Clinical Study Protocol

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[^{14}C] AZD8931 – A Phase I, Open Label Study of the Absorption, Metabolism, Excretion, and Pharmacokinetics Following a Single Oral Dose to Healthy Male Subjects

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

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

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

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

AstraZeneca

PROTOCOL SYNOPSIS

[^{14}C] AZD8931 – A Phase I, Open Label Study of the Absorption, Metabolism, Excretion, and Pharmacokinetics Following a Single Oral Dose to Healthy Male Subjects

Principal Investigator

Study centre and number of subjects planned

The study will be performed at a single study centre in 6 healthy male subjects.

Study period	Phase of development
Estimated date of first subject enrolled	Clinical pharmacology
Estimated date of last subject completed	

Objectives

Primary objective

To characterise the absorption, metabolism, excretion, and pharmacokinetics of a single oral dose of 160 mg [^{14}C] AZD8931 in healthy male subjects.

Secondary objective

To further determine the safety and tolerability of a single oral dose of 160 mg [^{14}C] AZD8931 in healthy male subjects.

Exploratory objectives

1. Collect optional blood samples for DNA extraction and storage to enable an investigation into the impact of polymorphisms on the absorption, distribution,

metabolism, and excretion-related genes, eg, the effect of cytochrome P450 2D6 genotype on AZD8931 pharmacokinetics (the data will be reported separately)

2. Perform possible exploratory analysis of significant metabolites in plasma, urine, and faecal samples (the data will be reported separately)

Study design

This is an open label, single dose study of the excretion of radioactivity, absorption, metabolism, pharmacokinetics, safety, and tolerability following a single oral dose of [^{14}C] AZD8931 conducted at a single study centre in 6 healthy male subjects.

Target subject population

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

Investigational product, dosage and mode of administration

Each subject will receive a single oral dose of 160 mg [^{14}C]-labelled AZD8931, containing 7.4 MBq (200 μCi) administered as an oral solution.

Comparator, dosage and mode of administration

None

Duration of treatment

A single dose of AZD8931 will be administered. The study will consist of 3 visits. Visit 1, Screening will take place within 28 days before Visit 2, Day 1. Visit 2 will be the residential period when each subject will be resident in the study centre for 11 days from Day -1 until Day 11 (240 hours postdose). Visit 3, Follow-up will occur 5 to 10 days after the last sample has been collected.

Outcome variable(s):

- Pharmacokinetics

  AZD8931 and o-desmethyl AZD8931 (AZD8931 metabolite) whole blood and plasma concentrations will be used to assess the following parameters, as applicable:

  Area under the plasma concentration-time curve from zero to infinity (AUC); area under the plasma concentration-time curve from zero to the time of the last quantifiable radioactivity or concentration ($AUC_{(0-t)}$); area under the plasma concentration-time curve from zero to 12 hours ($AUC_{(0-12)}$); area under the plasma concentration-time curve from zero to 24 hours ($AUC_{(0-24)}$); maximum plasma concentration (C_{max}); time to maximum plasma concentration (t_{max}); terminal half-life ($t_{½\lambda z}$); apparent plasma clearance (CL/F); apparent volume of distribution during terminal phase (V_z/F); volume of distribution at steady state (V_{ss}/F);

metabolite to parent ratio of AUC (MR_{AUC}); and metabolite to parent ratio of C_{max} (MR_{Cmax}).

Whole blood, plasma, urine, and faeces radioactivity data will be used to assess the following parameters, as applicable:

AUC from whole blood and plasma radioactivity-time curvel; amount of radioactivity excreted in urine (Ae_u); amount of radioactivity excreted in faeces (Ae_f); amount of radioactivity excreted in urine and faeces (Ae_{u+f}); radioactivity excreted in urine as a percentage of dose (fe_u); radioactivity excreted in faeces as a percentage of dose (fe_f); and radioactivity excreted in urine and faeces as a percentage of dose (fe_{u+f}).

The ratio of plasma AZD8931 concentration versus plasma radioactivity, the ratio of plasma o-desmethyl AZD8931 concentration versus plasma radioactivity, and the ratio of whole blood radioactivity versus plasma radioactivity will be calculated at each time point for each subject.

The ratio of plasma AZD8931 AUC versus plasma radioactivity AUC, the ratio of plasma o-desmethyl AZD8931 AUC versus plasma radioactivity AUC, and the ratio of whole blood radioactivity AUC versus plasma radioactivity AUC will be calculated for each subject.

- Safety

  Adverse events, physical examinations, ophthalmology assessments, vital signs, electrocardiograms, and clinical laboratory assessments.

Statistical methods

No formal statistical hypothesis testing will be performed in this study. All data collected and parameters derived for the study population, sample size, pharmacokinetics, and safety will be summarized descriptively.

Pharmacokinetic radioactivity and concentration data as well as derived pharmacokinetic parameter data will be summarized by matrix (blood, plasma, urine, and faeces) and analyte (radioactivity, AZD8931, and o-desmethyl AZD8931) using descriptive statistics and graphically displayed as appropriate.

Adverse events will be collected from the time of signing informed consent throughout the treatment period and including the follow-up period. All adverse event data will be listed for all subjects. The number of adverse events experienced following dosing will be summarized in tables using Medical Dictionary for Regulatory Activities system of nomenclature by system organ class and preferred term; with preferred term sorted according to associated total subject incidence (in descending order). These summary tables will also be produced with severity of adverse event added as an additional classification factor. Similarly, the number of

serious adverse events, other significant adverse events, adverse events that led to discontinuation, and treatment related adverse events will be summarized.

Additional post-hoc summary and/or analysis may be performed as appropriate.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
λ_z	Terminal elimination rate constant
%AUCex	Percentage of AUC obtained by extrapolation
ADME	Absorption, distribution, metabolism, and excretion
ADR	Adverse drug reaction
AE	Adverse event (see definition in Section 6.3.1)
Ae_f	Amount of radioactivity excreted in faeces
Ae_u	Amount of radioactivity excreted in urine
Ae_{u+f}	Amount of radioactivity excreted in urine and faeces
ARSAC	Administration of Radioactive Substances Advisory Committee
ATP	Adenosine triphosphate
AUC	Area under the concentration- or radioactivity-time curve from zero to infinity
$AUC_{(0-t)}$	Area under the concentration-time curve from zero to the time of last quantifiable concentration or radioactivity
$AUC_{(0-12)}$	Area under the concentration-time curve from zero to 12 hours
$AUC_{(0-24)}$	Area under the concentration-time curve from zero to 24 hours
BMI	Body mass index
CL/F	Apparent plasma clearance
C_{max}	Maximum concentration
CRF	Case Report Form (electronic)
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variance
CYP	Cytochrome P450
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
EDC	Electronic Data Capture
EGFR	Epidermal growth factor receptor
fe_f	Radioactivity excreted in faeces as percentage of dose

Abbreviation or special term	Explanation
fe_u	Radioactivity excreted in urine as percentage of dose
fe_{u+f}	Radioactivity excreted in urine and faeces as percentage of dose
GCV	Geometric mean CV
HER	Human epidermal growth factor receptor
HIV	Human immunodeficiency virus
ICRP	International Commission on Radiological Protection
LIMS	Laboratory Information Management System
LLOQ	Lower limit of quantitation
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MR_{AUC}	Metabolite to parent ratio of AUC
MR_{Cmax}	Metabolite to parent ratio of C_{max}
NA	Not applicable
NQ	Not quantifiable
OAE	Other significant adverse event (see definition in Section 11.1.1)
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
Rsq	Coefficient of determination
SAD	Single ascending dose
SAE	Serious adverse event (see definition in Section 6.3.2).
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse reaction
$t_{½\lambda z}$	Terminal half-life
t_{max}	Time to maximum concentration
UVA	Ultraviolet light wavelength A
UVB	Ultraviolet light wavelength B
V_{ss}/F	Volume of distribution at steady state
V_z/F	Apparent volume of distribution during terminal phase
WHO	World Health Organisation

1. INTRODUCTION

1.1 Background

AZD8931 is an oral, equipotent inhibitor against epidermal growth factor receptor (EGFR), erbB2 and erbB3, in development for the treatment of solid tumours.

