AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD6765
Study Code	D6702C00030
Edition Number	1
Date	29 March 2011

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

Study dates: First subject enrolled: 20 September 2010
Last subject last visit: 15 October 2010

Phase of development: Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre

One study centre in the United Kingdom.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To assess the distribution, metabolism and elimination of AZD6765 and total radioactivity after single-dose (150 mg) intravenous administration of [^{14}C]-labelled AZD6765	AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, CL, V_z, V_{ss}, λ_z and $t_{1/2}$ for plasma AZD6765, plasma radioactivity and whole blood radioactivity Plasma AZD6765 to plasma radioactivity concentration and pharmacokinetic (PK) parameter ratios, whole blood radioactivity to plasma radioactivity concentration and PK parameter ratios, and distribution of radioactivity into red blood cells Cumulative Ae, cumulative fe and CL_r for AZD6765 in urine	Pharmacokinetic
To evaluate the excretion of ^{14}C (mass balance) in urine and faeces after a single intravenous dose of 150 mg [^{14}C]AZD6765	Cumulative Ae and cumulative fe of radioactivity in urine and faeces Total cumulative fe of radioactivity (urine + faeces) CL_r of radioactivity in urine	Pharmacokinetic
Secondary	**Secondary**	
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	NA (to be addressed in an addendum to this CSR)	Pharmacokinetic
To evaluate safety and tolerability after a single intravenous administration of [^{14}C]AZD6765	Adverse events; laboratory variables (haematology, clinical chemistry and renal panel, urinalysis), vital signs (blood pressure, pulse rate and body temperature), physical examination, 12-lead electrocardiogram (ECG), Columbia-Suicide Severity Rating Scale (C-SSRS), neurological examination	Safety
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	NA	Pharmacogenetic

Ae: Amount of an analyte recovered in urine, faeces, or both combined; AUC: Area under the concentration-time curve in the sampled matrix from zero (pre-dose) extrapolated to infinity; $AUC_{(0-t)}$: Area under the concentration-time curve in the sampled matrix from zero (pre-dose) to time of last quantifiable concentration; CL: Systemic clearance; CL_r: Renal clearance; C_{max}: Maximum concentration in the sampled matrix; CSR: Clinical Study Report; fe: Percent of administered dose or radioactivity recovered in urine or faeces or both combined; $t_{1/2}$: Apparent terminal half-life; t_{max}: Time of maximum concentration in the sampled matrix; Vz: Apparent volume of distribution at the terminal phase; V_{ss}: Steady-state volume of distribution; λ_z: Apparent terminal rate constant.

Study design

This was an open-label study conducted at 1 study centre, in 6 healthy males aged 37 to 51 years, to assess the distribution, metabolism and excretion of [^{14}C]AZD6765. Each subject was to be administered a single intravenous infusion over 60 minutes.

The study comprised 3 visits: Visit 1 (enrollment and Screening), 30 days before Visit 2; Visit 2 (treatment visit) was a residential treatment period consisting of 12 days and 11 nights; and Visit 3 (follow-up), 7 to 10 days after discharge.

Target subject population and sample size

Six healthy males aged 35 to 60 years, including at least 2 Asian subjects, with a normal creatinine clearance of ≥60 mL/min, body mass index between 19 and 30.5 kg/m^2, weighing at least 50 kg to 100 kg (both inclusive) and who had provided written informed consent.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Table S2 Investigational products

Investigational product	Dosage form, strength, dosing schedule and route of administration	Manufacturer	Formulation number	Batch number
[^{14}C]AZD6765	Solution for infusion 3 mg/mL, 111 KBq/mL, 50 mL	AstraZeneca R&D Mölndal	10-003534AZ	10-003593AZ

Subjects received 150 mg [^{14}C]AZD6765 as a 60 minute intravenous (iv) infusion. However, the actual concentration of the [^{14}C]AZD6765 iv dosing solution was 99% of the label claim (ie, 2.97 mg/mL; 110 KBq/mL).

Duration of treatment

Single intravenous infusion over 60 minutes

Statistical methods

Demography and baseline data, pharmacokinetic (PK) data and safety data were summarised and listed using appropriate summary statistics. The safety data address the secondary objective to assure the safety of all subjects by assessment of adverse events (AEs), laboratory measurements, vital signs, physical examination, electrocardiogram (ECG), Columbia-Suicide Severity Rating Scale (C-SSRS) and neurological examinations.

Subject population

Enrolled: 6 subjects

Randomised: 6 subjects

Completed: 6 subjects

Summary of pharmacokinetic results

Key PK parameters for AZD6765 in plasma and urine, radioactivity in whole blood and radioactivity in plasma and urine are summarised in the table below.

