokinetics, Safety and Tolerability of Selumetinib (AZD6244, ARRY-142886) (Hyd-Sulfate) following a Single Oral Dose in Subjects with Renal Impairment and Healthy Subjects

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden.

AstraZeneca Research and Development site representative

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Date

The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1			

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change

AstraZeneca

PROTOCOL SYNOPSIS

An Open-label Comparative Study of the Pharmacokinetics, Safety and Tolerability of Selumetinib (AZD6244, ARRY-142886) (Hyd-Sulfate) following a Single Oral Dose in Subjects with Renal Impairment and Healthy Subjects

Principal Investigator

Study center and number of subjects planned

This study may be conducted at 1 to 2 study centers in the United States. It is expected that a maximum of 48 subjects will be sufficient to fulfil the objectives of this study with 12 subjects recruited into the ESRD and healthy subjects' groups and 8 renally impaired subjects recruited into each of the mild, moderate, and severe renal impairment groups.

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

Objectives

Stage 1

Primary Objective

To investigate the pharmacokinetics (PK) of a single 50 mg administration of selumetinib in subjects with end-stage renal disease (ESRD) compared to healthy subjects.

Secondary Objectives

1. To further assess the safety and tolerability of a single 50 mg oral administration of selumetinib in subjects with ESRD and in healthy subjects.

2. To characterize the PK of the N-desmethyl and amide metabolites after oral administration of single doses of selumetinib in subjects with ESRD and in healthy subjects.

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.

The exploratory analysis will be reported separately.

Stage 2

Primary Objective

To investigate the PK of a single 50 mg administration of selumetinib in renally impaired subjects with mild, moderate, severe or ESRD compared to healthy subjects.

Secondary Objectives

1. To further assess the safety and tolerability of a single 50 mg oral administration of selumetinib in subjects with mild, moderate, and severe renal impairments.

2. To characterize the PK of the N-desmethyl and amide metabolites after oral administration of single doses of selumetinib to subjects with mild, moderate or severe renal impairment.

Exploratory Objective

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

The exploratory analysis will be reported separately.

Study design

This study is an open-label, comparative, 2-part (Stage 1 and Stage 2) design conducted at 1 to 2 study centers. Subjects will be classified at screening on the basis of their renal function using the Cockroft-Gault formula to estimate creatinine clearance (CrCL).

Stage 1: will include 12 healthy subjects (Group 1) and 12 subjects with ESRD requiring dialysis (Group 5). Healthy subjects in Group 1 will participate in 1 treatment period. Subjects with ESRD (Group 5) will participate in 2 treatment periods in order to study these renally impaired subjects under both non-dialysis and dialysis conditions. There will be a washout period of at least 7 days between investigational product administrations. After a screening period of up to 28 days (relative to Day 1), subjects will be admitted on Day -1 of the study. Initially 8 healthy subjects will be enrolled after completion of at least 8 ESRD subjects to allow for appropriate demographic matching.

Healthy subjects will receive a single oral 50 mg administration (2 x 25 mg capsules) of selumetinib on the morning of Day 1 with approximately 240 mL of water. Healthy subjects

will remain in the study center until completion of all study procedures (approximately 72 hours postdose) and will be asked to return to the study center for a follow-up visit (Visit 3), 3 to 7 days following discharge.

Twelve subjects with ESRD (Group 5) requiring dialysis will participate in 2 treatment periods in order to study these subjects under both non-dialysis and dialysis conditions. There will be a washout period of at least 7 days between investigational product administrations. In Treatment Period 1, subjects will receive a single oral administration of 50 mg (2 x 25 mg capsules) selumetinib on Day 1 after completion of a dialysis session. Subjects will remain in the study center until the start of their next dialysis session (approximately 72 hours postdose).

Subjects will return to the study center after a washout period of at least 7 days from the first investigational product administration and admitted on Day -1 for Treatment Period 2. On Day 1 of Treatment Period 2, the ESRD group (Group 5) will receive a single oral administration of 50 mg selumetinib under fasted conditions (as in Treatment Period 1), 1 hour prior to the start of a dialysis session. Subjects will return to the study center for a follow-up visit (Visit 4) 3 to 7 days following discharge at Treatment Period 2.

Stage 2: Stage 2 will be conducted only if renal impairment in the ESRD group shows a change in selumetinib exposure as defined by the ESRD group mean area under the plasma concentration-time curve (AUC) of selumetinib being >1.5 x the group mean of healthy subjects. This trigger may occur based on comparison of 12 ESRD subjects with the first 8 healthy subjects or with 12 ESRD subjects with all 12 healthy subjects.

All available safety, tolerability and PK data from Stage 1 will be reviewed to assess the effect of renal impairment on selumetinib. A decision will be made by the Safety Review Committee (SRC) to determine whether to conduct Stage 2 and which renal impairment group(s) to include.

A total of 24 subjects, 8 subjects in each group with mild (Group 2), and/or moderate (Group 3), and/or severe (Group 4) renal impairment, will be enrolled in Stage 2 to receive 50 mg of selumetinib. The SRC would decide if all or only selected renal impairment group will be included in Stage 2. Study procedures for screening, treatment and follow-up periods will be the same as those described for the healthy subjects control group (Group 1).

Target subject population

Subjects will be classified at screening on the basis of their renal function using the Cockroft-Gault formula to categorize subjects as mild, moderate, severe renal impairment. The remaining 4 healthy subjects will be matched to the entire renal impairment population if additional groups are enrolled. Healthy subjects with normal renal function (CrCL ≥80 mL/min) will be matched for gender, age (±10 years) and body mass index (BMI) (±15%) to the mean age and BMI of subjects in the ESRD group.

Investigational product, dosage and mode of administration

A single oral administration of, 50 mg (2 x 25 mg) selumetinib capsule with approximately 240 mL water. Healthy subjects will receive 1 single dose selumetinib on 1 occasion. Subjects with ESRD will receive a single dose selumetinib on 2 occasions separated by at least 7 days between investigational product administrations once under non-dialysis (administered after completion of dialysis) and once under dialysis conditions (administered 1 hour before commencement of dialysis). If the study continues to Stage 2, renally impaired subjects with mild, moderate, and severe renal impairment will receive 1 single dose selumetinib on 1 occasion.

All subjects should be fasted from 2 hours before investigational product administration (fluids are allowed up to 1 hour before administration of investigational product and again 2 hours after investigational product administration) and remain fasted for 4 hours after investigational product administration, except the water needed to consume the investigational product (240 mL).

Comparator, dosage and mode of administration

None

Duration of treatment

The study duration for healthy subjects and subjects with mild, moderate and severe renal impairment will include 3 visits and be approximately 5 weeks: a maximum of 28 days (relative to Day 1) for screening (Visit 1), a 4-day residency (Visit 2), and a follow-up visit 3 to 7 days following discharge (Visit 3).

The study duration for subjects in the ESRD group (Group 5) will include 4 visits and be approximately 6 weeks: a maximum of 28 days (relative to Day 1) for screening (Visit 1), 2 periods of a 4-day residency (Visits 2 and 3), and a follow-up visit 3 to 7 days following discharge at Treatment Period 2 (Visit 4).

Outcome variable(s):

- Pharmacokinetic

The primary PK parameters will be: maximum observed plasma concentration (C_{max}), area under plasma concentration-time curve from zero extrapolated to infinity (AUC), and area under plasma concentration-time curve to time of last measurable concentration ($AUC_{[0-t]}$) for selumetinib if AUC is not reportable in more than 80% of subjects.

The secondary PK parameters will be: time to reach maximum observed concentration administration (t_{max}), area under the plasma concentration time curve from zero to 12 hours postdose ($AUC_{[0-12]}$), terminal rate constant (λ_z), terminal elimination half-life ($t_{1/2}$), apparent oral clearance (CL/F), apparent volume of distribution at steady state (V_{ss}/F), apparent volume of distribution during the terminal phase (V_z/F), mean residence time (MRT), fraction unbound (f_u), free C_{max} ($C_{max,\,u}$), free AUC (AUC_u), free $AUC_{(0-t)}$ ($AUC_{[0-t],u}$), unbound CL/F (CL/F_u),

the amount of drug excreted in urine (A_e) the fraction of dose excreted in urine (f_e), renal clearance (CL_R) for selumetinib and AUC, C_{max}, t_{max}, $t_{1/2}$, λ_z, $AUC_{(0-12)}$, $AUC_{(0-t)}$, the metabolite to parent AUC and C_{max} ratios (MR_{AUC} and MR_{Cmax}), A_e, f_e, and CL_R for N-desmethyl selumetinib (and the amide metabolite, if deemed appropriate). Additionally, time-matched area under the plasma concentration time curve from 1 to 5 hours postdose ($AUC_{[1-5]}$), cumulative amount extracted during dialysis ($Ad_{[1-5]}$), and dialysis clearance (CL_D) will be calculated for Group 5, Period 2 only for both selumetinib and appropriate metabolites.

- Safety

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

Statistical methods

Pharmacokinetic data will be listed and summarized by renal function group, as appropriate.

For statistical evaluation of renal impairment, log-transformed C_{max} and AUC (or $AUC_{[0-t]}$ if AUC is not reportable in more than 80% of the subjects) of selumetinib and N-desmethyl selumetinib will be separately analyzed using a linear fixed effect analysis of variance model with renal impairment group as a fixed effect. Transformed back from the logarithmic scale, geometric least-squares means together with confidence intervals (2-sided 95%) for C_{max} and AUC will be estimated and presented. Also, ratios of geometric least-squares means (renal group versus normal) together with confidence intervals (2-sided 90%) will be estimated and presented. For ESRD subjects (Group 5), data from off dialysis (Period 1) only will be included in these analyses.

To assess the potential differences between Period 1 (off dialysis) and Period 2 (on dialysis) in ESRD subjects (Group 5), C_{max} and AUC (or $AUC_{[0-t]}$ if AUC is not reportable in more than 80% of the subjects) will be analyzed using a repeated measures analysis of variance model on the log-transformed data. The model will include period as a repeated fixed effect. Transformed back from the logarithmic scale, geometric least-squares means together with confidence intervals (2-sided 95%) for C_{max} and AUC will be estimated and presented. Also, ratios of geometric least-squares means (Group 5 Period 2 versus Period 1) together with confidence intervals (2-sided 90%) will be estimated and presented.