The EGFR family includes 4 members; EGFR/erbB1, erbB2/human epidermal growth factor receptor (HER) 2, erbB3/HER3, and erbB4/HER4, and has been identified as a promising target for anti-cancer therapy. Ligand binding to the EGFR, erbB3, and erbB4 receptors induces receptor homo- and hetero-dimerisation, leading to phosphorylation of critical sites in the tyrosine kinase domain, and subsequent activation of downstream pathways involved in cellular proliferation and survival (Olayioye et al 2000). The preferred dimerisation partner for the other family members is erbB2. Even though it has no ligand it does become activated following dimerisation and erbB2-containing dimers exert the most potent mitogenic signal (Graus Porta et al 1997).

Aberrant EGFR and erbB2 activity have been identified in a number of human malignancies and are notable for their association with a more aggressive disease course and poor clinical outcome (Sjogren et al 1998; Nicholson et al 2001). In human tumours, activation occurs through receptor over-expression, autocrine growth factor loops, or the presence of activating mutations in the kinase domain (Voldborg et al 1997).

Epidermal growth factor receptor activation is seen in tumour types such as non-small cell lung cancer, breast, colorectal, and head and neck cancer. Over-expression of erbB2 is seen in a proportion of breast, ovarian, bladder, and gastric malignancies. Recent data suggest that simultaneous inhibition of EGFR, erbB2, and erbB3 may be of particular value in certain segments of breast cancer.

AZD8931 is being developed as a selective, oral, adenosine triphosphate (ATP)-competitive inhibitor of both EGFR and erbB2 receptor tyrosine kinases, with the expectation that it will provide superior efficacy compared to currently available inhibitors of either target alone. Nonclinical in vitro and in vivo assays have demonstrated activity against both receptor tyrosine kinases in enzyme assays, cell receptor phosphorylation, cell proliferation and survival, in in vivo pharmacodynamic (PD) assays, and xenograft tumour growth models.

A series of safety pharmacology and genetic toxicology studies, in addition to toxicology studies in rats and dogs, have been conducted with AZD8931.

AZD8931 was not genotoxic in either in vitro or in vivo assays.

On repeat administration of AZD8931 in rats, gastrointestinal toxicity was dose limiting. Epithelial degeneration and atrophy, consistent with the pharmacology of the compound, was evident on histopathological examination of a number of tissues including the skin and

gastrointestinal and genitourinary tracts. There was evidence of reversibility following a 4-week recovery period.

In dogs, repeat administration of AZD8931 was associated with epithelial degeneration and atrophy in the cornea, skin, gastrointestinal tract, and genitourinary tract. These findings are consistent with the pharmacology of AZD8931 and there was evidence of reversibility of findings following a 4-week recovery period.

Dose limiting toxicity on repeat administration in the dog was corneal epithelial ulceration and in the 1-month study resulted in the termination of one high dose animal following 7 days of dosing due to a severe ulceration. In surviving animals recovery of less severe corneal ulceration was observed in life, despite continued dosing. In a single ascending dose (SAD) study in the dog, corneal translucency was observed in life but a mild corneal epithelial ulceration was seen on histopathology. Gastrointestinal toxicity was dose limiting in the SAD study.

In vitro assays indicate a potential for QT-prolongation and arrhythmia with AZD8931. There was no evidence of QT-prolongation in the in vivo cardiovascular studies. Intravenous administration of AZD8931 in an anaesthetised dog model at a dose of 30 mg/kg resulted in hyperkalaemia with associated electrocardiogram (ECG) waveform changes. Hyperkalaemia was not seen following oral dosing to conscious dogs. Reductions in arterial blood pressure were also observed at this dose level in anaesthetised dogs. In a dog SAD study, at doses of 7.1 mg/kg and above, AZD8931 produced reversible reductions in arterial blood pressure.

Dose related increases in plasma glucose, generally accompanied by increases in plasma cortisol have been observed in dogs following oral administration of AZD8931. Hyperglycaemia had reversed by 24 hours. The insulin response to hyperglycaemia appeared to be attenuated at high plasma levels of AZD8931.

A potential photo toxicity risk with AZD8931 has been identified based on the light absorption profile of the compound and a positive result in the fibroblast 3T3 cell assay.

To date the AZD8931 AstraZeneca clinical development programme comprises a completed Phase I SAD study in healthy subjects (Study D0102C00001), a completed Phase I food effect study in healthy subjects (Study D0102C00011), an ongoing Phase I multiple ascending dose (MAD) study in patients with advanced cancer (Study D0102C00002), an ongoing Phase I dose escalation study in Japanese patients with advanced solid tumours (monotherapy) or advanced breast cancer (in combination with paclitaxel) (Study D0102C00010), and an ongoing Phase I/II study in combination with paclitaxel comprising a dose escalation component (in patients with advanced solid malignancies) and a randomised, double-blind component (in patients with breast cancer) (Study D0102C00003). As of 01 November 2010, 111 subjects (64 healthy subjects and approximately 12048 patients with advanced cancer [mostly patients with advanced breast cancer]) have received single or multiple oral doses of AZD8931 twice daily either as monotherapy or in combination with paclitaxel chemotherapy or anastrozole endocrine therapy in AstraZeneca-sponsored studies.

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

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

1.2 Research hypothesis (Not applicable)

1.3 Rationale for conducting this study

There is presently little in vivo data on the metabolic conversion of AZD8931 in man, or the routes and rates of excretion of AZD8931 or any metabolites. This mass balance study will provide definitive information about the metabolic fate, excretion, and pharmacokinetics (PK) of [^{14}C] AZD8931 and the resultant data will be used to establish the degree of similarity between the metabolism of AZD8931 in humans and the various species used during the toxicity evaluation.

1.4 Benefit/risk and ethical assessment

The potential for adverse drug reactions (ADRs) associated with AZD8931 are based on the adverse event (AE) profile of the class of drugs that inhibit the EGFR and/or erbB2 signalling pathways, and from observations from nonclinical and clinical studies of AZD8931. Specific subject selection criteria and appropriate safety assessments have been incorporated into the clinical programme for AZD8931 based on the potential adverse effects and ADR profile.

The tolerability and initial PK of AZD8931 monotherapy was investigated in a Phase I study (Study D0102C00001) in 40 healthy male subjects. On the basis of all safety data, AZD8931 has shown a favourable safety profile, being tolerated as single oral doses ranging from 2.5 to 200 mg in healthy subjects. Rash/acne type events were reported, consistent with the known safety profile of the erbB1 tyrosine kinase inhibitor class. No subjects experienced clinically relevant changes in safety parameters such as physical examinations (including ophthalmologic assessments), blood pressure, pulse, ECG parameters, urinalysis, clinical chemistry, or haematological assessments. Asymptomatic corneal epithelial changes, detected by fluorescence staining, were noted in 1/5 of the healthy subjects treated with 200 mg in the study. These findings were suggestive of superficial desquamation, and an external ophthalmology expert confirmed that normal environmental factors (eg, swimming in chlorinated water) could result in similar observations. These findings were seen on Day 5 only and began resolving within a few hours after being noticed. Complete resolution was documented 3 days later. The external ophthalmologist providing corneal evaluation expertise to the AZD8931 clinical studies has deemed these findings as highly unlikely to be drug related. Based upon the comprehensive review of the safety data, PK data and statistical analyses of ECGs, it was concluded that no changes in QTc of any clinical concern were seen at the exposures reached in this study.

