Clinical Study Protocol

Drug Substance	AZD6765
Study Code	D6702C00030
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Date	[redacted]

A Phase I, Open-label, Single-Centre Study to Assess the Distribution, Metabolism and Excretion of [^{14}C]AZD6765 after a Single-Dose Intravenous Administration to Healthy Male Subjects

Sponsor:

AstraZeneca [redacted]

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

[redacted]

AstraZeneca

PROTOCOL SYNOPSIS

A Phase I, Open-label, Single-Centre Study to Assess the Distribution, Metabolism and Excretion of [14C]AZD6765 after a Single-Dose Intravenous Administration to Healthy Male Subjects

Principal Investigator

[redacted]

Study centre(s) and number of subjects planned

This study will be conducted at one centre:

[redacted]

A sufficient number of subjects will be enrolled to ensure that 6 healthy male subjects (including at least 2 but no more than 3Asian subjects) complete the study

Study period		Phase of development
Estimated date of first subject enrolled	[redacted]	Clinical Pharmacology (Phase I)
Estimated date of last subject completed	[redacted]	

Objectives

Primary Objectives

1. To assess the distribution, metabolism, and elimination of AZD6765 and total radioactivity after single-dose (150 mg) intravenous administration of [^{14}C] labelled AZD6765

2. To evaluate the excretion of ^{14}C (mass balance) in urine and faeces after a single intravenous dose of 150 mg [^{14}C] AZD6765

Secondary Objectives

1. To identify and profile the metabolites in selected samples of urine, faeces and plasma following a single intravenous dose of 150 mg [^{14}C] AZD6765

2. To evaluate safety and tolerability after a single intravenous administration of [^{14}C] AZD6765

Exploratory Objective

To collect an additional blood sample for genetic analysis and to store the DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD6765. The exploratory objectives will not be reported in the clinical study report.

Study design

The study is a Phase I, open-label, study to assess the distribution, metabolism and excretion of [^{14}C] AZD6765 after a single-dose intravenous administration to healthy male subjects. The study will be conducted at a single centre.

Target subject population

Healthy male subjects aged 35 to 60 years (to include at least 2 but no more than 3 Asian subjects). The healthy subject age range for this study will be 35 to 60 years. This age range will allow comparison with pharmacokinetic data generated in previous studies performed in healthy subjects and patients of a similar range in age.

Investigational product, dosage and mode of administration

A single intravenous infusion (5.55 MBq (equivalent to 150 μCi), 150 mg) of [^{14}C] AZD6765 infused over 60 minutes via syringe pump.

Comparator, dosage and mode of administration

Not applicable.

Duration of treatment

Each subject will receive a single dose of [^{14}C] AZD6765 infused over 60 minutes.

Outcome variable(s):

- Safety

  Adverse events, blood pressure and pulse, haematology, clinical chemistry, renal panel, urinalysis, physical examination, electrocardiogram and symptoms of suicidality.

- Pharmacokinetics

  Percentage of radioactive dose recovered in urine and faeces and total radioactivity; concentrations and pharmacokinetics of total radioactivity in blood and plasma; plasma and urine concentrations and pharmacokinetics of AZD6765; and metabolite profiling and identification in selected pools of plasma and excreta.

Pharmacokinetic parameters to be calculated for plasma AZD6765, plasma and whole blood radioactivity include: maximum concentration, time of maximum concentration, area under the concentration-time curve from zero to time of last measurable concentration, area under the concentration-time curve from zero to time x, area under the concentration-time curve from zero extrapolated to infinity, apparent terminal half-life, systemic plasma clearance, steady-state volume of distribution, apparent volume of distribution, maximum concentration ratio of plasma AZD6765 to plasma radioactivity, maximum concentration ratio of whole blood radioactivity to plasma radioactivity, area under the concentration-time curve ratio of plasma AZD6765 to plasma radioactivity, and area under the concentration-time curve ratio of whole blood radioactivity to plasma radioactivity.

Pharmacokinetic parameters to be calculated for urine AZD6765, and urine and faecal radioactivity include: amount recovered in urine, cumulative amount recovered in urine, percent of administered dose recovered in urine, renal clearance, amount recovered in faeces, cumulative amount recovered in faeces, percent of administered dose recovered in faeces and total cumulative percent of administered dose recovered in urine and faeces combined.

Statistical methods

No formal statistical hypothesis testing will be performed in this study. The statistical analysis will be descriptive and consist of subject listings, graphs and descriptive statistics of pharmacokinetic concentrations and parameters for blood, urine, and faeces. Descriptive statistics will include geometric mean, coefficient of variation, arithmetic mean, standard deviation, median, minimum and maximum 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
DME	Distribution, metabolism and excretion
Ae_u	Amount of AZD6765 recovered in urine
AE	Adverse event (see definition in Section 6.4.1)
Ae_f	Amount of AZD6765 recovered in faeces
ALT	Alanine aminotransferase
ARSAC	Administration of Radioactive Substances Advisory Committee
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve from zero extrapolated to infinity
%AUCex	Percentage of AUC obtained by extrapolation
AUC_t	Area under the concentration-time curve from zero to last measurable concentration
AUC_x	Area under the concentration-time curve from zero to time x where x is a specific time postdose such as 24 h or 48 h postdose
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CL	Systemic plasma clearance
CLr	Renal clearance
C_{max}	Maximum concentration
CNS	Central nervous system
Cp	Concentration in plasma
CPA	Clinical Pharmacology Alliance
CRP	C-reactive protein
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CSSRS	Columbia Suicide Severity Rating Scale
C_t	Last measurable concentration in a profile
Cum Ae_u	Cumulative amount of AZD6765 recovered in urine
Cum Ae_f	Cumulative amount of AZD6765 recovered in faeces

Abbreviation or special term	Explanation
CV%	Arithmetic coefficient of variation
Cwb	Concentration in whole blood
DAE	Discontinuation of Investigational Product due to Adverse Event
DNA	Deoxyribonucleic acid
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
eCRF	Case Report Form (electronic)
EDC	Electronic data capture
FDA	Food and Drug Administration
fe_f	Percent of administered dose recovered in faeces
fe_{tot}	Total percent of administered dose recovered in urine and faeces combined
fe_u	Percent of administered dose recovered in urine
GCP	Good Clinical Practice
GCV%	Geometric coefficient of variation
GGT	Gamma glutamyl transferase
GMP	Good manufacturing practice
HIV	Human immunodeficiency virus
Ht	Haematocrit
ICF	Informed consent
ICH	International Conference on Harmonisation
IP	Investigational Product
iv	Intravenous
LIMS	Laboratory Information Management System
LLOQ	Lower Limit of Quantification
LSLV	Last Subject Last Visit
MCH	Mean cell haemoglobin
MCV	Mean cell volume
MDD	Major depression disorder
MedDRA	Medical Dictionary for Regulatory Affairs
MRT	Mean residence time
NA	Not applicable

Abbreviation or special term	Explanation
NMDA	N-methyl-D-aspartate
NOAEL	No observable adverse effects
NQ	Non-quantifiable
OAE	Other Significant Adverse Event (see definition in Section 11.1.1)
OTC	Over the counter
PDF	Portable document format
PI	Principal Investigator
PK	Pharmacokinetic
PL	Plasma AZD6765
PR	Plasma radioactivity
rbc	Red blood cells
RCC	Reticulocyte count
Rsq	Goodness of fit statistic for calculation of λ_z (Coefficient of determination)
SAE	Serious adverse event (see definition in Section 6.4.2).
SD	Standard deviation
SOP	Standard operating procedure
$t_{1/2}$	Terminal half-life
TCA	Tricyclic antidepressants
t_{max}	Time of maximum concentration
TRD	Treatment-resistant depression
V_{ss}	Steady state volume of distribution
V_z	Apparent volume of distribution
wbc	White blood cell
WBR	Whole blood radioactivity
WHO	World Health Organisation
λ_z	Apparent terminal rate constant