If the study proceeds to Stage 2, then the data from both stages will be analyzed together. The primary analysis for Stage 2 will be the regression model described below and an exploratory analysis will be performed using a linear fixed effect analysis of variance similar to the above model.

The relationship between log-transformed pharmacokinetic parameters (C_{max} and AUC) and creatinine clearance will be assessed using a regression model across renal function groups (with the exception of Group 5 Period 2). Creatinine clearance will be included in the model as a continuous effect. Other covariates (eg, body mass index) may be included if appropriate. Results will be presented for the slope and the associated 90% confidence intervals for the

creatinine clearance parameter from the model. The p-value testing if the slope is different from zero will be presented. Additionally, estimates of the mean PK parameters and 90% confidence intervals will be made at the median creatinine clearance of each of the renal function groups.

As an exploratory analysis, a linear fixed effect analysis of variance model with renal impairment group as a fixed effect will be performed using data from all five renal impairment groups (with the exception of Group 5 Treatment Period 2).

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

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

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
λ_z	Terminal elimination rate constant
$\%AUC_{ex}$	Percentage of AUC obtained by extrapolation
$Ad_{(1-5)}$	Cumulative amount of analyte excreted in dialysis over the 4 hour dialysis period
AE	Adverse event (see definition in Section 6.3.1)
A_e	Amount of analyte excreted in the urine
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under plasma concentration time curve from zero to infinity
AUC_u	Unbound area under plasma concentration time curve from zero to infinity
$AUC_{(0-t)}$	Area under plasma concentration time curve from zero to last quantifiable time point
$AUC_{(1-5)}$	Area under plasma concentration time curve from 1 to 5 hours postdose
$AUC_{(0-12)}$	Area under plasma concentration time curve from zero to 12 hours postdose
BLQ	Below the lower limit of quantification
BMI	Body mass index
Bpm	Beats per minute
CI	Confidence interval
CL/F	Apparent oral clearance
CL/F_u	Unbound apparent oral clearance
CL_D	Dialysis clearance
CL_R	Renal clearance
CPA	Clinical Pharmacology Alliance
CPK	Creatine phosphokinase
CrCL	Creatinine clearance
CSA	Clinical Study Agreement
CSP	Clinical study protocol
CSR	Clinical study report

Abbreviation or special term	Explanation
CV%	Coefficient of variation
C_{max}	Maximum plasma concentration
$C_{max,u}$	Maximum unbound plasma concentration
CYP	Cytochrome P450
DAE	Discontinuation of investigational product due to adverse event
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ESRD	End-stage renal disease
FDA	Food and Drug Administration
f_e	Fraction excreted in urine
$f_{u,av}$	Average fraction unbound
f_u	Fraction unbound
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GCV%	Geometric coefficient of variation
GMP	Good Manufacturing Practice
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IRB	Institutional Review Board
LIMS	Laboratory information management system
LLOQ	Lower Limit of quantification
LSLV	Last subject last visit
LVEF	Left ventricular ejection fraction
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase kinase
Min	Minimum
MRT	Mean residence time
MR_{AUC}	Metabolite to selumetinib AUC ratio
MR_{Cmax}	Metabolite to selumetinib C_{max} ratio

Abbreviation or special term	Explanation
N	Number of data points included in the log-linear regression analysis used to determine λ_z (a minimum of 3 data points will be used for λ_z determination)
NA	Not applicable
ND	Not determined
NOEL	No observed effects level
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OAE	Other significant adverse event (see definition in Section 11.2)
OTC	Optical coherence tomography
pCRF	Paper case report form
PK	Pharmacokinetic(s)
Rsq	Coefficient of determination
SAE	Serious adverse event (see definition in Section 6.3.2).
SD	Standard deviation
SPF	Sun protection factor
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reactions
$t_{1/2}$	Terminal half life
t_{max}	Time to C_{max}
V_{ss}/F	Apparent volume of distribution at steady state
V_z/F	Apparent volume of distribution
ULN	Upper limit of normal

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 program for oncology indications is the responsibility of AstraZeneca. Phase II studies are ongoing in subjects with non-small cell lung cancer (NSCLC) and subjects receiving adjuvant treatment for differentiated thyroid cancer, and a Phase III study in advanced NSCLC is planned.

1.1.1 Summary of relevant pre clinical and clinical information to date

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

Selumetinib was not mutagenic or clastogenic in vitro, but produced increases in micronucleated immature erythrocytes in mouse bone marrow micronucleus studies. Investigatory studies showed this to be predominantly via an aneugenic mechanism and this is entirely consistent with disruption of normal spindle function due to the known pharmacological action of 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. Subjects will be asked to adhere to strict restrictions regarding contraception use and avoid semen donation.

To date (as of 15 November 2013), approximately 1930 subjects with cancer and approximately 50 healthy subjects have received selumetinib. Clinical experience with selumetinib as monotherapy and in combination with other anti-cancer agents is described in the current version of the selumetinib IB.

Following single oral doses of 75 mg (3 x 25 mg blue capsules) in subjects (Study D1532C00066), exposures of maximum plasma concentration (C_{max}) 1150 ng/mL and area under the plasma concentration-time curve from time zero to infinity (AUC) 3680 ng.h/mL were achieved. These exposures were slightly lower than those achieved in subjects on white capsules (Study D1532C00005) 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

It is anticipated that intended subject population (subjects with advanced NSCLC, biliary, thyroid and uveal cancers) for treatment with selumetinib will include individuals with varying degrees of renal impairment. Renal impairment may impact the ability to excrete drugs and thus could result in increased exposures and increased toxicity. In order to ensure that renally impaired subjects receive the appropriate dose of selumetinib it is important to quantify the impact of the degree of renal impairment on the pharmacokinetics (PK) of selumetinib and its metabolites. Currently subjects with a creatinine clearance <50 mL/min are excluded from clinical studies with selumetinib. The data generated from this study may allow subjects with a broader range of renal function to enter future studies.

In animals, selumetinib is eliminated predominantly via the hepatic route with little being excreted in urine. In humans very little selumetinib is eliminated in urine and it is therefore considered unlikely that excretion of selumetinib will be significantly reduced in subjects with renal impairment. Therefore, this study is to be conducted using a 2-stage approach with the initial stage (Stage 1) exploring the effect of end-stage renal disease (ESRD) on the PK of selumetinib compared with the PK in healthy subjects. Only in the event of a change in selumetinib exposure large enough to warrant a dosage adjustment, will subjects with mild, moderate, and severe renal impairment be recruited in Stage 2. In Stage 1 healthy subjects and subjects with ESRD will receive 2 single dose of selumetinib.

1.3 Clinical safety

1.3.1 Adverse events in healthy subjects

In a Phase 1 study conducted in healthy subjects aged 18 to 55 years, to compare the PK profiles of selumetinib from different formulations (Study D1532C00066), healthy subjects 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, electrocardiogram (ECG) parameters or left ventricular ejection fraction (LVEF [measured by echocardiogram]). The most common adverse events (AEs) reported were: contact dermatitis (to ECG electrodes [25.9%]), headache (11.1%), raised creatine phosphokinase (CPK) (due to physical exertion [11.1%]) and nasal congestion (7.4%). No serious 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 subjects

A summary of AEs reported within 24 hours of a single dose of 75 mg selumetinib monotherapy treatment in advanced cancer subjects is provided in Table 1. Adverse event data are available from Study D1532C00005 and Study D1532C00020 (65 advanced cancer subjects in total). The most frequently reported AEs were decreased blood potassium (3/65 subjects [4.5%]), diarrhea, headache, and nausea (each reported for 2/65 subjects

[3.0%]). The event of decreased blood potassium occurred in 3 subjects. All 3 subjects had a low potassium value at baseline. All events (further decrease or similar value/baseline) were considered unrelated to selumetinib by the investigator. Confounding factors included concomitant medications such as diuretics and steroids. These events were not considered to be clinically significant findings. All other AEs were reported in only 1 subject each.

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

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

MedDRA: Medical Dictionary for Regulatory Activities

a Study D1532C00005 (A; 25, 50, 75, 100 mg 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 subjects, 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), and dry mouth.
- Skin and subcutaneous: rashes (including dermatitis acneiform and exfoliative rash), dry skin, and paronychia.
- General: facial and/or peripheral edema, fatigue/asthenia, and pyrexia.
- Respiratory: dyspnea.
- Eye: blurred vision.
- Physical assessments: increased blood pressure and reduced LVEF.
- Laboratory changes: increases in serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT), hypoalbuminemia, and hyperphosphatemia, which may be associated with an increase in calcium x phosphate product requiring therapeutic intervention.

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

The following AEs have been reported in some advanced cancer subjects 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 CPK.

Further information on selumetinib can be found in the IB.

1.4 Benefit/risk and ethical assessment

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

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

A maximum of one single dose will be administered to subjects during this study. In view of the available pre-clinical and clinical data and the study specific risk management procedures, the risk is considered to be minimal (see Section 5.1).

2. STUDY OBJECTIVES

Stage 1

2.1 Primary objective

To investigate the PK of a single 50 mg administration of selumetinib in subjects with ESRD compared to healthy subjects.

2.2 Secondary objectives

1. To further assess the safety and tolerability of a single 50 mg oral administration of selumetinib in subjects with ESRD and in healthy subjects.

2. To characterize the PK of the N-desmethyl and amide metabolites after oral administration of single doses of selumetinib in subjects with ESRD and in healthy subjects.

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.

The exploratory analysis will be reported separately.

Stage 2

2.4 Primary objective

To investigate the PK of a single 50 mg administration of selumetinib in subjects with mild, moderate, severe or ESRD compared to healthy subjects.

2.5 Secondary objectives

To further assess the safety and tolerability of a single 50 mg oral administration of selumetinib in subjects with mild and moderate and severe renal impairments.

To characterize the PK of the N-desmethyl and amide metabolites after oral administration of single doses of selumetinib to subjects with mild, moderate or severe renal impairment.

2.6 Exploratory objective

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

The exploratory analysis will be reported separately.