The effect of food on the PK of AZD8931 was investigated in 24 healthy subjects receiving a single dose of 160 mg AZD8931 in a 3-period cross-over study (Study D0102C00011). No deaths or serious adverse events (SAEs) were reported in this food-effect study. Adverse

events were reported for 21 of the 24 healthy subjects (88%) participating in the study. Skin-type AEs were reported by 75% of the subjects. Skin-type AEs, excluding application site reactions, were reported by 67% of the subjects. All of the skin-type AEs were considered to be mild (Common Terminology Criteria for Adverse Events [CTCAE] grade 1), except for the macular rash (CTCAE grade 2) reported by the subject who was discontinued from the study. There were no clinically relevant changes in potassium, glucose, other safety laboratory variables, vital signs, ECG, or physical examination.

For this current study subjects will be instructed to use sunscreen (with a sun factor of >30) for up to 3 months after administration of the investigational product due to the phototoxicity risk. Baseline and postdose ophthalmology assessments, and ad hoc AE-triggered assessments will be performed to monitor ocular surface and vision effects.

Further information regarding the benefit/risk profile can be found in the Investigator's Brochure.

2. STUDY OBJECTIVES

2.1 Primary objective

To characterise the absorption, metabolism, excretion, and PK of a single oral dose of 160 mg [^{14}C] AZD8931 in healthy male subjects.

2.2 Secondary objective

To further determine the safety and tolerability of a single oral dose of 160 mg [^{14}C] AZD8931 in healthy male subjects.

2.3 Exploratory objectives

1. Collect optional blood samples for DNA extraction and storage to enable an investigation into the impact of polymorphisms on the absorption, distribution, metabolism, and excretion (ADME)-related genes, eg, the effect of cytochrome P450 (CYP) 2D6 genotype on AZD8931 PK (the data will be reported separately)

2. Perform possible exploratory analysis of significant metabolites in plasma, urine, and faecal samples (the data will be reported separately)

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This is an open label, single dose study conducted at a single study centre in 6 healthy male subjects. All subjects will receive a single dose of [^{14}C] AZD8931 on Day 1.

The study will consist of 3 visits. Visit 1, Screening will take place within 28 days before Visit 2, Day 1. Visit 2 will be the residential period when each subject will be resident in the study centre for 11 days from Day -1 until Day 11 (240 hours postdose). Visit 3, Follow-up will occur 5 to 10 days after the last sample has been collected.

The study flow chart is presented in Figure 1 and the study assessments in Table 1.

Figure 1 Study flow chart

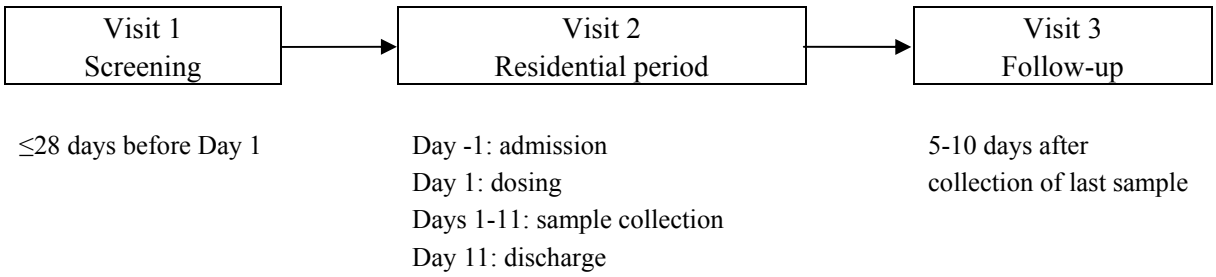

Table 1 Study assessments

Visit	Visit 1 (screening)	Visit 2 (residential period)		Visit 3 (Follow-up)
Day	**≤28 days before Visit 2**	**Day -1**	**Days 1-11**	**5-10 days after last sample collection**
Inclusion/exclusion criteria	X			
Informed consent	X			
Demographic data	X			
Medical history	X			
Drugs of abuse and alcohol urine screen	X[o]	X		
Serology for hepatitis and HIV	X			
Height and weight measurements	X			X[n]
Admission to study centre		X		
Dosing			X[f]	
Discharge from study centre			X[g]	
Adverse event recording	X	X	X	X
Concomitant medications	X	X	X	
Vital signs[a]	X		X[h]	X
12-Lead electrocardiogram	X		X[h]	X
Safety clinical laboratory evaluations	X	X	X[i]	X
Physical examination	X			X
Ophthalmology	X			X
Blood sample for pharmacogenetics (optional)	X[e]			
Blood sampling for total radioactivity count and AZD8931 and its metabolite (if feasible) concentration[b]			X[j]	
Blood sampling for metabolite profiling			X[k]	
Urine sampling for total radioactivity count and metabolite profiling[c]			X[l]	
Faeces sampling for total radioactivity count and metabolite profiling[c,d]			X[m]	

[a] Supine blood pressure and pulse.
[b] Additional collections of blood samples (5.7 mL) at 24-hour intervals may cease if no radioactivity is detected in 2 consecutive plasma samples.
[c] Additional 24-hour collection of urine and/or faeces may continue until 90% total recovery is achieved or recovery in urine/faeces in the 24-hour period is less than 1% of the total administered dose of radioactivity.

[d] Toilet paper (first 2 wipes) collected for the first 48 hours postdose.
[e] Timing of sample collection at the discretion of the study centre.
[f] Day 1 (0 hours).
[g] Day 11 (after the 240 hours postdose sample has been collected).
[h] Predose, 24 hours postdose, and Day 11.
[i] 24 hours postdose, and Day 11.
[j] Predose, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours postdose.
[k] 1, 4, 6, 12, and 24 hours postdose.
[l] Predose (-12 to 0 hours), 0 to 6, 6 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168, 168 to 192, 192 to 216, and 216 to 240 hours postdose.
[m] Predose (-48 to 0 hours), 0 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168, 168 to 192, 192 to 216, and 216 to 240 hours postdose.
[n] Weight only.
[o] Drugs of abuse only.

HIV: human immunodeficiency virus
If a subject vomits within 2 hours of dosing, the vomit should be retained for radioactivity analysis.

3.2 Rationale for study design, doses and control groups

This is a Phase I study to investigate the metabolism, excretion, and PK of [^{14}C] AZD8931 in man and the number of subjects is based on the desire to gain adequate information whilst exposing as few subjects as possible to the investigational product and procedures. Therefore, 6 subjects will be enrolled for this study.

Healthy subjects are considered appropriate for this study because the data obtained will not be influenced by any disease process or concomitant medication which would inevitably be present in patients. Entry will be restricted to subjects who have not been exposed to significant amounts of radiation as part of their occupation or from other sources such as X-rays.

The design of this study is standard for this type of study.

The age range (≥50 years) is higher than normally used in studies in healthy subjects, which is in accordance with the Administration of Radioactive Substances Advisory Committee (ARSAC) policy for studies where radioactive material is given. The age range is chosen to minimise the risk of disruption to fertility possibly caused by the radiation.

Healthy subjects will receive one oral dose of a solution of [^{14}C] AZD8931 (nominal total dose of no more than 160 mg AZD8931, 200 μCi/7.4 MBq). A dose of 160 mg AZD8931 was selected to give an adequate concentration of radioactivity for quantification of AZD8931 routes of excretion and metabolism. In the AZD8931 clinical programme, exposure to AZD8931 has increased proportionally with doses from 40 to 160 mg AZD8931 in healthy subjects and patients. A single dose of 160 mg AZD8931 was also investigated in the food effect study (Study D0102C00011). Therefore, a dose of 160 mg will provide information regarding excretion and metabolism that can be extrapolated to lower dose levels. The dose vessel will be rinsed with 2 x 50 mL water which must also be taken by the subject. This will give an effective dose equivalent of 4.7 mSv which falls within the radiolabeled category II dose, World Health Organisation (WHO) 1977 and category IIb, International Commission on Radiological Protection (ICRP) 1992 guidelines.