1. INTRODUCTION

1.1 Background

Major depression disorder (MDD) is associated with significant morbidity and mortality. Despite the availability of a wide range of antidepressant drugs, clinical trials indicate that 30% to 40% of MDD patients fail to respond to first-line antidepressant treatment, even with adequate dosage, duration, and compliance. Importantly, there is significant lag time in the onset of antidepressant action with current treatments before determining treatment failure. Treatment-resistant depression (TRD) represents up to 40% of all MDD patients, and is often only diagnosed after months of unsuccessful treatment (Lau 2008). In 2002, the European Union's Committee for Medicinal Products for human use defined these MDD patients as TRD: There are various treatment algorithms for depressed patients, but usually a patient is considered therapy resistant when consecutive treatment with two products of different classes, used for a sufficient length of time at an adequate dose, fail to induce an acceptable effect (CHMP 2002). Clearly, there is a significant need to develop novel and improved therapeutic agents for MDD. A therapy for MDD with a fast onset of action and an equal or better tolerability profile than existing therapies would provide a better treatment alternative, one that could potentially reduce both the time that patients suffer with symptoms and the risks associated with suicidal behaviour for patients suffering from MDD. Furthermore, maintenance of a successful therapy for the MDD patient is paramount.

It has been recognized that N-methyl-D-aspartate (NMDA) receptor blockade may provide a novel approach for the treatment of MDD (Isshii et al 1993; Yamakura et al 1993). Findings in 2 clinical studies (Berman et al 2000; Zarate et al 2006) showed rapid antidepressant effects for the NMDA antagonist, ketamine, administered intravenously in patients with MDD. A single IV dose of ketamine produced a rapid, profound, and sustained antidepressant response in patients with severe MDD. Unfortunately, ketamine has multiple risks that limit its utility for the treatment of MDD. AZD6765 is a low-affinity, use-dependent NMDA antagonist with a risk-benefit profile distinct from ketamine.

Preclinical study results indicate that AZD6765 has potential for renal, cardiovascular and neuropathological effects. Please refer to the Investigators Brochure (IB) for safety margins. While AZD6765 was effective in anti-convulsant models, dose-limiting toxicity in single and repeat dose studies in animals were central nervous system (CNS) effects, which include convulsions. Repeat dose toxicity studies with intravenous (iv) or oral administration in rats induced diuresis and identified target organs including heart, kidney and adrenals; most of the observed effects were reversible or partially reversible. In the dog, no target organ has been identified, except for CYP induction in the liver. AZD6765 had an effect on male mating performance and caused decreased pregnancy in female rats. In embryofetal developmental toxicity studies in the rat and rabbit, dose-related maternal toxicity and developmental toxicities were observed and a no observable adverse effects level (NOAEL) was not established in those studies. Since the exposures achieved in animals gave low safety margins versus the clinical dose, careful monitoring for these potential effects is incorporated in the

trial protocols to ensure the safety of all subjects given AZD6765 via an iv route in clinical trials.

Greater than 450 people have been administered AZD6765 at various iv doses (including single doses of 1 to 350 mg and multiple doses of up to 120 mg every 8 h for 3 days, preceded by various loading doses). AZD6765 loading doses of 160 mg in normal subjects and 250-460 mg in stroke patients were shown in previous studies to be generally tolerated up to a maximum plasma concentration (C_{max}) of 3500 ng/mL (17.7 μM).

In healthy subjects (including elderly subjects), intravenously administered AZD6765 rapidly distributes into tissues displaying biexponential distribution and elimination with a mean terminal half-life in the range of 9.31 to 15.0 h.

AZD6765 is well tolerated in all human clinical studies to date. No clinical studies in man have demonstrated adrenal cortical changes, nephrotoxicity or diuretic effects. The most common AEs in man were mainly CNS (transient dizziness, impaired concentration, somnolence, and nausea) and cardiovascular (transient postural hypotension and hypertension), based on clinical experience with the drug in both normal subjects and patients. No serious adverse events (SAEs) were observed in the normal subject studies. SAEs related to disease progression or associated conditions (myocardial infarction) did occur in the stroke trials but were not considered to be due to drug administration.

The sponsor will immediately notify the Principal Investigator of important safety information that becomes available during the study.

1.2 Rationale for conducting this study

There is a substantial medical need to develop drugs for the treatment for MDD and TRD. This is the second distribution, metabolism, elimination (DME) study to be conducted for AZD6765 (See SA-IBX-0002). Total recovery for the first study, was inadequate (only approximately 80%). Approximately 70% of radiolabelled compound (parent and metabolite) appeared in the urine. The major organ of metabolism remains to be elucidated. The rational for the current study is to attempt to improve on total recovery and determine the DME objectives detailed below, using modern methods. The results of this study will be essential for the design of future clinical pharmacology Phase I (e.g. chronic hepatic disease) and Phase III (dose selection) studies.

1.3 Benefit/risk and ethical assessment

Radiolabelled single dose administration risk is low: Health risks from exposure to radioactivity in this mass balance study are considered to be negligible. Subjects will receive a radioactive dose of 150μCi [^{14}C] AZD6765 which equates to an effective dose of 0.83mSv. This corresponds to a WHO category II (ICRP category IIa) study.

Radiolabelled studies should be conducted utilizing the administration of the minimum amount of radioactivity necessary to achieve the study objectives. Subjects will receive the radio-labelled substance once to minimize the exposure of radioactivity.

This DME study is specifically designed to expose the least number of confined subjects to the highest dose at the slowest practicable iv infusion rate for PK profile determination: The infusion will be stopped if acute CNS, cardiovascular (eg ECG vital sign) changes occur.

The major risk for subjects who participate in the study is from adverse events induced by AZD6765 (as summarised above). There is a slight risk of infection or bruising that may occur as a result of phlebotomy.

The risk for exacerbating anxiety or suicidality is low for this study. Columbia Suicide Severity Rating Scale (CSSRS) will be included to monitor for these risks. The CSSRS is a low-burden, clinician administered tool designed to track suicidal risks throughout any treatment trial and is considered the "gold standard" for assessment. The measure succinctly covers the full spectrum of suicidality addressing behaviour and ideation. Suicidality assessment is now required by the Food and Drug Administration (FDA) in many clinical trials. It is also the prospective version of the Columbia suicide classification system commissioned by the FDA, which provided the data of their safety analyses, and is used across numerous industry and National Institute of Mental Health -sponsored studies in the US.

It is concluded that a single AZD6765 IV dose and the radiation within the range detailed, together with the safety monitoring procedures, are not expected to pose any foreseeable risk of inflicting harm or injury. There is not expected to be any therapeutic benefit to the healthy subjects participating in this study The potential benefits of a future improved treatment of MDD are considered to outweigh any foreseeable risks.

2. STUDY OBJECTIVES

2.1 Primary objectives

1. To assess the distribution, metabolism, and elimination of AZD6765 and total radioactivity after single-dose (150 mg) intravenous administration of [^{14}C]-labelled AZD6765

2. To evaluate the excretion of ^{14}C (mass balance) in urine and faeces after a single intravenous dose of 150 mg [^{14}C] AZD6765

2.2 Secondary objectives

1. To identify and profile the metabolites in selected samples of urine, faeces and plasma following a single intravenous dose of 150 mg [^{14}C] AZD6765

2. To evaluate safety and tolerability after a single intravenous administration of [^{14}C] AZD6765

2.3 Exploratory objective

To collect an additional blood sample for genetic analysis and to store the DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD6765. The exploratory objectives will not be reported in the clinical study report.