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This study is an, open-label, comparative, 2-part (Stage 1 and Stage 2) design conducted at 1 to 2 study centers.

Up to 48 subjects will be classified at screening on the basis of their renal function as provided in Table 2 using the Cockroft-Gault formula to estimate creatinine clearance (CrCL):

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

[a] for females

Table 2 Classification of renal function based on estimated creatinine clearance

Degree of renal impairment	Estimated creatinine clearance
Normal Renal Function (healthy subjects [Group 1])	>80 mL/min
Mild Renal Impairment (Group 2)	50 to 80 mL/min
Moderate Renal Impairment (Group 3)	30 to <50 mL/min
Severe Renal Impairment (Group 4)	<30 mL/min
ESRD (Group 5)	requiring hemodialysis, no CrCL calculation

CrCL: creatinine clearance; ESRD: End-stage renal disease

Stage 1

Stage 1 will be an open-label, comparative group study with 12 evaluable subjects with ESRD requiring dialysis (Group 5) and 12 healthy subjects (Group 1). Healthy subjects in Group 1 will participate in 1 treatment period. Subjects with ESRD (Group 5) will participate in 2 treatment periods in order to study these subjects under both non-dialysis and dialysis conditions. There will be a washout period of at least 7 days between investigational product administrations. Initially 8 healthy subjects will be enrolled after completion of at least 8 ESRD subjects to allow for appropriate demographic matching. Subjects will attend the study center for screening within 28 days of the first investigational product administration. Written informed consent will be obtained prior to any study procedures. Subjects will be admitted to the study center in the morning of Day -1. Subjects will remain in the study center until the completion of the study assessments and procedures scheduled on Day 4 (discharge).

Stage 1 will consist of 3 treatment periods. Twelve healthy subjects in Group 1 will participate in 1 treatment period, where they will receive a single oral 50 mg administration (2 x 25 mg capsules) of selumetinib on the morning of Day 1 with approximately 240 mL of water. Healthy subjects should be fasted from 2 hours before investigational product administration (water is allowed up to 1 hour before administration of investigational product for the consumption of the investigational product [240 mL]) and remain fasted for 4 hours after investigational product administration. Healthy subjects (Group 1) will return to the study center for a follow-up visit (Visit 3) 3 to 7 days after the last investigational product administration.

Twelve subjects in Group 5 with ESRD requiring dialysis will participate in 2 treatment periods in order to study these subjects under both non-dialysis and dialysis conditions. There will be a washout period of at least 7 days between investigational product administrations. In Treatment Period 1, subjects will receive a single oral 50 mg administration (2 x 25 mg capsules) of selumetinib on Day 1 after completion of a dialysis session. Subjects should be fasted from 2 hours before investigational product administration (water is allowed

up to 1 hour before administration of investigational product for the consumption of the investigational product [240 mL]) and remain fasted for 4 hours after investigational product administration. Subjects will remain in the study center until the start of their next dialysis session (approximately 72 hours postdose). Subjects will return to the study center after a washout period of at least 7 days from the first investigational product administration and admitted on Day -1 for Treatment Period 2.

On Day 1 of Treatment Period 2, the ESRD group (Group 5) will receive a single oral 50 mg dose of selumetinib under fasted conditions (as in Treatment Period 1), 1 hour prior to the start of a dialysis session. Subjects will remain in the study center until the completion of the study assessments and procedures scheduled on Day 4 of Treatment Period 2.

Subjects will return to the study center for a follow-up visit (Visit 4) 3 to 7 days following discharge.

All available safety, tolerability and PK data from Stage 1 will be reviewed to assess the effect of renal impairment on selumetinib. A decision will be made by the Safety Review Committee (SRC) to determine whether to conduct Stage 2 and which renal impairment group(s) to include.

Stage 2

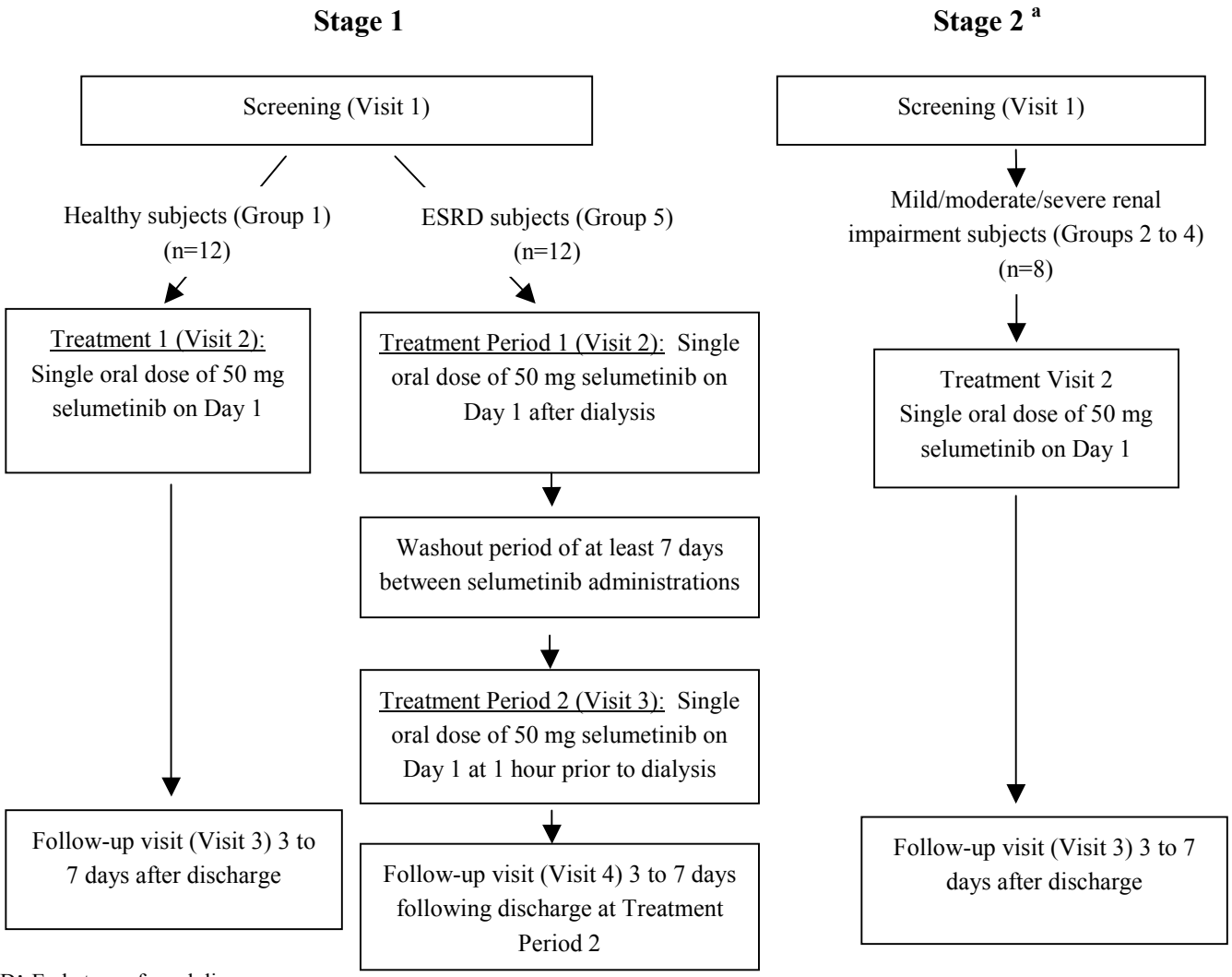
Stage 2 will be conducted only if renal impairment in the ESRD group (12 subjects) show a change in selumetinib exposure as defined by the ESRD group mean AUC of selumetinib being >1.5 x the group mean of healthy subjects (8 subjects or 12 subjects). See section 3.3 Safety Review committee for decision tree details. Stage 2 may be conducted in renally impaired subjects with mild (Group 2) and/or moderate (Group 3) and/or severe renal impairment (Group 4) as judged by the Cockcroft-Gault formula.

Subjects in Stage 2 will be screened during a 28-day screening period (relative to Day 1). Eight subjects will be enrolled per group, and will receive a single administration of 50 mg (2 x 25 mg) selumetinib on the morning of Day 1. Subjects will remain in the study center until the completion of the study assessments and procedures scheduled on Day 4 (discharge).

Subjects will return to the study center for a follow-up visit 3 to 7 days following discharge. Study procedures for screening, treatment and follow-up periods will be the same as those described for the healthy subjects control group.

The study flow chart and study plan is provided below in Figure 1 and Table 3.

Figure 1 Study flow chart



ESRD: End-stage of renal disease

a Stage 2 will only be conducted if necessary based on Stage 1 information.

Table 3 Study Plan

Visits	**Screening**		**Treatment**				**Follow-up** 3 to 7 days following discharge
Healthy subjects + mild/moderate/severe renal impairment subjects	**Visit 1**		**Visit 2**				**Visit 3**
ESRD group	**Visit 1**		**Visits 2 and 3** (At least 7 day washout between investigational product administrations for ESRD on dialysis subjects)				**Visit 4**
Days	**-28 to -2**	**-1[a]**	**1**	**2**	**3**	**4**	
Assessment							
Informed consent[b]	X						
Pharmacogenetic informed consent (optional)		X					
Inclusion/exclusion	X	X					
Estimate creatinine clearance[c]	X	X					
Demography	X						
Medical/surgical and smoking history	X						
Hepatitis B surface antigen, hepatitic C antibodies, and HIV screen	X						
Eye examination[d]	X						
Alcohol (breathalyzer)/ urine drug screen[e]	X	X					

Visits	**Screening**	**Treatment**				**Follow-up** 3 to 7 days following discharge
Healthy subjects + mild/moderate/severe renal impairment subjects	**Visit 1**	**Visit 2**				**Visit 3**
ESRD group	**Visit 1**	**Visits 2 and 3** (At least 7 day washout between investigational product administrations for ESRD on dialysis subjects)				**Visit 4**
Days	**-28 to -2**	**-1[a]**	**1**	**2**	**3**	**4**	
Assessment							
Height/weight and BMI calculation	X	X[f]					X[f]
Admission[a]		X					
Physical examination	X						X
Brief physical examination		X				X	
Vital signs: Supine blood pressure and pulse rate[g]	X	X	X	X	X	X	X
Clinical chemistry/hematology[h]	X	X			X	X	X
Urinalysis/urine microscopy[i]	X	X	X		X	X	X
Administer investigational product[j]			X				
Paper ECG (12-lead)[k]	X	X	X	X	X	X	X
Echocardiogram	X[l]						
Optional genotyping blood collection[m]			X[m]				