Although 40 mg twice daily has been chosen as a clinically feasible dose for long-term dosing, AZD8931 has been well tolerated as single oral doses ranging from 2.5 mg up to 200 mg in healthy male subjects.

Sampling times for PK assessments and the duration of the sampling period for blood, urine, and faeces are based on the clinical data from previous studies with AZD8931 and radioactivity studies in pre-clinical species. The duration of the collection has been chosen to ensure that virtually no radioactivity remains to be excreted after the sampling is completed.

4. SUBJECT SELECTION CRITERIA

The Investigator should keep a record, the subject screening log, of subjects who entered pre-study 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.

4.1 Inclusion criteria

For inclusion in the study subjects should fulfil the following criteria:

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

2. Healthy male subjects aged 50 to 65 years, inclusive

3. Subjects should be non-smokers or ex-smokers who have stopped smoking for >3 months before Visit 1 and have not used nicotine products for >3 months

4. Regular daily bowel movements (ie, production of at least one stool per day)

5. Body mass index (BMI) between 19 and 30 kg/m^2, inclusive

6. Weight between 50 and 100 kg, inclusive

7. Suitable veins for cannulation or repeated venepuncture

4.2 Exclusion criteria

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

1. Previous allocation to treatment in the present study

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

3. History or presence of gastrointestinal, hepatic, renal disease, surgical procedure, or any other condition known to interfere with the ADME of drugs

4. Any clinically significant illness, medical/surgical procedure or trauma within 4 weeks before dosing

5. Any clinically significant abnormalities in physical examination, vital signs, or clinical laboratory assessments as judged by the Investigator

6. Positive results on screening tests for serum hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (HIV)

7. Inadequate bone marrow reserve as demonstrated by an absolute neutrophil count $\leq 2.5 \times 10^9$/L and platelet count $\leq 200 \times 10^9$/L

8. Any clinically important abnormalities in rhythm, conduction, or morphology of a resting ECG with a measureable QTc interval of >450 msec twice within a 24-hour period, as judged by the Investigator

9. Known or suspected history of significant drug abuse

10. Positive screen for drugs of abuse at screening (excluding alcohol) or on admission (including alcohol) to the study centre

11. History of alcohol abuse or excessive intake of alcohol defined as regular weekly intake of 28 units of alcohol or more (1 unit=25 mL spirits, 125 mL wine, 250 mL beer or lager)

12. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the Investigator, or history of hypersensitivity to AZD8931, its excipients, or drugs with a similar chemical structure or class

13. Use of any prescribed or non-prescribed medication including drugs with hepatic enzyme-altering properties, such as St John's wort, antacids, analgesics, herbal remedies, vitamins, and minerals during 2 weeks (or longer depending on the medication's half-life) before dosing until after Follow-up. Occasional use of paracetamol and non-steroidal nasal decongestant is permitted at the discretion of the Investigator.

14. Blood donation within 1 month before screening or any blood donation/blood loss greater than 500 mL during the 3 months before screening

15. Receipt of another new chemical entity (defined as a compound which has not been approved for marketing) or participation in any other clinical study that included drug treatment within 3 months before dosing in this study, or participation within 1 month of dosing in this study in a methodological study where no drugs were administered. Note: The period of exclusion begins at the time of the post-study medical examination of the previous study. Subjects consented and screened but not dosed in a previous Phase I study are not excluded based on this criterion.

16. Judgement by the Investigator that the subject should not participate in the study if the subject is considered unlikely to comply with study procedures, restrictions, or requirements

17. Subjects who are unwilling to use one of the recommended highly effective methods of contraception during the study and for 3 months after dosing

18. Subjects who are exposed to radioactivity as part of their occupation

19. Subjects who have been exposed to radiation levels above background (eg, through X-ray examination) of >5 mSv in the last year, >10 mSv in the last 5 years, or a cumulative total of >1 mSv per year of life

20. Participation in a previous radiolabelled study within the 12 months before screening

21. Involvement in the planning or conduct of the study (applies to both AstraZeneca, , and study centre staff)

22. Prior diagnosis of dry eye syndrome, or an eyelid or eyelash abnormality

23. Subjects who have used contact lenses within 6 weeks before screening and who require the use of contact lenses during the study

24. History or current evidence of any of the following:

    - Any eye injury in the previous 3 months or a prior eye injury still associated with persistent or recurrent symptoms or impairment of vision

    - Corneal surgery (laser refractive surgery performed more than 3 months before the start of the study is allowed and should be recorded in the surgical history)

    - Orbital irradiation

    - Collagen vascular, chronic inflammatory, or degenerative disease with eye involvement (eg, rheumatoid, Sjögren's syndrome, systemic lupus erythematosus)

    - Clinically significant ocular surface disease, ie, diseases of the conjunctiva and cornea (including atopic keratoconjunctivitis, Stevens-Johnson syndrome, ocular cicatricial pemphigoid, or chemical burns, Herpes simplex, or Herpes zoster virus eye disease)

25. Evidence of maculopathy in subjects with impaired visual acuity defined as best corrected near visual acuity <0.4 and/or best corrected distance visual acuity (including pinhole) <0.7, in one or both eyes

26. Current diagnosis of acneform, psoriasis, or severe atopic eczema rash requiring treatment

Genetic research exclusion criteria:

1. Previous allogenic bone marrow transplant

2. Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.

Procedures for withdrawal of incorrectly enrolled subjects see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

Subjects will be required to:

- Subjects must be willing to use barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/bream/suppository), unless their partners are post-menopausal, surgically sterile, or are using acceptable contraceptive methods (oral contraceptive, implant, long-term injectable contraceptive, or intra-uterine device). In addition, subjects must agree to continue to take similar contraceptive precautions until 3 months after the dose of AZD8931
- Abstain from donating sperm for 3 months after dosing
- Abstain from donating blood during the study and for at least 3 months after the last visit
- Abstain from using drugs of abuse
- Use sunglasses (where possible) and skin cream with an ultraviolet light wavelength A (UVA) and ultraviolet light wavelength B (UVB) protection with a sun factor of >30 if exposed to sunlight and avoid the use of sun tanning booths during the study and for 3 months after dosing
- Caffeine-containing drinks or foods (eg, coffee, tea, cocoa, chocolate, and cola) are permitted during the study but the level of intake should not be changed
- Abstain from eating sweet corn, tomato skin, and chewing gum
- Abstain from drinking alcohol from 72 hours before admission to the study centre continuing until discharge from the study centre and also from 72 hours before the follow-up assessments
- Abstain from consuming poppy seeds from enrolment until after the follow-up assessments

- Fast from 2 hours before the planned start of dosing until 2 hours after dosing. Water is allowed up to 1 hour predose and from 1 hour after dosing (except for water used to rinse the dosing vessel). Subjects should also be fasted from 2 hours before safety blood and safety urine sample collection throughout the study

- Remain in the study centre for 10 days after dosing and should return to the study centre for the follow-up visit

- Refrain from strenuous activity that is not within their normal weekly routine beginning from 72 hours before screening and 5 days before admission to the study centre until after the follow-up assessments have been performed

- Refrain from actively trying to lose weight from screening until after Follow-up

- While resident in the study centre subjects will receive a high fibre diet

5.2 Subject enrolment and initiation of investigational product

The Principal Investigator will:

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

2. Assign the potential subject a unique enrolment number, beginning with "E0001001"

3. Determine subject eligibility. See Sections 4.1 and 4.2

4. Assign eligible subjects a unique subject number, beginning with "101"

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

Any subject who discontinues from the study before completion may be replaced at the discretion of the Investigator in order to ensure that data from a minimum of 4 evaluable subjects is obtained.