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 study to assess the distribution, metabolism and excretion of [^{14}C] AZD6765 after a single intravenous dose administration.

The study will be conducted at a single centre. A sufficient number of subjects will be enrolled to ensure that 6 subjects complete the study. The subjects will be healthy male subjects aged 35 to 60 years (including at least 2 but no more than 3 Asian subjects).

The study will comprise 3 visits: Visit 1 (enrollment and screening), Visit 2: treatment visit and Visit 3 (follow-up). The screening visit will take place within 30 days prior to Visit 2. Visit 2 will be a residential treatment period consisting of 12 days and 11 nights. Each subject will be administered a single intravenous (iv) infusion (5.55 MBq, 150 mg) of [^{14}C] AZD6765 infused over 60 minutes via syringe pump.

To be eligible for discharge, subjects need to meet the discharge criteria of plasma radioactivity levels below the limit of quantitation and total recovery (urine and faeces) of >90% of administered dose OR total radioactivity in urine collections less than 1% of the administered dose for 2 consecutive 24 h intervals and total radioactivity in fecal collections less than 1% of the administered dose for at least one 24 h interval. If the discharge criteria are not met after 240 h post dose, additional 24 h collections of plasma, urine, and faeces will be obtained until the subject has met the discharge criteria. If the subjects do not reach the discharge criteria after a further 48 h they will be instructed to continue collections of urine and faeces at home.

The follow-up visit will be 7 to 10 days after discharge from Visit 2. Figure 1 outlines the assessments at each visit

All subjects will be asked to participate in the pharmacogenetic component of the study. Participation in this part of the study is voluntary and if a subject declines to participate there will be no penalty. The subject will not be excluded from any aspect of the main study.

Figure 1 Study Plan

Assessments	**Screening**	**Admission**		**Residential Period**		**Follow-Up**
	Visit 1	**Visit 2**		**Visit 2**		**Visit 3**
Day	**Day -30 to Day -1**	**Day -1**	**Day 1**	**Day 2 to Day 10**	**Day 11**	
Informed Consent	X					
Demography	X					
Medical/Surgical History	X					
Inclusion/Exclusion	X	X				
Physical Exam	X	X			X	X
Clinical Chemistry/Hematology/ Urinalysis/Renal panel	X	X[m]		X	X	X
Brief Neurological Exam[a]	X	X	X		X	X
HIV/hepatitis B and C Serology	X					
Urine Drug Screen	X	X				
Height/Weight/ BMI Calculation[b]	X	X			X	X
Supine BP/Pulse[c]	X	X[m]	X	X	X	X
Standing BP/Pulse[d]	X	X[m]	X	X	X	X
Oral Temperature[e]	X	X	X	X	X	X
12-Lead Safety ECG[f]	X	X	X		X	X
[^{14}C] AZD6765 Administration			X[g]			
Plasma Collection[h]			X	X	X	
Urine Collection[i]			X	X	X	
Fecal Collection[j]			X	X	X	

Assessments	Screening	Admission		Residential Period		Follow-Up
	Visit 1	Visit 2		Visit 2		Visit 3
Day	Day -30 to Day -1	Day -1	Day 1	Day 2 to Day 10	Day 11	
Genetic Sample Collection[k]			X			
Concomitant Medication Review	X	X	X	X	X	X
Adverse Events[l]		X	X	X	X	X
CSSRS	X	X[m]	X[n]	X[o]	X	X
Discharge from Clinical Unit[p]					X	

a On Day 1, the brief neurological examination will be performed at 2 h post dose.
b Height will be evaluated and BMI calculated at Screening only.
c Supine blood pressure and pulse will be measured after the subject has rested in the supine position for at least 10 minutes. It is preferable to use the same arm and blood pressure cuff for each evaluation. Supine blood pressure will be evaluated at Screening, on Day –1, and on Day 1 at pre-dose, 15 min, 45 min, and at 1.5, 2, and 5 h post dose. All evaluations after Day 1 should be performed once in the morning. A window of ±15 minutes will be in effect when more than one evaluation takes place at the same time. The supine blood pressure at Day 1 pre-dose will serve as the baseline
d Standing blood pressure (and the calculation of orthostatic blood pressure) should be performed after the subject has been standing for at least 3 minutes. It is preferable to use the same arm and blood pressure cuff for each evaluation. Standing blood pressure will be performed immediately following supine blood pressure assessment at Screening, on Day –1, and on Day 1 at pre-dose and 2 h post-dose. The standing blood pressure at Day 1 pre-dose will serve as the baseline.
e During the residential period, oral temperature will be assessed each day in the morning.
f Safety ECGs will be performed after the subject has rested in the supine position for at least 10 minutes. On Day 1 a safety ECG will be collected just prior to the start of the infusion (baseline) and after completion of the infusion.
g Subjects will receive a light breakfast (toast and 240 mL drink of water, milk decaffeinated coffee or decaffeinated tea) 2 h prior to the administration. The subject will then not be allowed any food or drink from finishing their breakfast until 1 h postdose.
h Blood and plasma for PK analysis and radioactivity evaluation will be collected at the times listed in Figure 2. PK samples will be obtained from the opposite arm as the AZD6765 infusion site.
i Urine samples for PK and radioactivity evaluation will be collected at the times shown in Figure 3.
j Faecal samples will be collected at the times shown in Figure 3. Toilet tissue will be collected for the first 48 h.
k The sample for genetic analysis will be collected once, preferably on Day 1 and only after a separate informed consent has been obtained.
l SAEs will be collected from signing the ICF, adverse events will be collected from admission to the Follow-up Visit.
m Baseline
n Pre-dose and 24 h postdose
o Day 5 only

p Subjects will be discharged from the clinical unit after completion of all study related procedures on Day 11. In case discharge criteria have not been met, subjects will remain at the clinical unit (for additional urine and faecal sampling for radioactivity analysis) for a further 48 h. If the subjects do not reach the discharge criteria they will be instructed to continue collections of urine and faeces at home

Figure 2 Time schedule for pharmacokinetic blood sampling

Day	Time (h)[a]	Whole blood total radioactivity (2 mL)	Plasma total radioactivity (2 mL blood)	AZD6765 (6 mL)	Metabolite profiling and identification
1	Predose	x	x	x	6 mL blood
1	0.25	x	x	x	
1	0.5	x	x	x	
1	1	x	x	x	
1	1.25	x	x	x	
1	1.5	x	x	x	
1	2	x	x	x	6 mL blood
1	2.5	x	x	x	
1	3	x	x	x	
1	4	x	x	x	6 mL blood
1	6	x	x	x	2 x 6 mL blood
1	8	x	x	x	
1	12	x	x	x	4 x 6 mL blood
2	24	x	x	x	4 x 6 mL blood
2	36	x	x	x	
3	48	x	x	x	4 x 6 mL blood
4	72	x	x	x	
5	96	x	x	x	
6	120	x	x	x	
7	144	x	x	x	
8	168	x	x	x	
9	192	x	x	x	
10	216	x	x	x	
11	240	x	x	x	

[a] Time in h relative to the start of infusion

Figure 3 Schedule of urine and faecal sample collections

Day	**1**			**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Hs	**Pre-Dose**	**0 to 6h**	**6 to 12h**	**12 to 24h**	**24 to 48h**	**48 to 72h**	**72 to 96h**	**96 to 120h**	**120 to 144h**	**144 to 168h**	**168 to 192h**	**192 to 216h**	**216 to 240h**
Urine Collection [b,d]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X
Faecal Collection [c,d]	X	0 to 24 h →			X	X	X	X	X	X	X	X	X

a One urine sample will be collected prior to dosing
b One aliquot of 5 mL urine for radioactivity determination , 2 aliquots of 5 mL urine for bioanalysis, (including the 1 aliquot for retention), 1 aliquot of 2.5 mL for metabolite analysis.
c All faecal samples will be prepared for homogenates for radioactivity determination.
d Additional 24 h collections of urine and/or faeces continue until the discharge criteria is met

3.2 Rationale for study design, doses and control groups

The design used in this protocol is standard for this type of study. Intravenous administration will be used to allow calculation of clearance and volume of distribution and to explore the metabolism and excretion of the compound, which will be used to further guide future clinical study designs.