Visits	**Screening**		**Treatment**				**Follow-up** 3 to 7 days following discharge
Healthy subjects + mild/moderate/severe renal impairment subjects	**Visit 1**		**Visit 2**				**Visit 3**
ESRD group	**Visit 1**		**Visits 2 and 3** (At least 7 day washout between investigational product administrations for ESRD on dialysis subjects)				**Visit 4**
Days	**-28 to -2**	**-1[a]**	**1**	**2**	**3**	**4**	
Assessment							
Pregnancy test (female subjects only)	X	X					
Follicle-stimulating hormone[p]	X						
PK blood collection for plasma concentrations and protein binding[n n]			X[n]	X[n]	X[n]	X[n]	
Urine collection[n]			X[n]	X[n]	X[n]	X[n]	
Dialysate collection[n]			X[n]				
Discharge						X	
Prior/concomitant medication	X	X	X	X	X	X	X
Record AEs/SAEs[o]	X	X[o]	X	X	X	X	X

AE: Adverse event; BMI: Body mass index; ECG: Electrocardiogram; HIV: Human immunodefiency virus; PK: Pharmacokinetic; SAE: Serious adverse event

After completion of Stage 1, a Safety Review Committee (SRC) will evaluate the safety, tolerability, and plasma PK of selumetinib to determine if Stage 2 will be conducted.

a Subjects will be admitted to the study center on Day -1.

b Informed consent will be collected prior to any procedures being performed.

c Creatinine clearance will be estimated using the Cockroft-Gault formula at screening and on Day -1, on healthy, mild, moderate and severe renally impaired subjects. The screening value will be used for enrollment; the Day -1 value (and classification) will be used for all statistical analyses.

d Ophthalmological examinations, including a slit-lamp examination, fundoscopy, best corrected near vision, and intraocular pressure measurement, will be performed at screening and on occurrence of any visual adverse events.

e Drugs of abuse screen for healthy subjects only. For Stage 2, urine samples for drugs of abuse screen will be collected from mild, moderate, and severe renal impaired subjects.

f Height and weight will be evaluated at screening. Only weight will be evaluated on Day -1 and at follow up.

g Pulse rate and blood pressure will be measured after the 12-lead ECG. Healthy subjects should be in a supine position for 10 minutes. Blood pressure and pulse rate to be recorded at screening and at follow-up. Supine blood pressure and pulse rate will be evaluated after the subject has rested in the supine position for at least 10 minutes prior to the evaluation. If possible, the same arm and equipment should be used for each evaluation (refer to Table 4 for time points).

h The subject will fast for 4 hours prior to any clinical laboratory evaluations at screening.

i A sample for urinalysis is to be collected along with the other clinical laboratory evaluations.

j All subjects will receive a single investigational product administration on Day 1. For the ESRD group, for Treatment Period 2, investigational product will be administered after dialysis and for Treatment Period 2, investigational product will be administered 1 hour prior to dialysis.

k A 12-lead paper ECG will be performed after the subject has rested in the supine position for 10 minutes prior to the evaluation (refer to Table 4 for time points).

l Echocardiogram will be performed for all subjects at baseline and for cause. Echocardiogram will be performed at screening as baseline for all subjects to exclude subjects with LVEF <55%. Additional echocardiogram may be performed for any cardiorespiratory AE (see section 6.3.10).

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

n Plasma, diasylate, and urine will be collected as per for the time points presented in Table 4.

o Adverse events as well as SAEs should be collected from signing of the informed consent as these are not healthy subjects and we need to know before dosing any AEs that could worsen.

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

Table 4 Detailed Study Plan

Time (hours)	PK Blood Collection [a,b]	Dialysate Collection[c]	Urine Collection[d]	12-lead Paper ECG	Supine Blood Pressure
0	X		X	X	X
0.5	X				
1	X	X			
1.5	X			X	X
2	X	X			
2.5	X				
3	X	X			
3.5	X				
4	X	X			
5	X	X			
6	X		X	X	X
8	X				
12	X		X		
18	X				
24	X		X	X	X
36	X		X		
48	X		X	X	X
72	X		X	X	X

ECG: Electrocardiogram; PK: Pharmacokinetic

a Blood samples (6 mL) for determination of selumetinib and metabolites plasma concentrations. In addition for all groups, other than Treatment Period 2 in ESRD subjects, initially 3 plasma samples will be analyzed for selumetinib protein binding, the 1, 6, and 24 hours postdose samples. The variability within the 3 samples will be reviewed and the number of samples analyzed for selumetinib protein binding may be increased to a total of 18 (all remaining postdose samples) if binding appears to be concentration or time-dependent.

b For ESRD subjects at Treatment Period 2, the timing of blood sample collections are the same as for Treatment Period 1, however, the sample scheduled for collection at 1 hour must be collected immediately before start of dialysis, and the sample scheduled at 5 hours must be collected immediately after dialysis completion rather than strictly adhering to the scheduled sampling times at 1 and 5 hours. For Treatment Period 2, the blood samples during and surrounding the hemodialysis session will be collected from predialyzer lines.

c Applicable to ESRD group at Treatment Period 2 only, the dialysate will be collected in custom buckets over 1 hour intervals throughout the entire (approximately 4 hours) dialysis period ie, 0 to 1, 1 to 2, 2 to 3, 3 to 4 hours from start of dialysis (which amounts to eg, 1 to 2, 2 to 3, 3 to 4, 4 to 5 hours postdose). The blood flow, dialysate flow rate, dialysate volume, and the make and model of the dialyzer will be recorded. The entire dialysate will be collected in hourly intervals, its volume recorded, and a sample retained for analysis.

d The urine collection intervals will be from -12 to 0 (predose), and 0 to 6, 6 to 12, 12 to 24, 24 to 36, 36 to 48, and 48 to 72 hours.

3.2 Rationale for study design, doses and control groups

This study is designed to investigate and to formally define the PK of selumetinib in subjects with renal impairment and to determine if selected doses are tolerated in this population. The study is designed using the principles embodied in the Food and Drug Administration (FDA) guidance on renal impairment studies (FDA Guidance for Industry May 1998).

The control group is comprised of healthy male and female subjects of non-childbearing potential to avoid interference from disease processes or other drugs. The selection criteria are defined such that healthy subjects selected for participation in the study are known to be free from any significant illness. Healthy subjects with normal renal function will be matched in gender, height, and weight, to subjects with ESRD requiring dialysis.

The ≥7-day washout period between selumetinib administrations to ESRD subjects is chosen to ensure subject safety and should yield minimal residual plasma concentrations at the start of Treatment Period 2. The choice to initiate dialysis 2 hours postdose during Treatment Period 2 corresponds to the average t_{max} of selumetinib and will allow for the optimal determination of dialysis clearance.

The results will support labeling statements with regard to posology.

A dose of 50 mg selumetinib will be administered in case of unexpected increases in exposure due to the renal disease in the renally impaired subjects. A similar dose will be used in the healthy subjects to allow direct comparison. In the ESRD group, subjects will receive 2 single doses of selumetinib with at least a 7-day washout between investigational product administrations. The exposure limits for selumetinib in healthy subjects is such that subjects can receive up to four single doses each not exceeding 75 mg with mean exposure required to stay below the exposure limits of C_{max} 1307 ng/mL and/or $AUC_{(0-12)}$ 4736 ng.h/mL. These limits are based on steady state exposures from patient study D1532C0005 at a 75 mg dose that was well tolerated. Exposures for a single dose at 75 mg in a volunteer study D1532C0066 (C_{max} 1150 ng/ml, $AUC_{(0-12)}$ 3130 ng/mL) were below the exposure limits. The dose set for ESRD subjects in the current study is 50 mg. Although renal impairment is not expected to increase exposure to selumetinib the dose has been set lower than the maximum 75 mg to ensure that subjects do not exceed the exposure limits. A 50 mg dose in the healthy control group has been set to match the dose in renally impaired subjects.

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 subject's genotype.

Preliminary data suggest that Japanese and non-Japanese Asian subjects may experience higher systemic drug exposure compared to Western healthy subjects who receive the same dose of selumetinib. Exclusion of Japanese and non-Japanese Asian subjects 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 subjects.

3.3 Safety Review Committee

After completion of Stage 1, an SRC will evaluate the safety, tolerability, and plasma PK of selumetinib to determine if Stage 2 will be conducted.

The SRC will consist of the following core members:

- Principal Investigator (Chair, voting member)
- AstraZeneca Medical Science Director or delegate (voting member)
- AstraZeneca Clinical Pharmacology Alliance (CPA) physician (voting member)
- Project Manager (nonvoting member)
- AstraZeneca CPA Program Director (nonvoting member)

The SRC may also request to have off-line support and input from the following functions as required:

- AstraZeneca Clinical Pharmacology Physician
- Study/Project physician
- PK Scientist
- AstraZeneca team Clinical Pharmacology Scientist
- and AstraZeneca Statisticians
- AstraZeneca and/or medical specialists (eg, Neurologist, ECG Center cardiologists, etc)
- AstraZeneca Subject Safety Physician

Attendance at the SRC meeting will be restricted only to the core members. Participation by others will be possible only if explicitly requested and judged critical by the principal investigator and considered to be essential to address the safety of the study. Under most circumstances, core SRC members will convey to the meeting the information from the functions providing off-line support as appropriate. Further internal or external experts may be consulted by the SRC as necessary. The Global Safety Physician or delegate should always be present at the SRC if there are safety issues for discussion.

The SRC will make the decision to continue with Stage 2 and decide which of the additional RI function groups would be enrolled, ie, all 3 groups or either severe and/or moderate and/or mild after reviewing all the available safety, tolerability, and PK data of 12 ESRD subjects:8 healthy subjects. If the ratio of ESRD group mean AUC to healthy

subjects group mean AUC is >1.5 then Stage 2 will be required with the remaining 4 healthy subjects to match with the remaining renal impaired population in Stage 2. However if the ratio is <1.5 but approaching 1.5, the SRC may still decide to proceed to Stage 2.