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

Subjects who fail to meet the inclusion criteria or meet any of the exclusion criteria should not, under any circumstances, be enrolled or dosed. There can be no exceptions to this rule.

Where subjects that do not meet the selection criteria are incorrectly started on treatment, or where subjects subsequently fail to meet the study criteria post initiation, a discussion should

occur between the AstraZeneca Clinical Pharmacology Alliance Physician and the Investigator regarding whether to continue or discontinue the subject from treatment.

The AstraZeneca Clinical Pharmacology Alliance Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the subject should have their study therapy stopped.

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

5.5 Treatments

5.5.1 Identity of investigational product(s)

The investigational product will be administered as a 2 mg/mL oral solution to achieve a 160 mg dose in an acceptable volume (80 mL). To obtain a solution of 2 mg/mL it is necessary to include citric acid monohydrate and tri-sodium citrate as buffers to control the pH to 4.5.

The 2 mg/mL radiolabeled solution contains diluted [^{14}C] AZD8931 difumerate, citric acid monohydrate, tri-sodium citrate, and water. [^{14}C] AZD8931 difumerate (diluted with unlabelled AZD8931 difumerate to approximately 0.84 μCi/mg) is dissolved in 0.01 M citrate buffer to produce a clear, colourless oral solution. The investigational product will be provided as unit doses in Type III amber glass bottles.

Investigational product	**Dosage form and strength**		**Manufacturer**
[^{14}C] AZD8931	Oral solution 160 mg AZD8931, 200 μCi/7.4 MBq		AstraZeneca
Components	**Quantity (% w/v)**	**Function**	**Standard**
Diluted [^{14}C] AZD8931 difumerate[a]	0.2978	Active	AstraZeneca
Citric acid monohydrate	0.063	Buffer	Ph Eur, BP
Tri-sodium citrate dihydrate	0.157	Buffer	Ph Eur, BP
Water for injection	To 100	Solvent	Ph Eur

[a] 1 g of AZD8931 is equivalent to 1.489 g of AZD8931 difumerate.

5.5.2 Doses and treatment regimens

Each subject will receive a single oral dose of 160 mg [^{14}C] AZD8931 administered on Day 1 as an oral solution. The dosing vessel will be rinsed with 2 x 50 mL water which must also be taken by the subject. This will give an effective dose equivalent of 4.7 mSv.

Water is allowed up to 1 hour predose and from 1 hour after dosing (except for water used to rinse the dosing vessel).

5.5.3 Labelling

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

The labels will include blank lines for the E code and the Investigator's name. AstraZeneca will label each bottle with a permanently affixed label stating that the material is for Clinical Trial Use Only.

5.5.4 Storage

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

The investigational product will be supplied frozen (-20°C) and protected from light. Each 100 mL Type III amber glass bottle will have an 80 mL fill volume.

The investigational product will be thawed out and shaken according to the detailed handling instruction before dosing to subjects.

5.6 Concomitant and post-study treatment(s)

Use of concomitant medications, herbal supplements, and/or ingestion of foods that significantly modulate CYP3A4 and/or CYP2C6 activity or which are significantly metabolised by CYP3A4 and/or CYP2D6 should be avoided. Any prescribed or non-prescribed medication including drugs with hepatic enzyme-altering properties, such as St John's wort, antacids, analgesics, herbal remedies, vitamins, and minerals should be avoided during 2 weeks (or longer depending on the medication's half-life) before dosing until after Follow-up.

Subjects should abstain from using any medication, over-the-counter remedies, herbal medications, high-dose or "mega" vitamins, or medicines purchased via the Internet from 2 weeks before dosing until after Follow-up. Use of 1 g paracetamol 6 hourly (to a maximum daily dose of 4 g) is permitted, however the Investigator should be informed so it can be recorded.

Subjects should not use any eye drops or ointment for treatment of eye symptoms, unless prescribed by the Investigator, until 1 week after dosing.

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

5.7 Treatment compliance

The administration of the investigational product should be recorded in the appropriate sections of the CRF.

Treatment compliance will be assured by supervised dosing of the investigational product by the Investigator or delegate.

5.7.1 Accountability

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

The study centre staff will account for the investigational product dispensed to the subject.

Study centre staff will account for all investigational products received at the study centre, unused investigational products and for appropriate destruction/return. Certificates of delivery, destruction/return should be signed.

5.8 Withdrawal from study

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

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- AE
- Severe non-compliance to the Clinical Study Protocol as judged by the Investigator and/or AstraZeneca
- Risk to the subject as judged by the Investigator and/or AstraZeneca
- Incorrectly enrolled subject
- Subject is lost to Follow-up

5.8.1 Procedures for withdrawal of a subject from the study

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

Any subject who discontinues from the study before completion may be replaced at the discretion of the Investigator in order to ensure that data from a minimum of 4 evaluable subjects is obtained.

6. COLLECTION OF STUDY VARIABLES

The timing of the assessments described in this section is detailed in Table 1 and Figure 1.

6.1 Recording of data

The Investigator will ensure that data are recorded on the electronic CRF as specified in the Clinical Study Protocol and in accordance with the instructions provided.

The Investigator will ensure the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed electronic CRFs. A copy of the completed electronic CRFs will be archived at the study centre.

6.2 Data collection and enrolment

Each subject will undergo screening in the 28 days before Visit 2. This will consist of:

1. Obtaining written informed consent before starting any study specific procedures
2. Recording of demographic data (date of birth, sex, race)
3. Height, weight, and calculation of BMI
4. A standard medical, medication, and surgical history with review of the inclusion and exclusion criteria with the subject
5. A complete physical examination
6. Habits of nicotine and alcohol use
7. Vital signs
8. Recording of a resting 12-lead paper ECG
9. A blood sample for routine clinical chemistry and haematology, and screen for hepatitis B surface antigen, antibodies to hepatitis C virus and antibodies for HIV
10. A urine sample for routine urinalysis and drugs of abuse screen (excluding alcohol)
11. Assessment of AEs
12. Assessment of any concomitant medication
13. Ophthalmology assessment
14. Blood sample for pharmacogenetics (optional)

6.2.1 Follow-up procedures

A medical examination will be performed 5 to 10 days after the last sample collection. This will be similar to the one performed at the pre-entry visit and will include a complete physical examination, vital signs, recording of a 12-lead ECG, a blood sample for laboratory safety assessments, a urine sample for urinalysis, ophthalmology assessment, and assessment of any AEs or required medication.

6.3 Safety

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

6.3.1 Definition of adverse events

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

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject 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 to the Clinical Study Protocol.

6.3.3 Recording of adverse events

Time period for collection of adverse events

Adverse events will be collected from time of signature of informed consent (screening) throughout the treatment period and including Follow-up.

Serious adverse events will be recorded from the time of informed consent.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last AE assessment in the study will be followed-up by the Investigator for as long as medically indicated, but without further recording in the CRF. 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
- 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 discontinuation 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 hospitalisation
- Date of discharge
- Probable cause of death

- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Description of AE

The following intensity ratings will be used:

- 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)

The CTC grades 1 through 5 correspond to the above intensity ratings as follows: grade 1=mild AE, grade 2=moderate AE, grade 3=severe AE, grade 4=life-threatening or disabling AE, grade 5=death related to AE.

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

Causality collection

The Investigator will assess causal relationship between the 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 to the Clinical Study Protocol.

Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study staff: "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 CRF. When collecting AEs the recording of diagnoses is preferred (when possible) to recording a list of

signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs will be summarised in the Clinical Study Report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, and other safety variables 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 laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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

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 CRF.