Based on data from previous clinical studies in healthy subjects, an iv dose of 150 mg of AZD6765 is expected to be the highest dose used, and allow accurate characterization of PK variables.

The duration of the PK sampling period for blood, urine and faeces is based on prior clinical studies and believed to be adequate enough to ensure that maximum recovery of radioactive material is achieved.

The study will be performed in healthy subjects to aid in compliance with complex study procedures and to avoid interference with disease processes and other concomitant medications. The inclusion and exclusion criteria are chosen to select subjects who are known to be free from significant illness.

The healthy volunteer age range for this study will be 35 to 60 years. This age range will allow comparison with pharmacokinetic data generated in previous studies performed in healthy subjects and patients of a similar range in age.

4. SUBJECT SELECTION CRITERIA

Investigator(s) 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 based on the medical judgement of the Investigator:

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

   Healthy male subjects aged 35 to 60 years with suitable veins for cannulation or repeated venipuncture.

2. Male subjects must be willing to use accepted contraceptive methods, avoid unprotected sex, and donating sperm until 3 months after drug administration.

3. Subjects must have a normal creatinine clearance of ≥60 mL/min

4. If 4 subjects are already enrolled and a subject self reports as Asian, then they must meet the following criteria for Asian:

Subjects who self-identify their race as Asian will be asked to choose the sub-category of Japanese, Chinese, Korean, Vietnamese, Thai, Laotian or Cambodian. The subject must have been born in the identified sub-category country. The subject will be asked to identify the race of parents and grandparents. Only those subjects with both parents and grandparents matching the self-reported Asian sub-category of the subject will be qualified as Asian for this study.

5. Have a body mass index (BMI) between 19 and 30.5 kg/m^2 and weigh at least 50 kg and no more than 100 kg

6. Regular bowel movements, at least once per day (self reported)

7. Be able to understand and comply with the requirements of the study as judged by the investigator.

For inclusion in the genetic component of the study, subjects must fulfil the following additional criterion:

8. Provision of signed, written and dated informed consent for genetic research. If a subject declines to participate in the genetic component of the study, there will be no penalty or loss of benefit to the subject. The subject will not be excluded from other aspects of the study described in this Clinical Study Protocol, so long as they consent.

4.2 Exclusion criteria

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

1. History of any clinically significant medical, neurologic or psychiatric 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 of the subject's ability to participate in the study: This includes seizure activity, psychosis and repeated episodes of major depression.

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

3. A history of symptomatic orthostatic hypotension (ie, postural syncope).

4. Any clinically significant illness, medical/surgical procedure or trauma within 4 weeks of the first administration of investigational product.

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

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

7. Abnormal vital signs as defined by the Principal Investigator.

8. Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG as determined by the Principal Investigator or Sponsor.

9. Past (within 1 year of enrollment) or present alcohol or substance abuse.

10. Consumption of alcohol within 72 h of admission to the clinical unit.

11. Positive screen for drugs of abuse at screening visit and at admission to the clinical unit.

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

13. Any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade or other products containing grapefruit or Seville oranges within 72 h of the first administration of investigational product. Any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange

14. marmalade or other products containing grapefruit or Seville oranges within 72 h of

15. the first administration of investigational product.

16. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, other than seasonal allergies, as judged by the investigator or history of hypersensitivity to drugs with a similar chemical structure or class to AZD6765.

17. Excessive intake of containing (more than 5 units or equivalent per day): One caffeine unit is contained in the following items: one (175 ml) cup of coffee, two (350 ml) cans of cola, one (350 ml) glass of tea, ½ (120 ml) cup of energy drink (e.g. Red Bull) or three (3 x 30 g) chocolate bars within 72 h prior to Visit 2.

18. Use of drugs that induce or inhibit the hepatic metabolising CYP3A4 enzymes within 2 weeks prior to admission:

    – Inducers: carbamazepine, phenytoin, barbiturates, rifampin, rifabutin, glucocorticoids, thioridazine and St. John's Wort.

- Inhibitors: ketoconazole (except for topical use), itraconazole, fluconazole, erythromycin, clarithromycin, nefazodone, troleandomycin, indinavir, nelfinavir, ritonavir, and saquinavir.

19. Plasma or blood product donation within one month of screening or any blood donation/blood loss > 500mL during the 3 months prior to screening

20. Single arm preference for phlebotomy: The iv placement versus blood sampling and blood pressures readings must be from opposite arms. The subject must be willing to have procedures performed on either arm.

21. Has received another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment within 3 months (if half-life was < 24 h) of the first administration of investigational product in this study, or has participated in a methodological study where no drugs were given within one month of the first administration of investigational product in this study. The period of exclusion begins at the time of the post-study medical of the prior study. Note subjects consented and screened but not dosed in previous phase I studies are not excluded.

22. History of major head trauma, especially if loss of consciousness.

23. Subjects who have received any radiolabelled study drug within 12 months of the Screening Visit.

24. Subjects who are monitored for radioactivity as part of their occupation.

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

26. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

27. Judgment by the investigator that the subject should not participate in the study if considers subject unlikely to comply with study procedures, restrictions and requirements.

28. Subjects who are at risk of suicidality as assessed by the Columbia suicide severity rating scale.

In addition, the following is considered a criterion for exclusion from the genetic research:

29. Previous bone marrow transplant

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

31. Procedures for withdrawal of incorrectly enrolled subjects see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

The following restrictions apply for the specified times during the study period:

1. Remain in the clinical unit from the evening before dosing until completion of all study related assessments on Day 11 or up to 48 h later if the discharge criteria have not been met.

2. Collect samples of urine and faeces if necessary for the determination of total radioactivity for up to 11 days and if any are required beyond 11 days to meet discharge criteria.

3. Fast for 2 h prior to the administration of investigational product and for 1 h after the administration of study drug. Water will be allowed until 2 h before the dose administration and may be resumed 1 h after dose administration.

4. Eat and drink only the standardized meals and drinks provided (apart from water) during the residential period.

5. Refrain from strenuous physical activity, which is not in the subject's normal daily routine, from 7 days prior to Day 1 through the Follow-up visit.

6. Refrain from the use of any prescribed or non-prescribed (OTC) medication and/or herbal remedies from 2 weeks prior to Day 1 through the Follow-up visit. Acetaminophen will be allowed at the discretion of the investigator for pain relief.

7. Refrain from intake of alcohol from 7 days prior to Day 1 through the Follow-up Visit.

8. Abstain from the consumption of more than 5 units of caffeine-containing product per day within 24 h of Day1. One caffeine unit is contained in the following items: one (175 mL) cup of coffee, two (350 mL) cans of cola, one (350 mL) glass of tea, ½ (120 mL) cup of energy drink (e.g. Red Bull) or three (30 g) chocolate bars. No more than 3 units of caffeine per day will be allowed during the in-house periods of the study.

9. Refrain from using drugs of abuse and consuming goods that contain poppy seeds from the Screening Visit through the Follow-up Visit.