If the ratio is <1.5 the remaining 4 healthy subjects will be recruited to match the ESRD group subjects. If the ratio is >1.5 with 12 ESRD subjects:12 healthy subjects then Stage 2 will be initiated.

If consensus among the voting SRC members cannot be reached, then the principal investigator, who has the ultimate responsibility for the safety of the subjects, will make the final decision on the continuation to Stage 2 of the study. In any event, progression to Stage 2 can only occur if agreed by the principal investigator.

The decisions of the SRC on progression of the study will be documented and provided to all the appropriate parties involved with the study, including the pharmacist to enable investigational product preparation for Stage 2.

4. SUBJECT SELECTION CRITERIA

Investigator should keep a record, the subject screening log, of subjects who entered screening.

Each subject 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.

After completion of 8 out of the 12 ESRD subjects, healthy subjects will be recruited and matched to the ESRD populations with regard to gender, age, and body mass index (BMI):

- Age: The healthy control group will be similar to the ESRD groups. This will be achieved by including healthy subjects within the age range of the ESRD group (±10 years to the mean).

- BMI: The healthy control group will be similar to the BMI of the ESRD group. This will be achieved by including healthy subjects within the BMI range of the ESRD group (±15% to the mean).

4.1 Inclusion criteria

For inclusion in the study all subjects should fulfill the following criteria:

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

2. Male and female (non-childbearing potential) subjects aged18 years or more with suitable veins for cannulation or repeated venipuncture.

3. Have a weight of at least 50 kg (110 lbs) and body mass index (BMI) between 18 and 40 kg/m^2, inclusive.

4. Negative screen for human immunodeficiency virus (HIV) and negative results for serum hepatitis B surface antigen and hepatitis C antibodies.

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

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

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

   Pregnancy tests for females showing borderline or indeterminate results, may be repeated and these females could be included if clearly not pregnant.

For inclusion in the study, **healthy subjects** must fulfill the following additional criteria:

6. Must be in good health as determined by a medical history, physical examination, 12-lead ECG, clinical laboratory evaluations, and an ophthalmic examination performed before the administration of the investigational product.

7. Healthy subjects must have an estimated CrCL >80 mL/min, as assessed by the investigator.

For inclusion in the study, **subjects with renal impairment** must fulfill the following additional criteria:

8. Stable renal function (eg, no clinically significant change in estimated CrCL within 3 months or longer prior to screening, as determined by the investigator or stable on hemodialysis for 3 months).

   - Subjects must meet the criteria for renally impaired subjects as specified for Stage 1 and/or Stage 2 of the study.

For inclusion in the **optional genetic component** of the study for all subjects:

9. Provision of informed consent for genetic research. If a subject declines to participate in the genetic component of the study, there will be no penalty or loss of benefit to the subject. The subject 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

Both subjects and healthy subjects fulfilling the following criteria should be excluded from the study:

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, third party contractors, and/or staff at the study center).

2. Any 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.

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

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

5. 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 should ends 30 days after the final dose. Note: subjects consented and screened but not dosed in previous Phase I studies are not excluded.

6. Subjects who smoke more than 10 cigarettes or the equivalent in tobacco per day.

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

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

9. Currently receiving or taking any medication known to have moderate or strong cytochrome P450 (CYP)3A4 inducer/inhibitory effects from 30 days prior to the first administration of investigational product until the follow-up visit.

10. In the opinion of the investigator, any evidence of additional severe or uncontrolled systemic disease (eg, currently unstable or uncompensated hepatic, cardiovascular, or respiratory disease) or laboratory finding, physical examination, hematology, clinical chemistry, urinalysis, vital signs, or 12-lead ECG that makes it undesirable for the subject to participate in the study.

11. Subjects who have had a clinically significant acute illness within 4 weeks of the first administration of the investigational product (Day 1).

12. Baseline LVEF <55% measured by echocardiography.

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

14. Subjects who, in the opinion of the principal investigator, must not participate in the study.

15. Current or past history of central serous retinopathy or retinal vein thrombosis, intraocular pressure >21 mmHg or uncontrolled glaucoma.

16. Subjects who have received any medications known to chronically alter drug absorption or elimination processes within 30 days of the first investigational product administration.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. History of, or current alcohol or drug abuse, as judged by the investigator, or positive screen for alcohol or drug abuse (except for prescription medications, which are verified by the investigator) at screening or on admission at screening or admission to the study center on Day -1.

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

18. A suspected or manifested infection according to the International Airline Transportation Association (IATA) Categories A and B infectious substances.

19. Any clinically significant abnormalities in clinical chemistry, hematology or urinalysis results as judged by the investigator.

20. Subjects who cannot communicate reliably with the investigator

Any of the following is regarded as a criterion for exclusion from the study for **healthy subjects** only:

21. Subjects who consume more than 28 units of alcohol per week or who have a significant history of alcoholism (1 unit of alcohol equals ½ pint [285 mL] of beer or lager, one glass [125 mL] of wine or $^1/_6$ gill [25 mL] of spirits).

22. Absolute neutrophil count <1300/mm^3 or 1.3 x 10^9 L for healthy subjects. If a subject has findings marginally below these limits, a repeat test is allowed, at the investigator's discretion, within the 28 day period between Visit 1 and Visit 2.

23. Any clinically significant disease or disorder (eg, cardiovascular, pulmonary, gastrointestinal, liver, renal, neurological, musculoskeletal, endocrine, metabolic, malignant, psychiatric, major physical impairment) which, in the opinion of the

principal investigator, may put the healthy volunteer at risk because of participation in the study, influence the results of the study, or influence the healthy volunteer's ability to participate in the study.

24. Judgment by the investigator that the subject 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.

25. Uncontrolled hypertension (BP ≥150/95 mmHg despite medical therapy).

Any of the following is regarded as a criterion for exclusion from the study for **renally impaired subjects** only:

26. Presence of unstable medical (eg, diabetes) or psychological conditions which, in the opinion of the investigator, would compromise the subject's safety or successful participation in this study.

27. Serum phosphate: >8.0 mg/dL

28. Subjects with an active renal transplant (subjects who have previously received a renal transplant and are currently undergoing dialysis due to transplant failure may be enrolled).

29. Significant change in dose regimen of medically required medication within the 2 weeks before prestudy examination, additions to their routine medication (prescribed) and/or the use of unallowed co-medication in the 3 weeks prior to admission to the study center. Minor changes to medications that require frequent dose adjustment, such as analgesia, can be made up to 2 weeks prior to Day 1 as agreed between the principal investigator and AstraZeneca.

30. Absolute neutrophil count <1200/mm^3 or 1.2 x 10^9 L for subjects with renal impairment. If a subject has findings marginally below these limits, a repeat test is allowed, at the investigator's discretion, within the 28 day period between Visit 1 and Visit 2.

Cardiac exclusion criteria:

31. Abnormal resting vital signs (after resting for 10 minutes) of supine blood pressure (SBP) >180 mmHg or <110 mmHg, or <65 mmHg diastolic blood pressure (DBP), or supine heart rate ≥100 beats per minute (bpm) or ≤35 bpm. However, for subjects with well controlled hypertension on antihypertensive medication; SBP <110 mmHg but not lower than 90 mmHg, or DBP <65 mmHg but not lower than 50 mmHg, is acceptable.

32. Uncontrolled hypertension (BP ≥150/95 mmHg despite medical therapy) (mildly impaired group only)

33. Acute coronary syndrome within 6 months prior to administration of the investigational product.

34. Angina (Canadian Cardiovascular Society grade II to IV) despite medical therapy (Appendix E).

35. Symptomatic heart failure (New York Heart Association Class II to IV, see Appendix E).

36. Prior or current cardiomyopathy as defined by:

- known hypertrophic cardiomyopathy
- known arrhythmogenic right ventricular cardiomyopathy
- previous moderate or severe impairment of left ventricular systolic function (LVEF <45% on echocardiography or equivalent on MuGA) even if full recovery has occurred.

37. Severe valvular heart disease.

38. Atrial fibrillation with a ventricular rate >100 bpm on 12-lead ECG at rest.

39. Use of concurrent medication, particularly the use of drugs which affect CrCL such as cephalosporin antibiotics, ascorbic acid, trimethoprim, cimetidine, quinine within 7 days of admission to the study center (Day -1).

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

40. Previous bone marrow transplant.

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

5. STUDY CONDUCT

5.1 Restrictions during the study

The following restrictions will be applied in this study:

- For both Stage 1 and Stage 2 of the study, subjects should be fasted from 2 hours before investigational product administration and subjects remain fasted for 4 hours after investigational product administration. No fluids will be allowed from 1 hour

prior to administration of the investigational product until 2 hours after administration of the investigational product, except the water needed to consume the investigational product (240 mL) (see Section 5.5.2).

- Abstain from alcohol from 48 hours before administration of the investigational product until 120 hours after administration of the investigational product and consume no more than 2 units of alcohol per day from 120 hours after administration of the investigational product until the follow-up visit.

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

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

- Subjects are only allowed to smoke ≤10 cigarettes or the equivalent in tobacco per day.Blood donation will not be allowed at any time during the study and up to 3 months after the follow-up visit.

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

- During admission to the study center subjects will receive a standard diet (and beverages) which excludes all alcohol and grapefruit-containing products. No additional food or beverages must be consumed while in the study center.

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

  Acceptable methods for male subjects' partners include:

  – Implants, injectables, combined oral contraceptives (which must all be combined with barrier methods of contraception), some intrauterine devices, vasectomized partner (which must all be combined with barrier methods of contraception), and total sexual abstinence. When this is in line with the preferred and usual lifestyle of the subject (periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent subjects have to agree to use

one of the above mentioned contraceptive methods, if they start sexual activities 12 weeks after the last administration of the investigational product.

Acceptable methods for male subjects include:

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

- Subjects should not take Vitamin E supplements or multivitamin supplements from 1 day before until 72 hours post investigational product administration. Throughout the study, subjects should avoid the addition of any concomitant medications, in particular any that are likely to affect the metabolism of selumetinib (eg, CYP1A2 or 3A4 inhibitors or inducers), unless considered clinically essential for management of concurrent conditions.