If any SAE occurs in the course of the study, then Investigators or other study centre staff inform appropriate AstraZeneca representatives within one day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

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

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other study centre staff will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

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

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

6.3.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in Table 1.

The laboratory variables that will be measured are listed in Table 2.

Table 2 Laboratory safety variables

Clinical chemistry	Haematology	Urinalysis
Serum (S)-Albumin	Blood (B)-Haemoglobin	Urine (U)-Haemoglobin
S-Alanine aminotransferase	B-Haematocrit	U-Protein
S-Aspartate aminotransferase	B-Erythrocyte	U-Glucose
S-Alkaline phosphatase	B-Leukocyte	U-Creatinine
S-Bilirubin, total	B-Leukocyte differential count (absolute)	
S-Calcium, total		
S-Cholesterol	B-Platelet count	
S-Creatinine	B-Red cell count	
S-C-reactive protein	B-Reticulocyte count	
S-Glucose, fasting	B-Mean corpuscular volume	
S-Potassium	B-Mean corpuscular haemoglobin	
S-Sodium	B-Mean corpuscular haemoglobin concentration	
S-Gamma glutamyltransferase		
S-Urea		
S-Free thyroxine		
S-Thyroid stimulating hormone		

The samples for clinical chemistry, haematology, and urinalysis will be analysed using routine methods at

Blood will be tested for hepatitis B surface antigen, antibodies to hepatitis C virus, and antibodies to HIV at the screening visit.

Urine will be tested at the screening visit and Day -1 for the following drugs of abuse: alcohol (only Day -1), methadone, cannabis, cocaine, benzodiazepines, amphetamine, methamphetamines (including ecstasy), opiates, barbiturates, phencyclidine, and tricyclic antidepressants. The test will be performed at the study centre. If a subject tests positive for drugs of abuse a retest will be performed, and they may be excluded from entering the study, as judged by the Investigator.

If any laboratory values outside the reference limits are suspected to be of clinical significance, as judged by the Principal Investigator and/or AstraZeneca, the sampling will be repeated. Subjects in whom the suspected clinical significance is confirmed at repeated sampling will either not be included or, if already included (started treatment), the deviating values will be monitored until normalisation or for as long as the Investigator considers necessary.

For blood volume see Section 7.1

6.3.6 Physical examination

Physical examinations will be performed at the times indicated in Table 1.

A complete physical examination will be performed and will include an assessment of the general appearance ,respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities), and neurological systems.

6.3.7 ECG

The ECG assessments will be performed at times indicated in Table 1.

6.3.7.1 Resting 12-lead ECG

Electrocardiograms will be recorded in the supine position after the subject has rested in this position for at least 10 minutes. Only the overall evaluation will be captured in the CRF. Any abnormalities (including QTc values) should be reviewed by a cardiologist or an appropriately qualified person.

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

6.3.8 Vital signs

Vital signs assessments will be performed at the times indicated in Table 1.

6.3.8.1 Pulse and blood pressure

Supine blood pressure and pulse rate will be measured using standard equipment with an appropriate cuff size after 10 minutes rest on a bed.

6.3.9 Ophthalmology

Baseline and postdose ophthalmology assessments will be performed at the time indicated in Table 1.

The same ophthalmic expert will perform ophthalmic assessments on each occasion where possible. The ophthalmic assessment will be performed at baseline and again post-study.

The following assessments will be performed in the order stated:

- Visual acuity (best corrected) using both distance and near vision charts and Amsler grid text
- Schirmer's test without anaesthesia – read after 5 minutes (this test should be done before instillation of stains or dilatory agents) – pre-study examination only
- Slit lamp examination:
  - Evert lid and assess for presence of tarsal, fornicial, bulbar, and circumcorneal hyperaemia. Before staining, photograph any abnormalities to be captured
  - Apply 1 drop of 2% fluorescein followed by 1 drop of normal saline
  - Photograph any abnormalities
- Fundoscopy following pupil dilation and intraocular pressure measurement will be performed at pre-study examination only, but may be repeated at the ophthalmologist's discretion. Fundoscopy may be the last appropriate test.

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 (as detailed above) will be performed.

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

6.4 Pharmacokinetics

6.4.1 Collection of samples

Blood samples (see Table 3) for determination of AZD8931 and o-desmethyl AZD8931 (if feasible) concentrations in plasma as well as total radioactivity in whole blood and plasma will be taken at the times presented in the study assessments (Table 1).

Blood samples (see Table 3) for metabolite profiling will be taken at the times presented in the study assessments (Table 1). The metabolite profiling and identification in plasma will be described in a separate report.

Urine and faeces samples for determination of total radioactivity in urine and faeces will be taken at the time intervals presented in the study assessments (Table 1). The metabolite profiling and identification in urine and faeces will be described in a separate report.

Blood, urine, and faeces samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual. The date and time for collection of blood, urine, and faeces samples will be recorded in the Electronic Data Capture (EDC) System.

For blood volume see Section 7.1.

6.4.2 Determination of drug concentration

Samples for determination of AZD8931 and o-desmethyl AZD8931 concentrations in plasma will be analysed by . Samples for determination of radioactivity in blood, plasma, urine, and faeces will be analysed by a laboratory to be appointed on behalf of AstraZeneca.

Full details of the analytical method used will be detailed in a separate bioanalytical report.

6.5 Pharmacogenetics

6.5.1 Collection of pharmacogenetic samples

The blood sample for genetic research will be obtained from the subjects at screening (timing of sample collection at the discretion of the study centre). Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding subjects who may discontinue 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 screening, it may be taken at any visit until the last study visit. Only 1 sample should be collected per subject for genetics during the study. Samples will be collected, labelled, 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 presented in Table 3.

Table 3 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	5	5	25
	Haematology	2	5	10
	Serology	3.5	1	3.5
Pharmacokinetic determination of AZD8931 and o-desmethyl AZD8931 (if applicable) concentrations in plasma		3	17	51
Whole blood total radioactivity		2	17	34
Plasma total radioactivity		2	17	34
AZD8931 metabolite profiling		10	5	50

Table 3 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	5	5	25
	Haematology	2	5	10
	Serology	3.5	1	3.5
Pharmacogenetics		10	1	10
Total				217.5

Additional collections of blood may continue at 24-hour intervals until radioactivity counts are <3 times the background count on 2 consecutive samples. However, the maximum volume to be drawn from each subject will not exceed 500 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 25 years following the Last Subject's Last Visit in the study. The results from future analysis will not be reported in the Clinical Study Report but separately in a Scientific Report.

7.2.1 Pharmacokinetic and/or pharmacodynamic samples

Samples will be disposed of after the Clinical Study Report has been finalised, unless retained for future analyses, see below.

Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites and/or to further investigate reproducibility of incurred samples and/or to further investigate stability of incurred samples. Any results from exploratory analyses to identify drug metabolites will be reported elsewhere. Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples and reported in a separate 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 confidentiality. Samples will be stored for a maximum of 25 years, from the date of the Last Subject's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

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

The samples and data for genetic analysis in this study will be single coded. The link between the subject enrolment 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 has requested disposal/destruction of collected samples not yet analysed.

7.3 Labelling and shipment of biohazard samples

The Principal Investigator will ensure that samples are labelled 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 unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

7.4 Chain of custody of biological samples

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

The Principal Investigator will keep full traceability of collected biological samples from the subjects while in storage at the study centre 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 life cycle through internal procedures, monitoring of the study centre, and auditing of external laboratory providers.

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

7.5 Withdrawal of informed consent for donated biological samples

If a 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 analysed, 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 is discontinued from further study participation.