10. Subjects should abstain from consuming grapefruit, grapefruit juice, or orange marmalade (made with Seville oranges) from the Screening Visit through the Follow-up Visit.

11. Abstain from nicotine use, smoking and drugs of abuse from 3 months prior to the Screening Visit through the Follow-up Visit.

12. Refrain from donating blood, plasma or blood products from Screening until 3 months after the Follow-up Visit.

13. Abstain from having unprotected sexual intercourse or fathering a child during the study and for 3 months after study. Subjects should not donate sperm and should ensure that their partners of child bearing potential use a reliable method of contraception, as well as using a barrier method themselves for 3 months after the last dose of study drug

14. Remain in a semi-recumbent position for 4 h following AZD6765 infusion.

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 potential subject a unique enrolment number, beginning with 'E0001'.

3. Determine subject eligibility. See Sections 4.1 and 4.2

4. Assign each subject a unique subject number in an ascending order beginning with 101.

Subject numbers will be assigned strictly sequentially as the healthy subjects become eligible for dosing. Healthy subjects fulfilling the eligibility criteria will be assigned subject numbers from number 101 to number 106.

5.2.1 Procedures for randomisation

The study will be open-label study of a single intravenous radiolabelled dose. Subjects will not be randomised but eligible subjects will be assigned a subject number prior to dosing.

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

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

Where subjects that do not meet the selection criteria are enrolled in error or 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 Treatments

5.4.1 Identity of investigational product(s)

[^{14}C] AZD6765 solution for infusion 3 mg/ml, 111 kBq/ml will be supplied in subject specific labelled containers by AstraZeneca, [redacted]

Table 1 Identity of investigational product

Investigational product	Dosage form and strength	Manufacturer
[^{14}C] AZD6765	Solution for infusion 3 mg/ml, 111 kBq/ml, 50 ml	AstraZeneca [redacted]

The responsible staff will transfer the AZD6765 solution for infusion to the a subject specific labelled syringe, according to the handling instructions provided by AstraZeneca

5.4.2 Doses and treatment regimens

Following a 2 h fast, each subject will be administered a single iv dose of a 5.55 MBq (equivalent to 150 μCi), 150 mg solution of [^{14}C] AZD6765 infused over 60 minutes via a syringe pump. Subjects will remain fasting for 1 h after the start/end of the infusion. Water will be allowed until 2 h before dose administration and may be resumed 1 h after dose administration.

After administration of the investigational product the extension set will be rinsed with saline, which will then be administered to the subject, to ensure that the complete dose is administered.

5.4.3 Labelling

The investigational product will be labelled at AstraZeneca [redacted] according to current EU Good Manufacturing Practice (GMP). The syringes and tubes will be provided and the syringe will be labelled by [redacted] The labels for the syringe will be provided by AstraZeneca.

The labels will fulfil GMP Annex 13 requirements for labelling and local regulatory guidelines.

5.4.4 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. The storage location will be locked and only accessible to authorized study site personnel. A description of the appropriate storage and shipment conditions are specified on the investigational product unit label.

5.5 Concomitant and post-study treatment(s)

Apart from paracetamol/acetaminophen (up to a maximum daily dose of 4 g) no concomitant medication or therapy will be allowed. The subjects should be instructed that no other medication is allowed including herbal remedies, vitamin supplements and over-the-counter products without the consent of the Investigator.

Medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator during the residential period. When any medication is required, it should be prescribed by the Investigator who should inform the AstraZeneca Clinical Pharmacology Alliance Physician. Following consultation with the Clinical Pharmacology Alliance Physician, the Investigator should determine whether or not the subject should continue in the study.

5.6 Treatment compliance

The administration of all medication (including investigational products) will be recorded in the appropriate sections of the eCRF.

Treatment compliance will be assured by supervised administration of the investigational product by the investigator or delegate. The dose, date, infusion start time, infusion stop time and any interruptions to the infusion of the investigational product will be recorded and checked by the monitor at monitoring visits

5.6.1 Accountability

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

The study personnel will account for all drugs dispensed to the healthy subject.

Study site personnel will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Destruction must not take place unless the responsible person at AstraZeneca has approved it. Certificates of delivery and destruction should be signed.

5.7 Discontinuation of investigational product

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

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance to study protocol

5.7.1 Procedures for discontinuation of a subject from investigational product

A subject that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed

by an investigator(s). Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); and study drug should be returned by the subject.

If a subject is withdrawn from study, see Section 5.8.

5.8 Withdrawal from study

Subjects are at any time free to withdraw from 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 adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4).

6. COLLECTION OF STUDY VARIABLES

The study assessments are described in the sections below and the timing of these assessments are detailed in the Study Plans (see Figure 1 to Figure 3).

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

1. 12-lead ECG
2. Blood pressure and pulse rate (and body temperature)
3. Pharmacokinetic blood sample
4. Pharmacokinetic urine sample
5. Safety laboratory assessment blood sample;

Predose assessments may be performed up to 60 minutes prior to dosing.

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

6.1 Recording of data

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

The Investigator ensures the accuracy, completeness, legibility (applicable for paper source documents) and timeliness of the data recorded and of the provision of answers to data queries according to the Project Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRF will be archived at the study site.

Procedures for data editing, entry and handling of the data query process will be described in the data management plan. See also Section 10.

6.2 Data collection and enrolment

At enrolment (Visit 2), each potential subject will provide informed consent prior to starting any study specific procedures.

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

Each subject will undergo screening during the 30 days prior to admission to confirm eligibility. This will consist of:

1. A standard medical, medication and surgical history with review of the inclusion and exclusion criteria with the subject
2. A complete physical examination including a brief neurological examination
3. Height, weight and calculation of BMI
4. Vital signs – resting supine and standing blood pressure BP, pulse rate and body temperature
5. Recording a resting 12-lead paper ECG
6. A blood sample for routine clinical chemistry, renal panel, haematology and screen for hepatitis B surface antigen, antibodies to hepatitis C virus and antibodies to HIV
7. CSSRS
8. A urine sample for routine urinalysis, drugs of abuse screen and cotinine.

After admission and before randomisation the investigator should reassess each subject to reconfirm eligibility.

6.2.1 Follow-up procedures

A post-study medical examination will be performed 7 to 10 days after discharge from the treatment period. This will be similar to the one performed at screening and will include a complete physical examination, neurological examination, CSSRS, weight, vital signs and oral temperature, recording a 12-lead paper ECG, a blood sample for clinical chemistry and haematology, a urine sample for urinalysis and assessment of any adverse events or concomitant medication.

6.3 Efficacy (Not applicable)

6.4 Safety

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

6.4.1 Definition of adverse events

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

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

6.4.2 Definitions of serious adverse event

A serious adverse event 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.

6.4.3 Recording of adverse events

Time period for collection of adverse events

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

SAEs 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 visit in the study are 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 collect for each AE;

- AE (verbatim)
- the date and time when the AE started and stopped
- 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 withdrawal from study (yes or no)
- outcome.

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)

- Causality assessment in relation to Other medication
- Description of AE.

The following intensity ratings will be used:

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, 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 personnel: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the 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, ECG and other safety

assessments should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a 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.

6.4.4 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 site personnel 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 adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel 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 reference document for definition of expectedness/listedness is the Investigator's Brochure for AZD6765

6.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the Study Plan (see Figure 1).