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

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

- Abstain from using drugs of abuse (except for prescription medication for mild, moderate and severe renal impaired subjects or ESRD subjects, which are verified by the principal investigator) 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.

- In addition subjects with renal impairment will be required to:

  - Refrain from taking any phosphate binders (eg, aluminium hydroxide and calcium carbonate) or bile acid sequestrants (eg cholestyramine/colestipol) within 10 hours before and 10 hours after dosing with Selumetinib

  - Refrain from taking drugs modifying gastric pH (H2 antagonists or proton pump inhibitors) from 24 hours before dosing with selumetinib until 24 hours after dosing with selumetinib

For concomitant medication restrictions, see Section 5.6.

If a subject does not comply with these restrictions or tests positive to any laboratory tests (eg, drug or alcohol) they may be excluded or withdrawn from the study, unless the subject with

mild, moderate, severe, or ESRD is using prescription medication approved by the investigator.

5.2 Subject enrollment and randomization and initiation of investigational product

The principal investigator will:

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

2. Assign potential subject a unique enrollment code, beginning with 'E#'.

3. Determine subject eligibility. See Section 4.1 and Section 4.2.

4. Assign eligible subject unique subject number, beginning with 1001.

If a subject withdraws from participation in the study, then his/her enrollment code cannot be reused. Subjects that withdraw from the study may be replaced and this will be determined on a case by case basis by AstraZeneca and the principal investigator.

5.2.1 Procedures for randomization

Subject numbers will be assigned strictly sequentially as subjects become eligible as defined below:

Renal impairment group	Subject numbers
Normal (Group 1)	1001-1012
ESRD (Group 5)	2001-2012
Mild (Group 2)	3001-3008
Moderate (Group 3)	4001-4008
Severe (Group 4)	5001-5008

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

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

The AstraZeneca CPA physician is to ensure all such contacts are appropriately documented.

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

5.5 Treatments

5.5.1 Identity of investigational product

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

Selumetinib capsules will be packaged in high-density polyethylene (HDPE) bottles.

5.5.2 Doses and treatment regimens

A single oral dose of 50 mg selumetinib will be administered in case of unexpected increases in exposure due to the renal disease in the renally impaired subjects. A similar dose will be used in the healthy subjects to allow direct comparison.

In the ESRD group (Group 5), subjects will receive 2 single doses of selumetinib with an at least 7 day washout between dose administration. Subjects with ESRD will initially receive their first single oral 50 mg selumetinib dose on Day 1 under fasted conditions after completion of a dialysis session (Period 1). In Period 2, the subjects will receive a single oral administration of 50 mg selumetinib under fasted conditions 1 hour prior to the start of a dialysis session.

The healthy control group and, if investigational product is administered in Stage 2, all other renal impaired groups (mild, moderate, severe) will receive a single oral dose of 50 mg selumetinib on Day 1.

5.5.3 Labelling

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

5.5.4 Storage

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

5.6 Concomitant and post-study treatment

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

nasal spray for relief of nasal congestion, if needed. Use of 1 g paracetamol 6 hourly (to a maximum daily dose of 4 g) is permitted, however the investigator should be informed so it can be recorded.

Use of prescription medication for a chronic medical condition in this demographically matched group is acceptable as long as the medical condition is stable and there have been no significant changes in the medical regimen within 6 weeks of Day 1 unless approved by the principal investigator and Sponsor. Subjects should not take Vitamin E supplements or multivitamin supplements from 1 day before until 72 hours post investigational product administration. Throughout the study, subjects should avoid the addition of any concomitant medications, in particular any that are likely to affect the metabolism of selumetinib (eg, CYP1A2, 2C19 or 3A4 inhibitors or inducers). Medications which affect CrCL such as cephalosporin antibiotics, ascorbic acid, trimethoprim, cimetidine, quinine within 7 days of admission to the study center (Day -1).

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

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

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

Other medication, which is considered necessary for the subject's safety and well being, may be given at the discretion of the investigator during the residential period and recorded in the appropriate sections of the pCRF.

5.7 Treatment compliance

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

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

5.7.1 Accountability

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

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

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

Any subject experiencing a visual AE should have a full ophthalmological examination. If a retinal abnormality is identified, an optical coherence tomography (OCT) scan is performed.

Subjects may be discontinued from investigational product in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment.
- AEs.
- Severe non-compliance to the study protocol.
- Any significant and clinically relevant changes in the safety parameters (eg, ECG, blood pressure, pulse rate, laboratory assessments, and AEs) making the continuation of investigational product administration unjustified.
- Risk to the subject as judged by the principal investigator and/or AstraZeneca.
- Incorrectly enrolled subjects.
- Lost to follow-up.

Withdrawn subjects may be replaced. Subjects who discontinue investigational product will be withdrawn from the study.

5.8.1 Procedures for discontinuation of a subject from investigational product

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

6. COLLECTION OF STUDY VARIABLES

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

- 12-Lead ECG.
- Vital signs.

- PK blood sampling.
- Safety laboratory assessments.

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

6.1 Recording of data

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

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

6.2 Data collection at enrollment and follow-up

6.2.1 Screening procedures

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

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

- Review of inclusion/exclusion criteria.
- Recording of demographic data (date of birth, gender, and race).
- Recording of medical/surgical history and smoking history.
- Ophthalmic examination (at screening).
- Urine sample for routine urinalysis and screening for drugs of abuse, in healthy subjects.
- Screening for drugs of abuse in healthy subjects.
- Calculation of CrCL.
- Alcohol screen.
- Recording of height and weight and calculation of BMI.
- A complete physical examination.

- Vital signs (supine blood pressure and pulse rate).
- Blood sampling for routine hematology, clinical chemistry, and screening for hepatitis B, C and HIV for all groups.
- Pregnancy test (females).
- Follicule stimulating hormone testing (for post-menopausal females only).
- 12-Lead ECG.
- Echocardiogram.
- Concomitant medication recording.
- Serious adverse event recording.

6.2.2 Follow-up procedures

Follow-up assessments will be conducted 3 to 7 days following discharge at Treatment Period 2 (of last period for ESRD) and will include recording of weight, 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, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

6.3.2 Definitions of serious adverse event

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

- Results in death.

- Is immediately life-threatening.
- Requires in-subject 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 renally impaired or ESRD subject/healthy subjects 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 AEs

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

Follow-up of unresolved AEs

Any AEs that are unresolved at the subject'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 pCRF. AstraZeneca retains the right to request additional information for any subject 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 investigational product.
- AE caused subject's withdrawal from study (yes or no).
- Outcome.

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

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

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

Causality collection

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

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

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

AEs based on signs and symptoms

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

AEs based on examinations and tests

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

If deterioration in a safety assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated safety result will be considered as additional information. Wherever possible the reporting investigator 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 subject shows an AST **or** ALT ≥3 x upper limit of normal (ULN) **or** total bilirubin ≥2 x ULN may need to be reported as SAEs, please refer to Appendix D 'Actions required in cases of combined increase of aminotransferase and total bilirubin – Hy's Law', for further instructions.

6.3.4 Reporting of serious adverse events

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

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

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

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

6.3.5 Laboratory safety assessment

Blood and urine samples for the determination of clinical chemistry, hematology, and urinalysis will be collected at the times indicated in Table 5 and Table 6. The urine drugs of abuse, alcohol breathalyzer test, and all other samples will be analyzed at the study center's local accredited laboratory (, unless stated otherwise. The date and time of sample collection will be recorded in the pCRF.

The laboratory variables to be measured are provided in Table 5.

Table 5 Safety laboratory variables

Biochemistry	**Hematology**
Sodium	Hemoglobin
Potassium	Hematocrit
Urea	Red blood cells
Creatinine	Mean corpuscular volume
Bicarbonate	Mean corpuscular hemoglobin concentration
Chloride	White blood cells
Glucose (fasting)	Neutrophils
Phosphate	Lymphocytes
Total Protein	Monocytes
Albumin	Eosinophils
Calcium	Basophils
Total bilirubin (Direct bilirubin if total bilirubin elevated)	Platelet count
Aspartate aminotransferase	**Urinalysis[b]**
Alanine aminotransferase	Leukocytes
Alkaline phosphatase	Nitrites
Lactate dehydrogenase	Urobilinogen
Gamma glutamyltransferase	Protein
Creatine kinase	pH
Amylase	Blood
Lipase	Specific gravity
Follicle stimulating hormone[a]	Ketones
	Bilirubin
	Glucose

Table 5 Safety laboratory variables

Virology[c]
Hepatitis B surface antigen
Hepatitis C antibody
Human immunodeficiency virus antibody

[a] Follicle-stimulating hormone will be tested only at screening and only for post-menopausal females.
[b] Microscopy should be performed if the urinalysis shows a positive result.
[c] At screening only.

At screening a blood sample will be collected to screen for hepatitis B surface antigen, hepatitic C antibodies, and HIV for all groups. Creatinine clearance will be calculated at screening and on Day -1 (ESRD exempted) using the Cockcroft-Gault formula:

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

[a] for females

A urine sample will be collected at screening and Day -1 of each treatment period to screen for the following drugs of abuse amphetamines, barbiturates, tricyclic antidepressants, cocaine, methadone, morphine, 3, 4-methylenedioxymethamphetamine (ecstasy), phencyclidine, tetrahydrocannabinol, and opiates. The urine sample taken for drug screen will only be done on healthy subjects, but not on anuric subjects in ESRD group. For Stage 2, urine samples for drugs of abuse screen will be collected from mild, moderate, and severe renal impaired subjects. Alcohol breathalyzer test will be performed at screening and Day -1 of each treatment period. For female subjects, a serum pregnancy test will be performed at screening, on Day -1, at discharge (Day 4), and at follow-up. Follicle-stimulating hormone will be tested only at screening, and only for post-menopausal females. If a subject tests positive to any of the aforementioned tests performed at screening he/she will be excluded from the study except for prescription medication for mild, moderate and severe renal impaired subjects, which have been verified and approved by the principal investigator.