The Principal Investigator will:

- Ensure subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensure that biological samples from that subject, if stored at the study centre, are immediately identified, disposed of/destroyed, and the action documented
- Ensure the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study centre
- Ensure that the subject and AstraZeneca are informed about the sample disposal

AstraZeneca will ensure 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 centre.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation/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 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 Ethics Committee (EC) should approve the final Clinical Study Protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable EC, and to the study centre staff.

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

The EC 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 Clinical Study Protocol should be re-approved by the EC annually.

Before enrolment of any subject into the study, the final Clinical 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, EC, and Principal Investigators with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions (SUSARs), where relevant.

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

A separate Informed Consent Form will be provided for genotyping.

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 Clinical Study Protocol, then these changes will be documented in a Clinical Study Protocol Amendment and where required in a new version of the Clinical Study Protocol (Revised Clinical Study Protocol).

The Amendment is to be approved by the relevant EC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for Revised Clinical Study Protocols.

AstraZeneca will distribute any subsequent Amendments and new versions of the Clinical Study Protocol to each Principal Investigator. For distribution to EC see Section 8.3.

If an Amendment requires a change to a study centre's Informed Consent Form, AstraZeneca and the study centre's EC 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 each EC.

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an EC may perform audits or inspections at the study centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the Clinical Study Protocol, Good Clinical

Practice, guidelines of the International Conference on Harmonisation, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT

9.1 Pre-study activities

Before the first subject is entered into the study, it is necessary for a representative of AstraZeneca to visit the study centre to:

- Determine the adequacy of the facilities
- Determine availability of appropriate subjects for the study
- Discuss with the Investigator(s) (and other staff involved with the study) their responsibilities with regard to Clinical Study Protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the Investigator

9.2 Training of study site personnel

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

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

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

9.3 Monitoring of the study

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

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the Clinical Study Protocol, that data are being accurately and timely recorded in the CRFs, 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 CRFs 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. 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 is 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(s) or other staff at the study centre needs information and advice about the study conduct.

9.3.1 Source data

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

9.4 Study agreements

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

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

9.4.1 Archiving of study documents

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

9.5 Study timetable and end of study

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

The study is expected to start in and to end by .

The study may be terminated at the study centre if the study procedures are not being performed according to Good Clinical Practice, 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 AZD8931.

10. DATA MANAGEMENT

Data management will be performed by .

A 21 Code of Federal Regulations part 11 compliant EDC system will be used for this study. Electronic CRFs will be produced by for each subject. The majority of study data collected will be either directly entered by clinical research staff or directly captured from devices onto the electronic CRF. Data will be available for AstraZeneca review via pre-defined reports extracted from the database at agreed intervals. The electronic CRFs must be kept in order and up-to-date so that they reflect the latest observations on the enrolled subjects.

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

Laboratory data are managed within the LIMS and only the date and time of sampling are recorded in the electronic CRF. Data that is not directly captured, eg, safety laboratory results and AE coding, are managed externally from the main study database. These data will be merged with the data from the main study database in post-production. Datasets supplied to the sponsor will contain all study data.

The informed consent 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.

All electronic CRF entries, corrections, and alterations must be made by the Investigator or other, authorised, study centre staff and only by individuals who have received training on the EDC system. Study centre staff may be allowed access to the system only after training is completed. Training must be documented and a log of all EDC users and their rights within the system be maintained.

The Data Management Plan will describe the methods used to collect, check and process clinical data in detail. It will also clarify the roles and responsibilities for the different functions and staff involved in the data management process.

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

AstraZeneca project standards. A PDF copy of the electronic CRF will be produced for each subject and included in the final delivery.

The EDC system will keep track of all data entry, alterations and query resolution in an audit trail. The audit trail will form an integral part of the database and will be archived alongside with the Dictionary coding. Medical coding is done using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and AstraZeneca Drug Dictionary.

Management of external data

Data management determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database. External data reconciliation will be done with the clinical database as applicable.

SAE/AE Reconciliation

Serious Adverse Event Reconciliation Reports are produced and reconciled with the Patient Safety database and/or the study centre.

Data verification and validation

The study data verification will be carried out by a site monitor comparing database entered data to source documents (ie, ECG printouts, laboratory results and other health records at the study centre). Questions and corrections will be noted and verified by the Investigator.

Pharmacogenetics

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples. The results from this genetic research may be reported in the Clinical Study Report for the main study, or in a separate report as appropriate.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of safety variable(s)

All AEs will be collected for each subject from the time when informed consent is obtained (Visit 1) until the follow-up visit. Adverse events that occur before dosing will be reported separately.

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

- Clinical laboratory tests: Day -1

- Vital signs (including supine and standing blood pressure): Day 1 predose
- ECG: Day 1 predose

11.1.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and discontinuations due to AEs. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

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

11.2 Calculation or derivation of pharmacokinetic variables

The PK analyses of the plasma concentration data for AZD8931 and o-desmethyl AZD8931, as well as the radioactivity data for whole blood, plasma, urine, and faeces, will be performed at . Pharmacokinetic analyses will be conducted according to Standard Operating Procedures and Work Instructions for PK analyses if not otherwise specified.

Pharmacokinetic parameters will be derived using noncompartmental method with WinNonlin Professional Version 5.2 or higher (Pharsight Corp., Mountain View, California, United States of America) or SAS® Version 9.1 or higher (SAS Institute, Inc., Cary, North Carolina, United States of America). The actual sampling times will be used in the PK parameter calculations. Nominal times will be used for any interim PK analyses.

The following PK parameters will be derived from AZD8931 and o-desmethyl AZD8931 (if feasible) whole blood and plasma concentration data:

- Area under the concentration-time curve from zero to infinity (AUC)
- Area under the concentration-time curve from zero to the time of the last quantifiable concentration or radioactivity ($AUC_{(0-t)}$)
- Area under the concentration-time curve from zero to 12 hours ($AUC_{(0-12)}$)
- Area under the concentration-time curve from zero to 24 hours ($AUC_{(0-24)}$)
- Maximum concentration (C_{max})
- Time to maximum concentration (t_{max})

- Terminal half-life ($t_{½\lambda z}$)
- Apparent plasma clearance (CL/F), for AZD8931 only
- Apparent volume of distribution during terminal phase (V_z/F), for AZD8931 only
- Volume of distribution at steady state (V_{ss}/F), for AZD8931 only
- Metabolite to parent ratio of AUC (MR_{AUC}) for AZD8931 and o-desmethyl AZD8931 only
- Metabolite to parent ratio of C_{max} (MR_{Cmax}) for AZD8931 and o-desmethyl AZD8931 only

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarised:

- Terminal elimination rate constant (λ_z). Lambda z and related parameters will be reported only if coefficient of determination (Rsq) is greater than or equal to 0.80
- The time interval (h) of the log-linear regression used to determine $t_{½\lambda z}$
- Number of data points included in the log-linear regression analysis
- Rsq for calculation of λ_z
- Percentage of AUC obtained by extrapolation (%AUCex). If the %AUCex is greater than 30%, then AUC will not be reported

Any anomalous concentration values observed at the predose time point shall be identified in the PK analysis review documentation with a description of how the value was treated for the computation.

If an anomalous concentration value is observed at the terminal phase and is judged as physiologically unreasonable, it will be excluded from computing PK parameter estimates.

The following PK parameters will be calculated from AZD8931 and o-desmethyl AZD8931 (if feasible) whole blood, plasma, urine, and faeces radioactivity data:

- Area under the whole blood and plasma radioactivity-time curve (AUC)
- Amount of radioactivity excreted in urine (Ae_u)
- Amount of radioactivity excreted in faeces (Ae_f)
- Amount of radioactivity excreted in urine and faeces (Ae_{u+f})

- Radioactivity excreted in urine as a percentage of dose (fe_u)
- Radioactivity excreted in faeces as a percentage of dose (fe_f)
- Radioactivity excreted in urine and faeces as a percentage of dose (fe_{u+f})

The ratio of plasma AZD8931 AUC versus plasma radioactivity AUC, the ratio of plasma o-desmethyl AZD8931 AUC versus plasma radioactivity AUC, and the ratio of whole blood radioactivity AUC versus plasma radioactivity AUC will be calculated for each subject.