The following laboratory variables will be measured:

Clinical chemistry	**Haematology**
Serum (S)-Albumin	Blood (B)-Haemoglobin
S-Alanine aminotransferase (ALT)	B-Haematocrit
S-Aspartate aminotransferase (AST)	B-Absolute leukocyte differential count (wbc)
S-Alkaline phosphatase	B-Erythrocyte
S-Bilirubin, total (and direct bilirubin if bilirubin (total) is elevated)	B-Leukocyte
S-Calcium, total	B-Leukocyte differential count (absolute)
S-Cholesterol	B-Platelet count
S-Creatinine[a]	B-Red cell count
S-C reactive protein (CRP)	B-Reticulocyte count (RCC)
S-Glucose	B-Mean cell volume (MCV)
S-Potassium[a]	B-Mean cell haemoglobin (MCH)
S-Sodium[a]	B-Mean cell haemoglobin concentration (MCHC)
S-Bicarbonate[a]	
S-Chloride[a]	**Urinalysis**
S-Gamma Glutamyltransferase (GGT)	Urine (U)-Glucose
S-Urea[a]	U-Haemoglobin
	U-Protein
	U-Leucocytes
	U-Bilirubin
	U-Urobilinogen
	U-Ketones
	U-Red Blood Cells
	U-pH
	U-Nitrite
	U-Specific Gravity

a Laboratory parameters that form the renal panel

Drugs of Abuse and Alcohol

U-Amphetamine	U-Benzodiazepines
U-Ethanol	U-Methadone Metabolites
U-Cannabinoids	U-Barbiturates
U-Cocaine	Urine Creatinine
U-Opiates	U-Morphine
U-Cotinine	U-Phencyclidine
U-Tricyclin anti-depressants (TCA)	U-Alcohol

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

The samples for clinical chemistry, haematology will be analysed using routine methods at the clinical unit.

For blood volume see Section 7.1

6.4.6 Physical examination

The timing of individual examinations are indicated in the Study Plan (Figure 1). A complete physical examination will be performed at enrolment (Visit 1) and at the follow up visit (Visit 3) and include an assessment of the following: general appearance, skin, mouth, teeth, throat, lymph nodes, thyroid, abdomen, musculoskeletal/extremities, cardiovascular, lungs and neurological. A brief physical examination (including general appearance, skin, abdomen, cardiovascular and lungs) will be performed at admission to Visit 2, discharge from Visit 2 and at follow-up. In the study database only information whether the assessment was performed or not is to be recorded as well as any AEs.

The result of the physical examination at Visit 1 will be recorded in the CRF as normal/abnormal with any abnormality specified.

At the physical examination at Visit 3, any new or aggravated clinically relevant abnormal medical finding as compared to the baseline assessment (Visit 1) should be reported as an AE.

Height will be measured in centimetres and weight in kilograms. Measurements should be taken without shoes and the same scale used for all measurements. BMI will be calculated from the height and weight.

6.4.7 ECG

6.4.7.1 Resting 12-lead ECG

At the times indicted in Figure 1, 12-lead paper print-out ECG (pECG) will be obtained after 10 minutes supine rest. The investigator may add extra 12-lead ECG safety assessments if there are any abnormal findings or if the investigator considers it is required for any other safety reason.

6.4.8 Vital signs

6.4.8.1 Pulse and blood pressure

Supine blood pressure and pulse rate will be measured using semi-automatic blood pressure recording device with an appropriate cuff size, after 10 minutes rest on a bed. Standing blood pressure and pulse will be measured standing after 3 minutes. For timings of assessments refer to Figure 1.

6.4.8.2 Body temperature

Body temperature will be measured in degrees Celsius using an automated thermometer at the times indicated in the Study Plan (see Figure 1).

6.4.9 Columbia Suicide Severity Rating Scale

Symptoms of suicidality will be evaluated using Columbia Suicide Severity Rating Scale (CSSRS) and will evaluate the proportions of subjects with suicidal behaviour and suicidal ideation occurrences at the times indicated in Figure 1.

6.4.10 Neurological Examination

A brief neurological examination to include mental status, cranial nerves, nystagmus, motor system, sensory system, reflexes, coordination, gait and station will be performed at the times indicated in Figure 1.

6.5 Pharmacokinetics

6.5.1 Collection of samples

Separate blood samples will be taken for the determination of total blood radioactivity, AZD6765 and [^{14}C] radioactivity in plasma and for metabolic profiling. Blood samples will be taken at the times presented in the Study Plan (Figure 1). The actual date and time of collection will be recorded.

Urine samples will be collected at the times indicated in Figure 1. The volume of each urine collection will be recorded. Urine samples (approximately 3 x 5 mL and 1 x 2.5 mL) for determination of investigation of AZD6765 and [^{14}C] AZD6765 in urine will be taken from the total urine sample provided during each collection period. One 5 mL aliquot of urine will be used for radioactivity determination, 2 x 5 mL aliquots for AZD6765 bioanalysis (including 1 aliquot for retention) and 1 x 2.5 mL sample for metabolite analysis.

Faecal samples will be collected and prepared for homogenates for radioactivity determination at the times indicated in Figure 1.

Vomitus where it occurs will only be collected and analysed from 0 to 24 h postdose.

Additional samples for blood, urine and faecal PK analysis may be collected until the subject meets the discharge criteria.

Samples will be collected, labelled stored and shipped as detailed in Laboratory Manual.

For blood volume see Section 7.1.

6.5.2 Determination of drug concentration

Samples for determination of [^{14}C] AZD6765 in whole blood, plasma and urine and total radioactivity in plasma, urine and faeces will be analysed by [redacted].

Concentrations of AZD6765 in human plasma and urine will be analyzed by [redacted] on behalf of [redacted], using an appropriate validated bioanalytical method.

Metabolite samples will be sent to AstraZeneca [redacted]

6.6 Pharmacogenetics

6.6.1 Collection of pharmacogenetic samples

The blood sample for genetic research will be obtained from the subjects who have given their consent for the pharmacogentic research. The genetic samples collected from this study may be pooled with those from other studies involving AZD6765. A retrospective analysis of the DNA may be carried out to explore the genetic factors important in the distribution, metabolism, elimination and response to AZD6765 including adverse effects may be performed. The analysis and results from the pharmacogenetic testing will not be part of the clinical study report.

The blood sample for genetic research will be obtained from the subjects at Visit 2, at or after randomisation. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, 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 as follows:

Table 2 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	3.5	13	45.5
	Haematology	2	13	26
	Serology	3.5	1	3.5
Pharmacokinetic	AZD6765	6	24[a]	144
	AZD6765 metabolite analysis	6	17	102
	Whole blood total radioactivity	2	24[b]	48
	Plasma total radioactivity	2	24[b]	48
Pharmacogenetics		10	1	10
Total				427

a Additional 24 h collection of plasma may be obtained until the subject has met the discharge criteria

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.

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 Section 7.4. Safety samples will be destroyed.

Key samples for investigation of metabolite identification will be retained for a maximum of 1 year following the finalisation of the Clinical Study Report. The results from the investigation will not be reported in the Clinical Study Report but separately in a bioanalytical/metabolism 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 up to 25 years, from the date of 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/randomisation 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 ensures 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 keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

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

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

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

7.5 Withdrawal of informed consent for donated biological samples

If a 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 withdrawn from further study participation.

The Principal Investigator:

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

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

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 ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Subject data protection

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

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

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

8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects.

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

The Ethics Committee should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

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

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

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

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

8.4 Informed consent

Any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation should be described in the informed consent form that is approved by an Ethics Committee.

The Principal Investigator(s) at each centre 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 Ethics Committee.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

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

The amendment should be approved by each Ethics Committee, the Administration of Radioactive Substances Advisory Committee (ARSAC) certificate holder and if applicable, also the national regulatory authority, before implementation. Local requirements should be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to the Principal Investigator. For distribution to Ethics Committee see Section 8.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee should approve the revised Informed Consent Form before the revised form is used.