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. Subjects in whom suspected clinical significance is confirmed will either not be included or if already enrolled will be followed until normalization or for as long as the investigator considers necessary.

NB. In case a subject/healthy subjects shows an AST **or** ALT ≥3 x ULN **or** total bilirubin ≥ 2x 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 3.

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

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

6.3.7 ECG

The 12-lead ECGs will be performed at the time points indicated in Table 4 after the subject has rested in the supine position for 10 minutes.

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

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

The original 12-lead ECG printouts with variables must be signed and dated and stored in the subject's/healthy subject's medical record as source data.

6.3.8 Vital signs

Vital signs will be measured at the time points indicated in Table 4.

6.3.8.1 Pulse rate 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 subjects 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) will be measured only at screening and body weight (kg) will be measured at screening, Day -1 (both Periods for ESRD), and at the follow-up visit. The BMI (kg/m^2) for each subject will be calculated at screening only. Subjects will be required to remove their shoes and wear light indoor clothing for these measurements.

6.3.9 Ophthalmology

A full ophthalmologic examination including a slit-lamp fundoscopy, best corrected visual acuity, and intra-ocular pressure measurement must be performed at screening for all subjects.

If a subject 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 subjects 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.

6.3.10 Echocardiogram

Echocardiogram will be performed to determine LVEF at screening.

A complete high quality standardized 2-D with Doppler echocardiographic examinations should be performed by an experienced sonographer (preferably with the same sonographer performing all studies for a given subjects) according to a specified CSP including evaluation of both systolic and diastolic function, and centrally read at a core laboratory for reference. Ejection fraction determinations should be determined quantitatively based on bi-plane measurements of end diastolic and end systolic left ventricular volumes.

An additional echocardiogram will be performed for any cardio respiratory AEs with no obvious diagnosis and management will be in accordance with local clinical practice.

6.4 Pharmacokinetics

6.4.1 Collection of samples

Venous blood samples for the determination of concentrations of selumetinib, N-desmethyl selumetinib, amide metabolite (if deemed appropriate), and selumetinib protein binding (approximately 6.0 mL of whole blood) in plasma will be taken at the times presented in the study plan (Table 3 and Table 4). The date and time of collection of each sample will be recorded on the pCRF. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Individual venipunctures for each time point may be performed or an in-dwelling catheter may be used. If the study center chooses to use an in-dwelling catheter, an additional 1 mL of blood will be collected to flush the catheter prior to each sampling. Following each sampling the catheter will be flushed with saline. Heparin may not be used to flush the catheter.
For blood volume see Section 7.1.

As shown in Table 4, pooled urine will be collected for the determination of selumetinib, N-desmethyl selumetinib, and amide metabolite (if deemed appropriate) in urine from predose

to 72 hours postdose. The start and stop date and time of collection for each pooled urine collection along with volume of the pooled urine sample will be recorded on the pCRF. Pooled urine will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

As shown in Table 4, dialysate will be collected in custom buckets over 1 hour intervals throughout the entire (approximately 4 hour) hemodialysis period for the determination of selumetinib, N-desmethyl selumetinib, and amide metabolite (if deemed appropriate) in dialysate from 1 hour to 5 hours postdose for the ESRD (Group 5), Period 2 only. The dialysate flow rate, dialysate volume, and the make and model of the dialyzer will be recorded in the pCRF. The entire dialysate will be collected. The start and stop date and time of collection for each dialysate collection along with the volume of the entire 1 hour dialysate sample will be recorded on the pCRF. Dialysate will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

6.4.2 Determination of drug concentration

Samples for determination of selumetinib, N-desmethyl selumetinib, and amide metabolite concentrations (if deemed appropriate) in plasma, urine, and dialysate (ESRD Group 5, Period 2 only) will be analyzed by , using an appropriate bioanalytical method. All samples will be analyzed. Full details of the analytical method used will be described in a separate bioanalytical report.

Samples to determine protein binding of selumetinib will also be performed at
Protein binding of selumetinib will initially be analyzed from the 1, 6, and 24 hour postdose samples. The variability within the 3 samples will be reviewed and the number of samples analyzed for selumetinib protein binding may be increased to all remaining postdose samples if binding appears to be concentration or time-dependent.

Full details of the analytical methods used will be described in a separate bioanalytical report.

All samples still within the known stability of the analytes of interest (i.e. selumetinib, N-desmethyl metabolite [and possible amide]) at time of receipt by the bioanalytical laboratory will be analyzed.

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

6.5 Collection of pharmacogenetic samples

The blood sample for genetic research will be obtained from the subjects at Visit 2, only from the subjects 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 subjects who may withdraw due to an AE, such subjects 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 subject 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 subject in this study is provided in Table 6.

Table 6 Volume of blood to be drawn from each subject (ESRD)

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	3.5	6	28
	Hematology	3	6	24
Hepatitis B surface antigen, hepatitic C antibodies, and HIV screen		6	1	6
Pregnancy test/follicle-stimulating hormone (females)[a]		3.5	6	14
Pharmacokinetics[b]		6	36	216
Pharmacogenetics (optional)		10	1	10
Total				**258**

HIV: human immunodeficiency virus

[a] Follicle-stimulating hormone will be tested only at screening, and only for post-menopausal females.

[b] 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.

Table 7 Volume of blood to be drawn from each subject (healthy subjects, mild, moderate, severe renal function groups)

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	3.5	4	14
	Hematology	3	4	12
Hepatitis B surface antigen, hepatitic C antibodies, and HIV screen		6	1	6
Pregnancy test/Follicle-stimulating hormone (females)[a]		3.5	1	14
Pharmacokinetics[b]		6	18	108
Pharmacogenetics (optional)		10	1	10
Total				**164**

HIV: human immunodeficiency virus
[a] Follicle-stimulating hormone will be tested only at screening, and only for post-menopausal females.
[b] 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 subject will not exceed 450 mL ie, the same volume as would be drawn during a regular blood donation.

7.2 Handling, storage and destruction of biological samples

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

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

7.2.1 Pharmacokinetic samples

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

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

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

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

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

7.2.2 Pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject/healthy subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of the last ESRD or renally impaired subject's/healthy subject's last visit, after which they will be destroyed. Deoxyribonucleic acid 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 subject/healthy subject enrollment/randomization code and the DNA number will be maintained and stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the subject/healthy subject has requested disposal/destruction of collected samples not yet analyzed.

7.3 Labelling and shipment of biohazard samples

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

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

7.4 Chain of custody of biological samples

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

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

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

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

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

7.5 Withdrawal of informed consent for donated biological samples

If a subject 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 subject will be withdrawn from further study participation. If a subject withdraws consent for the genetic component of the study, then they may continue in the study.

The principal investigator:

- Ensures subject's withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca.
- Ensures that biological samples from that subject, 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 subject and AstraZeneca are informed about the sample disposal.

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

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Subject data protection

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

AstraZeneca will not provide individual genotype results to subjects, 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 subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

8.3 Ethics and regulatory review

An Institutional Review Board (IRB) should approve the final study protocol, including the final version of the informed consent form and any other written information and/or materials to be provided to the healthy subjects. The principal 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 principal investigator should submit the written approval to AstraZeneca before enrollment of any subjects into the study.

The IRB should approve all advertising used to recruit subjects 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 enrollment of any subjects 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 investigators with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions (SUSARs), where relevant.

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

8.4 Informed consent

The principal investigator will:

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

8.5 Changes to the protocol and informed consent form

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

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

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

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

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

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

8.6 Audits and inspections

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

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first ESRD or renally impaired subject/healthy subject 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 subjects for the study.
- Discuss with the investigator (and other personnel involved with the study), their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a CSA between AstraZeneca and the investigator.

9.2 Training of study site personnel

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

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

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

9.3 Monitoring of the study

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

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

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

9.3.1 Source data

Refer to the CSA for location of source data.

9.4 Study agreements

The principal investigator at the study center should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency

between this clinical study protocol and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the CSA shall prevail.

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

9.4.1 Archiving of study documents

The investigator follows the principles outlined in the CSA.

9.5 Study timetable and end of study

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

The study is expected to start in Q1 2014 and to end by Q2 2014.

The study may be terminated at 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

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

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.

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

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

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

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

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

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

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of safety variables

11.1.1 Calculation of change-from-baseline

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

- Clinical laboratory tests: last measureable value taken prior to first investigational product administration.
- Vital signs: last measureable value taken prior to first investigational product administration.
- Paper 12-lead ECG: last measureable value taken prior to first investigational product administration.

If a subject 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 investigational product due to an AE (DAEs). Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the AstraZeneca CPA 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 analyses of plasma, urine, and dialysate concentration data for selumetinib and N-desmethyl selumetinib (and amide metabolite, if deemed appropriate) will be performed at

. Pharmacokinetic analyses will be conducted according to Standard Operating Procedures unless otherwise specified.

Pharmacokinetic parameters will be determined using standard noncompartmental methods with Phoenix® WinNonlin® Version 6.3 or higher (or SAS® Version 9.2 or higher . Actual elapsed time from dosing will be used for final plasma PK parameter calculations. Nominal times will be used for interim PK analyses. Pharmacokinetic parameter units will be consistent with the concentration units specified in the bioanalytical data.

The following plasma PK parameters will be determined for plasma selumetinib and N-desmethyl selumetinib (and the amide metabolite, if deemed appropriate):

AUC	Area under the plasma concentration-time curve from time zero extrapolated to infinity, calculated by linear up/log down trapezoidal summation
$AUC_{(0-t)}$	Area under the plasma concentration-time from time zero to the time of the last quantifiable concentration, calculated by linear up/log down trapezoidal summation
$AUC_{(0-12)}$	Area under the plasma concentration-time curve from time zero to 12 hours postdose, calculated by linear up/log down trapezoidal summation
$AUC_{(1-5)}$	Area under the plasma concentration-time curve from time 1 to 5 hours postdose, calculated by linear up/log down trapezoidal summation (Group 5, Period 2 only)
C_{max}	Maximum concentration, obtained directly from the observed concentration versus time data
t_{max}	Time to C_{max}
CL/F	Apparent oral plasma clearance (selumetinib only)
V_{ss}/F	Apparent volume at distribution steady state, (MRT)*CL/F (selumetinib only)
V_z/F	Apparent volume at distribution (selumetinib only)
$t_{1/2}$	Terminal half-life
$\lambda_{z,}$	Terminal rate constant
MR_{AUC}	AUC metabolite to parent ratio
MR_{Cmax}	C_{max} metabolite to parent ratio
MRT	Mean residence time (selumetinib only)

f_u	Fraction unbound, calculated as free concentration/total concentration, reported for every time free concentration is measured
$f_{u,av}$	Average fraction unbound (calculated taking the average of the 3 protein binding samples). This value will only be derived in the absence of concentration-dependent protein binding
AUC_u	Free AUC calculated as $AUC/f_{u,av}$ in the absence of concentration-dependent protein binding, or from unbound concentrations, as appropriate
$C_{max,u}$	Free C_{max} calculated as C_{max}/fu_{av} in the absence of concentration-dependent protein binding, or from unbound concentrations, as appropriate
CL/F_u	Unbound apparent oral clearance (selumetinib only)

No dose adjustment is required for clearance calculation since the selumetinib dose being administered is based on the free base equivalent.