Additional PK parameters will be determined if deemed appropriate.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 Safety analysis set

All subjects who receive at least one dose of investigational product and for whom any postdose data are available will be included in the safety analysis set.

12.1.2 Pharmacokinetic analysis set

The PK analysis set will include all healthy subjects who took at least one dose of AZD8931 and have at least one postdose PK measurement without important protocol deviations or violations thought to significantly affect the PK of the investigational product. Data from healthy subjects with deviations determined to affect PK will be excluded from the PK analysis set. A strategy for dealing with data affected by protocol violations and deviations will be agreed by the study team physician, pharmacokineticist, and statistician, prior to clean file and code break.

12.1.3 Interim pharmacokinetic analysis

Not applicable.

12.2 Methods of statistical analyses

The statistical analysis will be performed at , using Standard Operating Procedures and Work Instructions.

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

Missing data will result in a reduced sample size for the parameter. Since the statistical analyses will be predominantly descriptive presentations in tables and individual data listings, no action will be taken to handle missing data.

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

12.2.1 Subject characteristics

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

12.2.2 Safety and tolerability

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

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

All AEs will be collected for each subject from the time when informed consent is obtained (Visit 1) until the follow-up visit. Adverse events that occur before dosing will be reported separately.

Adverse events will be summarized by preferred term and system organ class using MedDRA nomenclature system (Version 12.0 or higher) by groups and treatments. Furthermore, listings of SAEs and AEs that led to discontinuation will be made and the number of volunteers who had any AEs, SAEs, AEs that led to discontinuation, and AEs with severe intensity will be summarised.

Tabulations and listings of data for vital signs, clinical laboratory tests, ECGs, and physical examination findings will be presented. Where applicable, data will be summarized for the absolute value at each scheduled assessment and for the corresponding change-from-baseline. For clinical laboratory tests, listings of values for each healthy subject will be presented with abnormal or out-of-range values flagged. Shift tables will be presented for laboratory values. Clinical laboratory data will be reported in Système International units in the Clinical Study Report. Exceptions to this recommendation are enzyme data (common examples are liver function tests alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase) for which IU/L may be used rather than the Système International unit ukat/L.

For ECG parameters, the QT correction factor will be based on the Fridericia's formula. Further categorical summaries of absolute QT and QTcF values (more than 450 ms, more than

480 ms, and more than 500 ms) and change from predose values in QT and QTcF values (more than 30 ms, and more than 60 ms) will also be produced.

12.2.3 Pharmacokinetics

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. A listing of urine and faeces sample collection start and stop times will be provided. A subject listing of all whole blood, plasma, urine, and faeces radioactivity-time data, as well as plasma AZD8931 and o-desmethyl AZD8931 concentration-time data will be presented.

Pharmacokinetic variables will be summarized by matrix (blood, plasma, urine, and faeces) and analyte (AZD8931, o-desmethyl AZD8931, and radioactivity) using appropriate descriptive statistics (eg, n, arithmetic mean, SD, and coefficient of variance [CV] %, geometric mean, and geometric CV [GCV], minimum, median, and maximum). The geometric mean is calculated as the exponential of the arithmetic mean calculated from data 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. Graphical presentations of PK variables will be used as appropriate.

The ratio of plasma AZD8931 concentration versus plasma radioactivity, the ratio of plasma o-desmethyl AZD8931 concentration versus plasma radioactivity, and the ratio of whole blood radioactivity versus plasma radioactivity will be calculated at each time point for each subject.

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

- At a time point where at least one value is above LLOQ but less than or equal to 50% values below LLOQ, all values below LLOQ are set to LLOQ and a mean (arithmetic and geometric) value and SD and CV (%) are calculated
- At a time point where more than half of the observations are below LLOQ only individual values are reported; mean, SD, geometric mean, and CV (%) will be set to not quantifiable (NQ). The minimum value and the median are set to less than LLOQ
- If all values are below LLOQ at any time point no descriptive statistics are calculated for that time point. Write not applicable (NA) in the field for SD and CV (%) and write less than LLOQ in fields for mean, geometric mean, minimum, median, and maximum in the table
- The number of observations greater than LLOQ (number of observations above LLOQ [N>LLOQ]) will be reported in the table

Figures of geometric mean radioactivity-time and concentration-time data will be presented on linear and semi-logarithmic scales by dosing regimen. Individual subject radioactivity-time

and concentration-time data will be graphically presented on linear and semi-logarithmic scales. Additional graphical presentations of PK data may be added at the discretion of the pharmacokineticist.

12.2.4 Interim analyses

Not applicable.

12.3 Determination of sample size

This is a Phase I study to investigate the metabolism, excretion, and PK of [^{14}C] AZD8931 in man and the number of subjects is based on the desire to gain adequate information whilst exposing as few subjects as possible to the study medication and procedures. Therefore 6 subjects will be recruited for this study.

12.4 Data monitoring committee

Not applicable.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator will be 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 Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician at the AstraZeneca Research and Development.

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

A dose of AZD8931 in excess of that planned in the Clinical Study Protocol will constitute an overdose. There is currently no known antidote to AZD8931 and treatment of an overdose should be supportive for the underlying symptoms. To date, no subject has experienced an overdose with AZD8931.

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

If an overdose on an AstraZeneca investigational product occurs in the course of the study, the Investigator or other study centre staff should inform appropriate AstraZeneca representatives **within one day**, ie, immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

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

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

13.3 Pregnancy

All outcomes of pregnancy in partners of subjects should be reported to AstraZeneca.

13.3.1 Maternal exposure

Women will not be included in this study.

13.3.2 Paternal exposure

Male subjects should refrain from fathering a child or donating sperm during the study and for 3 months following the dosing.

Pregnancy of the subjects' 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) from the date of dosing until 4 months after dosing should be reported to AstraZeneca and if possible be followed up and documented.

14. LIST OF REFERENCES

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Olayioye MA, Neve RM, Lane HA, Hynes NE. The Erb signalling network: receptor heterodimerisation in development and cancer. EMBO 2000;19:3159-3167.

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Clinical Study Protocol Appendix A

Drug Substance	AZD8931
Study Code	D0102C00007
Edition Number	1.0
Date	
Protocol Dated	

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

[^{14}C] AZD8931 – A Phase I, Open Label Study of the Absorption, Metabolism, Excretion, and Pharmacokinetics Following a Single Oral Dose to Healthy Male Subjects

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

I agree to the terms of this Clinical Study Protocol.

AstraZeneca Research and Development site representative

ASTRAZENECA SIGNATURE(S)

[^{14}C] AZD8931 – A Phase I, Open Label Study of the Absorption, Metabolism, Excretion, and Pharmacokinetics Following a Single Oral Dose to Healthy Male Subjects

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

I agree to the terms of this Clinical Study Protocol.

AstraZeneca Research and Development site representative

SIGNATURE OF PRINCIPAL INVESTIGATOR

[^{14}C] AZD8931 – A Phase I, Open Label Study of the Absorption, Metabolism, Excretion, and Pharmacokinetics Following a Single Oral Dose to Healthy Male Subjects

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

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

Centre No.:

Signature:

Clinical Study Protocol Appendix B

Drug Substance	AZD8931
Study Code	D0102C00007
Edition Number	1.0
Date	

Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

Clinical Study Protocol Appendix C

Drug Substance	AZD8931
Study Code	D0102C00007
Edition Number	1.0
Date	

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

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