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

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the 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 protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT BY ASTRAZENECA

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 investigational study site to:

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

9.2 Training of study site personnel

Before the first 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.

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 site, 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 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 centre needs information and advice about the study conduct.

9.3.1 Source data

The location of data identified as source will be provided in a source data identification document provided by [redacted].

9.4 Study agreements

The Principal Investigator at the 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 follows the principles outlined in the Clinical Study Agreement (CSA).

9.5 Study timetable and end of study

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

The study is expected to start in [redacted] and to end by [redacted].

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD6765.

10. DATA MANAGEMENT BY [redacted]

A 21 CFR part 11 compliant Electronic Data Capture system will be used for this study. Electronic CRFs will be produced by [redacted] for each subject. The majority of study data collected will be either directly entered by [redacted] 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 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 [redacted]. All source documents will be retained by [redacted]. 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 [redacted] laboratory information management system (LIMS) and only the date and time of sampling are recorded in the electronic CRF. Data that is not directly captured e.g. 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-site personnel and only by individuals who have received training on the electronic data capture system. Site staff may be allowed access to the system only after training is completed. Training must be documented and a log of all electronic data capture 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 personnel 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, pursuant to the prior approval by AstraZeneca. Final data will be extracted from the EDC system and delivered to AstraZeneca in the form of SAS® datasets in accordance with defined project standards. A portable document format (PDF) copy of the electronic CRF will be produced for each study 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 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 Investigational Site.

Data verification and validation

The SDV will be carried out by a [redacted] site monitor comparing database entered data to source documents (ie, ECG print-outs, laboratory results and other health records at the study site). Questions and corrections will be noted and verified by the Investigator.

11. EVALUATION AND CALCULATION OF VARIABLES

In all analyses, change-from-baseline variables will be calculated as the post-treatment value minus the value at baseline. Baseline will be defined as the last non-missing measurement before first dose. If no non-missing value exists before first dose, then the baseline value will be treated as missing.

11.1 Calculation or derivation of safety variable(s)

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 DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory, vital signs and 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 analysis of the ^{14}C radioactivity concentration data in whole blood , plasma, urine and faeces and for AZD6765 concentration data in plasma and urine will be performed at

[redacted] Standard Operating Procedures and Work Insructions will be used as the default methodology, unless otherwise specified.

Total ^{14}C radioactivity in whole blood and plasma will be converted to micromol/L equivalents of AZD6765 based on the actual specific activity of the dose. Pharmacokinetic parameters in whole blood and plasma will be derived using noncompartmental methods with WinNonlin® Professional Version 5.2 or higher, (Pharsight Corp., Mountain View, California). All PK computations will be performed using WinNonlin Professional 5.2, or higher; or SAS® Version 9.1, or higher (SAS Institute, Inc., Cary, North Carolina). Graphics may be prepared with SAS® Version 9.1, or higher; SigmaPlot® 9.0, or higher (Systat Software, Inc., Point Richmond, California); or WinNonlin Professional 5.2, or higher.

The following pharmacokinetic parameters will be calculated (if estimable) for plasma AZD6765 and for plasma and whole blood ^{14}C radioactivity using actual elapsed time from dosing:

C_{max}	Maximum concentration (ng/ml or ng_eq/mL) in the sampled matrix obtained directly from the observed concentration versus time data.
t_{max}	Time of maximum concentration (h), obtained directly from the observed concentration versus time data.
AUC_t	Area under the concentration-time curve (ng.h/mL or ng_eq.h/mL) in the sampled matrix from zero (predose) to time of last measurable concentration calculated by linear up/log down trapezoidal summation.
AUC_x	Area under the concentration-time curve (ng.h/mL or ng_eq.h/mL) in the sampled matrix from zero (predose) to time x, calculated by linear up/log down trapezoidal summation. This parameter will be calculated for plasma and whole blood radioactivity only, and the values of x used for the estimation will be at a specific time such as 24 and 48 h.
AUC	Area under the concentration-time curve (ng.h/mL or ng_eq.h/mL) in the sampled matrix from zero (predose) extrapolated to infinity, calculated by linear up/log down trapezoidal summation and extrapolated to infinity by addition of the last quantifiable concentration (C_t) divided by the elimination rate constant (λ_z): $AUC_t + C_t/\lambda_z$.

λ_z	Apparent terminal rate constant (1/h), determined by linear regression of the terminal points of the log-linear concentration-time curve. Visual assessment will be used to identify the terminal linear phase of the concentration-time profile. A minimum of three data points will be used for determination.
$t_{1/2}$	Apparent terminal half-life (h), determined as (ln (2))/λ_z.
CL	Systemic plasma clearance (L/h), calculated as actual dose administered divided by AUC.
V_{ss}	Steady-state volume of distribution, calculated as MRT * CL, where MRT is the mean residence time extrapolated to infinity.
V_z	Apparent volume of distribution (L), calculated as actual dose administered divided by the product of λ_z x AUC.
C_{max}(PL)/C_{max}(PR)	C_{max} ratio of plasma AZD6765 (PL) to plasma radioactivity (PR).
C_{max}(WBR)/C_{max}(PR)	C_{max} ratio of whole blood radioactivity (WBR) to plasma radioactivity (PR).
AUC(PL)/AUC(PR)	AUC ratio of plasma AZD6765 (PL) to plasma radioactivity (PR). This parameter will be calculated for each AUC parameter estimated in both matrices (eg AUC, AUC_t and AUC_x.
AUC(WBR)/AUC(PR)	AUC ratio of whole blood radioactivity (WBR) to plasma radioactivity (PR). This parameter will be calculated for each AUC parameter estimated in both matrices (eg AUC, AUC_t and AUC_x.

The following pharmacokinetic parameters will be calculated for diagnostic purposes and listed, but will not be summarized.

$t_{1/2, Interval}$	The time interval (h) of the log-linear regression to determine $t_{1/2}$.
$t_{1/2, N}$	Number of data points included in the log-linear regression analysis.
Rsq	Goodness of fit statistic for calculation of λ_z (Coefficient of determination). If Rsq is less than 0.80 then λ_z and related parameters will not be reported.
%AUCex	Percentage of AUC obtained by extrapolation, calculated as $[(C_t/\lambda_z)/AUC]x100$. If the extrapolated area is greater than 30% of AUC then AUC and related parameters will not be reported.

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

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

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

The following PK parameters will be computed from the urine total radioactivity and AZD6765 data:

Ae_u	Amount recovered in urine during each collection interval, calculated as [Urine concentration or concentration equivalent x Urine volume].
Cum Ae_u	Cumulative amount recovered in urine.
fe_u	Percent of actually administered dose/radioactivity recovered in urine during each collection interval and overall.
CLr	Renal clearance, calculated as [(Cum $Ae_{u(t)}/AUC_t$], where t is the longest collection duration shared by both Cum Ae and radioactivity AUC.

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

Ae_f	Amount recovered in faeces during each collection interval, calculated as [faecal radioactive concentration equivalent x faeces weight].
Cum Ae_f	Cumulative amount recovered in faeces.
fe_f	Percent of actually administered radioactivity recovered in faeces during each collection interval and overall.

Total radioactivity excreted:

The total recovery of radioactivity (fe_{tot}; percent of actually administered radioactivity recovered in urine and faeces overall) will be computed as the sum of the cumulative excretion (as % dose) in urine and faeces. If a subject vomits, the emesis product will be collected during the 0 to 24 h postdose period only for potential analysis of ^{14}C radioactivity, and if appropriate, included calculation of the total radioactivity excreted for this subject.