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

$t_{1/2}$, Interval	The time interval of the log-linear regress to determine $t_{1/2}$
N	Number of data points included in the log-linear regression analysis used to determine λ_z (a minimum of 3 data points will be used for λ_z determination)
Rsq	Coefficient of determination for calculation of λ_z (λ_z and related parameters will be reported only if Rsq is 0.800 or more)
$\%AUC_{ex}$	Percentage of AUC obtained by extrapolation (if the extrapolated area is greater than 20% then AUC for that specific profile will not be reported)

The following PK parameters will be computed from the urine and/or dialysate for selumetinib (and metabolites, if deemed appropriate):

A_e	Amount recovered in urine during each collection interval (t1 to t2), calculated as urine concentration or concentration equivalent x urine volume
$A_{e(0-t)}$	Cumulative amount recovered in urine during from time zero to the last quantifiable time point, calculated as the sum of the by-interval A_e

f_e	Percent of actually administered dose/ recovered in urine during each collection interval and cumulatively overall (A_e/dose*100 or $A_{e[0-t]}$/dose*100)
CL_R	Renal clearance calculated as $Ae_{(0-t)}/AUC_{(0-t)}$
A_d	Amount of analyte recovered in dialysate during each collection interval (t1 to t2), calculated as dialysate concentration or concentration equivalent x dialysate volume (Group 5, Period 2 only)
$Ad_{(1-5)}$	Cumulative amount of analyte recovered in dialysate over the entire dialysis period (approximately 4 hours) calculated as the sum of the by-interval A_d. (Group 5, Period 2 only)
CL_D	Dialysis clearance calculated as $Ad_{(1-5)}/AUC_{(1-5)}$ (Group 5, Period 2 only)

Additional parameters will be calculated, if deemed appropriate.

11.3 Statistical methods and sample size determination by

11.4 Description of analysis sets

11.4.1 Pharmacokinetic analysis set

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

11.4.2 Safety analysis set

All subjects who receives at least 1 administration of selumetinib and for whom any postdose data are available will be included in the safety population.

12. METHODS OF STATISTICAL ANALYSES

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

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, subjects who receive another dose than the one assigned will be analyzed as belonging to the correct study population (safety) but only included in the PK population for any dose-independent PK parameters.

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

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

12.1.1 Subject characteristics

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

12.1.2 Safety and tolerability

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

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

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

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

All AEs will be collected for each subject from screening Visit 1 to follow-up visit. All SAEs will be collected for each subject from the time when informed consent is obtained until the follow-up visit.

Adverse events will be listed for all subjects with AEs that occur before dosing indicated on the listing. The number of AEs experienced following administration of the investigational

product will be summarized in tables using the MedDRA (Version 13.0 or higher) System Organ Class and Preferred Term. These summary tables will also be produced with severity and causality of AEs added as additional classification factors. The number of AEs overall, SAEs, other significant AEs, AEs that lead to withdrawal, AEs of severe intensity, and causally-related AEs will be summarized. Any AE occurring postdose will be considered associated with the last dose of investigational product taken. 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 absolute value at each scheduled assessment and for the corresponding change-from-baseline.

For clinical laboratory tests, listings of values for each subject 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.

12.1.3 Pharmacokinetics

For qualitative variables, the population size (sample size and available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarized using appropriate descriptive statistics (eg, n, arithmetic mean, coefficient of variation [CV%], SD, geometric mean, geometric coefficient of variation [GCV%], min, median, and max). The geometric mean is calculated as the exponential of the arithmetic mean calculated from individual observations on a log scale. The GCV% is calculated as $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where s is the SD of the data on a log scale. Mean, SD, CV%, geometric mean, and GCV% will not be calculated for t_{max}; t_{max} will be summarized using median and range.

For descriptive statistics, concentrations below lower limit of quantitation (LLOQ) values will be handled as follows:

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

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

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

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

No imputations will be made from missing data.

A subject listing and descriptive statistics of all concentration-time data (separately for each analyte) will be presented by renal function group and treatment as appropriate. Data from subjects excluded from the PK analysis population will be included in the data listings, but not in the summaries. A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. Figures of geometric mean (± geometric SD) concentration-time data will be presented by analyte, as appropriate for each renal function group and treatment, as appropriate. Individual subjects' concentration-time data will be graphically presented on linear and semi-logarithmic scales. A listing with all urine concentrations, start and stop date/time of the pooled urine collections and urine volumes will be provided. A similar listing will be provided for dialysate.

Plasma, urine, and dialysate PK parameters will be listed, summarized, and presented graphically, as appropriate, using descriptive statistics by renal function group and analyte. Scatterplots of the individual parameter data (C_{max}, AUC, and $AUC_{[0-t]}$) and geometric means will be presented by analyte, renal function group, and parameter. Graphical presentations of other PK data may be added at the discretion of the pharmacokineticist.

Stage 1: For statistical evaluation of renal impairment, log-transformed C_{max} and AUC (or $AUC_{(0-t)}$ if AUC is not reportable in more than 80% of the subjects) of selumetinib and N-desmethyl selumetinib will be separately analyzed using a linear fixed-effect analysis of variance model with renal impairment group as a fixed effect. Transformed back from the logarithmic scale, geometric least-squares means together with confidence intervals (CIs) (2-sided 95%) for C_{max} and AUC will be estimated and presented. Also, ratios of geometric least-squares means (renal group versus. normal) together with CI (2-sided 90%) will be estimated and presented. For ESRD subjects (Group 5), on data from off dialysis (Period 1) will be included in these analyses.

To assess the potential differences between Period 1 (off dialysis) and Period 2 (on dialysis) in ESRD subjects (Group 5), C_{max} and AUC (or $AUC_{[0-t]}$ if AUC is not reportable in more than 80% of the subjects) will be analyzed using a repeated-measures analysis of variance model on the log-transformed data. The model will include period as a repeated-fixed effect. Transformed back from the logarithmic scale, geometric least-squares means together with CIs (2-sided 95%) for C_{max} and AUC will be estimated and presented. Also, ratios of geometric least-squares means (Group 5 Period 2 versus Period 1) together with CI (2-sided 90%) will be estimated and presented.

If the study proceeds to Stage 2, then the data from both stages will be analysed together to determine the necessary dose adjustments by renal function. The primary analysis for Stage 2 will be the regression model described below and an exploratory analysis will be performed using a linear fixed-effect analysis of variance similar to the above model.

The relationship between log-transformed pharmacokinetic parameters (C_{max} and AUC) and creatinine clearance will be assessed using a regression model across renal function groups (with the exception of Group 5 Period 2). Creatinine clearance will be included in the model as a continuous effect. Other covariates (eg, BMI) may be included if appropriate. Results will be presented for the slope and the associated 90% confidence intervals for the creatinine clearance parameter from the model. The p-value testing if the slope is different from zero will be presented. Additionally, estimates of the mean PK parameters and 90% confidence intervals will be made at the median creatinine clearance of each of the renal function groups.

As an exploratory analysis, a linear fixed-effect analysis of variance model with renal impairment group as a fixed effect will be performed using data from all five renal impairment groups.

12.1.4 Interim analyses

All available safety, tolerability and PK data from Stage 1 will be reviewed to assess the effect of renal impairment on selumetinib. A decision will be made by the SRC to determine whether to conduct Stage 2 and which renal impairment group(s) to include.

A table of summary statistics and a figure comparing the selumetinib AUC between groups will be presented.

Stage 2 will be conducted only if renal impairment in the ESRD group shows a mean AUC of selumetinib being greater than 1.5-fold that of subjects with normal renal function.

12.2 Determination of sample size

No formal sample size calculation has been performed for this study. It is considered that a minimum of 8 evaluable subjects in each group will provide adequate PK information to assess the effects of renal impairment on the PK of selumetinib, whilst exposing as few subjects as possible to the investigational product and procedures.

The number of subjects included is in line with the draft FDA Renal guidance (March 2010) as being a sufficient number to detect PK differences large enough to warrant dosage adjustment. As an example, using ln-C_{max} data from study AZD6244 D1532C00066, a minimum of 8 subjects per group provides approximately 80% chance that a 1-sided 95% confidence interval would exclude the possibility of a doubling in C_{max}. This assumes a geometric CV of 40.4% and expected ratio of 120%.

12.3 Data monitoring committee (not applicable)

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

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

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

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

13.2 Overdose

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

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

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

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

13.3 Pregnancy

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

13.3.1 Maternal exposure

Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur, the investigational product should be discontinued immediately and the pregnancy reported to AstraZeneca. If a subject becomes pregnant during the course of the study administration of selumetinib will be stopped.

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

If any pregnancy occurs in the course of the study, then investigators or other study center personnel 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 Subject Safety data entry site within 1 or 5 days for SAEs, see Section 6.3.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

13.3.2 Paternal exposure

Subjects should refrain from fathering a child or donating sperm during the study and for 12 weeks after the follow-up visit.

Pregnancy of the subject'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

FDA Guidance for Industry May 1998
Guidance for Industry: Pharmacokinetics in subjects with impaired renal function: study design, data analysis and impact on dosing and labeling. U.S. Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research (CDER), Centre for Biologics Evaluation and Research (CBER), May 1998.