Determination of metabolic profiling and metabolite identification will be performed on selected pools of plasma and excreta samples. The relative systemic exposure of any major metabolites will be calculated. This may be summarised in a separate study report.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 Safety analysis set

All subjects who received AZD6765 and for whom any post-dose data are available will be included in the safety analysis set.

12.1.2 Pharmacokinetic analysis set

The PK analysis set will include all subjects who receive at least 1 dose of AZD6765 and have at least 1 post dose PK measurement without important protocol deviations or violations thought to significantly affect the PK of the drug. A strategy for dealing with data affected by protocol violations and deviations will be determined by the pharmacokineticist as part of the review of the study data.

12.2 Methods of statistical analyses

12.2.1 General principles

The statistical analysis will be performed at [redacted] using [redacted] Standard Operating Procedures and Work Instructions.

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

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

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

12.2.2 Subject characteristics

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

12.2.3 Safety and tolerability

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

SAE will be collected from the time when informed consent is obtained until the end of study. Non-serious AEs will be collected from start of residential stay to end of the study. AEs that occur before dosing will be reported separately.

Adverse events will be coded using MedDRA vocabulary and summarised in frequency tables (frequency and proportion). Furthermore, listings of serious adverse events and adverse events that led to withdrawal will be made and the number of subjects who had any adverse events, serious adverse events, adverse events that led to withdrawal, and adverse events with severe intensity will be summarised.

Tabulations and listings of data for vital signs (orthostatic BP, pulse, and oral body temperature), clinical laboratory tests neurological and physical examination findings will be presented. Results from the CSSRS will be presented separately in a listing only. 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 subject will be presented with abnormal or out-of-range values flagged. Clinical laboratory data will be reported in the units provided by the clinical laboratory for the SRC meeting, and in Système International units in the Clinical Study Report. Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics, but will be included in subject listings.

12.2.4 Pharmacokinetics

No inferential analyses will be performed.

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. A listing of individual urine sample collection start and stop dates/times as well as urine volumes will be provided for each urine collection. A listing of individual faecal sample collection dates/times as well as sample weights will be provided. Pharmacokinetic variables will be summarised using appropriate descriptive statistics (eg, n, arithmetic mean, arithmetic coefficient of variation [CV%], standard deviation [SD], geometric mean, geometric coefficient of variation [GCV%], min, median, and max). The geometric mean is calculated as the exponential of the arithmetic mean calculated from individual observations

on a log scale. The GCV% is calculated as $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where s is the standard deviation of the data on a log scale. Mean, SD, CV%, geometric mean, and GCV% will not be calculated for t_{max}.

Non-quantifiable (NQ) values of plasma concentrations will be handled as follows:

- At a time point where at least 1 value is above LLOQ but less than or equal to 50% values are below LLOQ, all values below LLOQ will be set to LLOQ and a mean (arithmetic and geometric) value and SD (standard deviation) and coefficient of variation (CV% and GCV%) will calculated.

- At a time point where more than half of the observations are below LLOQ, only individual values will be reported; mean, SD, CV%, geometric mean and GCV% will be set to NQ. The minimum (min) value and the median will be set to less than LLOQ.

- If all values are below LLOQ at any time point, no descriptive statistics will be calculated for that time point. NA (not applicable) will be written in the field for standard deviation, CV%, and GCV% and <LLOQ will be written in fields for mean, geometric mean, min, median and max in the table.

- The number of observations greater than LLOQ [number of observations above LLOQ (N>LLOQ)] will be reported in the table.

A subject listing of all concentration-time data will be presented along with the descriptive statistics for all subjects. Figures of geometric mean concentration-time data will be presented for plasma and whole blood ^{14}C radioactivity concentrations and plasma AZD6765 concentrations combined, as appropriate (eg, AZD6765 and ^{14}C radioactivity in plasma combined; ^{14}C radioactivity in plasma and blood combined). Individual subject concentration-time data for the respective blood-based analyte combination will be graphically presented on linear and semi-logarithmic scales.

The ratio of plasma AZD6765 (parent) to plasma ^{14}C radioactivity concentrations (expressed as a percentage) for each sampling time will be listed by subject and summarized using descriptive statistics, to assess the contribution of unchanged drug to the total radioactivity in plasma over time.

A subject listing of whole blood/plasma ^{14}C radioactivity concentration-time ratios and percent distribution of radioactivity in blood cells will be presented and the data will be summarized by scheduled time using descriptive statistics.

Blood, plasma, urine, and faecal based pharmacokinetic parameters will be summarized using descriptive statistics. Geometric mean will not be calculated for t_{max}. Individual pharmacokinetic parameters will be presented along with descriptive statistics for all subjects.

Urine ^{14}C radioactivity data will be summarized by scheduled collection intervals using descriptive statistics. Individual urine recovery data will be presented along with the descriptive statistics for all subjects.

Faecal ^{14}C radioactivity data will be summarized using descriptive statistics. Individual faecal recovery data will be presented along with the descriptive statistics for all subjects.

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

12.3 Determination of sample size

This sample size (6 subjects) is based on experience from previous similar Phase I studies with other compounds and is considered to be sufficient to characterise the distribution, metabolism and elimination of AZD6765 and to gather safety and tolerability data for AZD6765. The sample size is sufficient to achieve the objectives of the study while exposing as few subjects as possible to study medication and procedures.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4**

In the case of a medical emergency the investigator may contact the Clinical Pharmacology Alliance Physician. If the Clinical Pharmacology Alliance Physician is not available, contact the Clinical Pharmacology Alliance Programme Director as detailed below:

Name	**Role in the study**	**Address & telephone number**
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
For SAE reporting AstraZeneca [redacted]	Fax number: [redacted]	
[redacted]	[redacted]	[redacted]

Name	Role in the study	Address & telephone number
[redacted]	[redacted]	[redacted]

13.2 Overdose

Doses in excess of that planned according to the protocol are considered an overdose. In case of known or suspected overdose, symptomatic treatment as well as monitoring of vital functions should be performed, based on the judgment of the investigator.

- 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 study drug occurs in the course of the study, then investigators or other site personnel 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 6.4.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Paternal exposure

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

Pregnancy of a subject's partner is not considered to be an adverse event. However, any conception occurring from the date of dosing until three months after dosing should be reported to AstraZeneca and followed up for its outcome and documented.

14. LIST OF REFERENCES

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Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Amlie R, Luckenbaugh DA, Charney DS, Manji HK. A randomized trial of an N-methyl-D-asparatate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006;63(8):856-64.

Clinical Study Protocol Appendix A

Drug Substance	AZD6765
Study Code	D6702C00030
Edition Number	1
Date	[redacted]
Protocol Dated	[redacted]

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Phase 1, Open-label, Single-Centre Study to Assess the Distribution, Metabolism and Excretion of [^{14}C]AZD6765 after a Single-Dose Intravenous Administration to Healthy Male Subjects

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

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

AstraZeneca Research and Development site representative

[redacted]

[redacted]

ASTRAZENECA SIGNATURE(S)

A Phase 1, Open-label, Single-Centre Study to Assess the Distribution, Metabolism and Excretion of [14C]AZD6765 after a Single-Dose Intravenous Administration to Healthy Male Subjects

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

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

AstraZeneca Research and Development site representative

[redacted]

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

SIGNATURE OF PRINCIPAL INVESTIGATOR

A Phase 1, Open-label, Single-Centre Study to Assess the Distribution, Metabolism and Excretion of [14C]AZD6765 after a Single-Dose Intravenous Administration to Healthy Male Subjects

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:

[redacted]

Clinical Study Protocol Appendix B

Drug Substance	AZD6765
Study Code	D6702C00030
Edition Number	1
Date	[redacted]

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	AZD6765
Study Code	D6702C00030
Edition Number	1
Date	[redacted]

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.