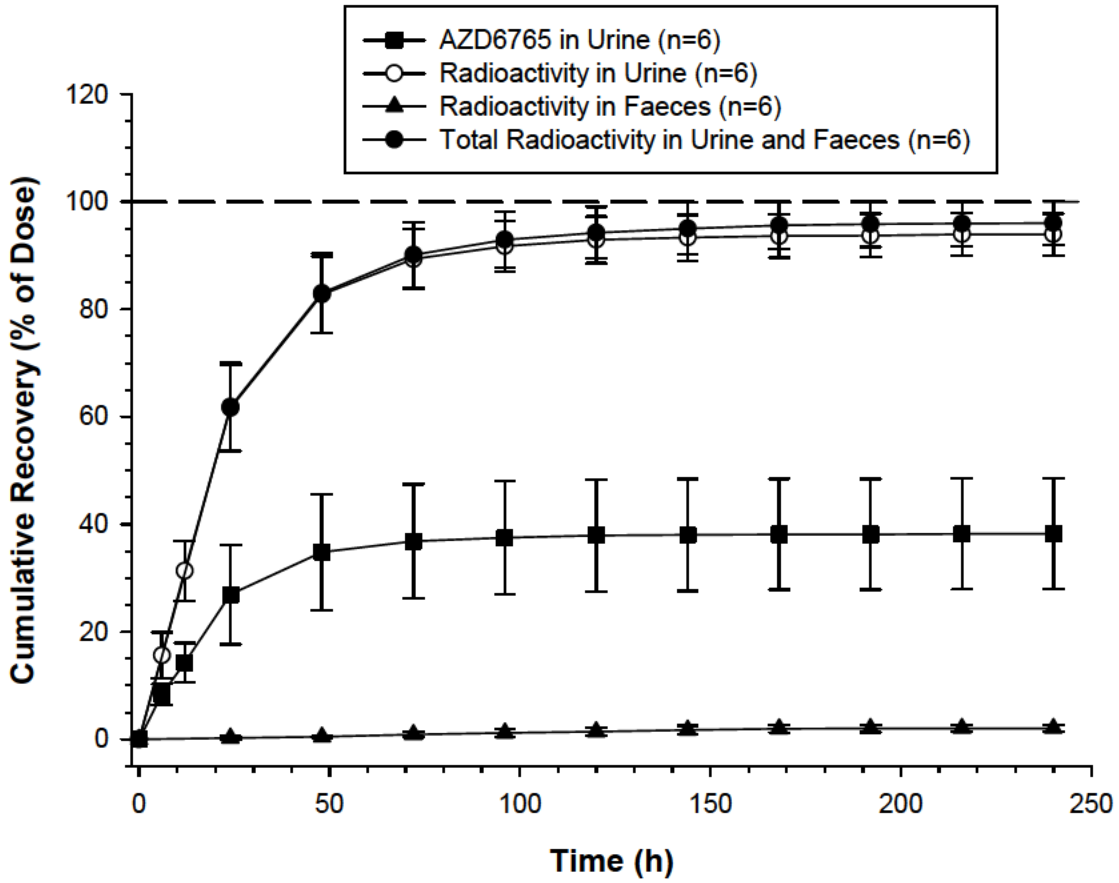
Table S3 Summary of pharmacokinetic parameters for AZD6765 and radioactivity in plasma, whole blood and urine

Parameter [a]	Geometric Mean (Geometric CV%)		
	AZD6765 in Plasma	Radioactivity in Plasma	Radioactivity in Whole Blood
Systemic Parameters			
AUC (ng [Eq]*h/mL)	17900 (20.8)	28600 (21.7)	22600 (19.8)
C_{max} (ng [Eq]/mL)	1270 (20.9)	1500 (19.5)	1320 (18.1)
t_{max} (h) [b]	1.04 (1.03, 1.28)	1.09 (1.03, 1.28)	1.04 (1.03, 1.28)
$t_{1/2}$ (h)	16.1 (20.1)	16.9 (25.2)	15.1 (22.4)
CL (L/h)	8.30 (20.9)	5.19 (21.7)	6.58 (19.8)
V_{ss} (L)	161 (9.0)	117 (8.2)	135 (8.1)
Renal Parameters			
CL_r (L/h)	3.07 (45.0)	4.87 (24.6)	NA

CV% coefficient of variation in percent; NA not applicable.
a Concentration-related parameters are expressed in units of ng for AZD6765 and ng-equivalents (ngEq) for radioactivity.
b Data presented for this parameter are median (minimum, maximum).
Note: Number of observations (n) was 6 for all parameters.

The cumulative percents of dose excreted as AZD6765 and radioactivity in urine, as radioactivity in faeces and as total radioactivity (urine + faeces) are shown in the figure below.

Figure S1 **Arithmetic mean (± SD) cumulative recoveries of AZD6765 and radioactivity in urine, faeces and both combined over time**



SD standard deviation

The results of this study showed that unchanged AZD6765 is the primary systemically available analyte after administration of an AZD6765 dose. AZD6765 accounted for 63% to 85% of the radioactivity in plasma (based on AUC and C_{max}, respectively) and the slopes for plasma radioactivity and whole blood radioactivity generally paralleled that of plasma AZD6765, indicating that AZD6765 is the primary driver of overall systemic distribution and elimination of drug product.

Radioactivity in blood was more concentrated in the extracellular fluid than in the red blood cells. Geometric mean percent of radioactivity distributed into red blood cells was low and time-independent, ranging from 20.6% to 38.2%. These results indicate that plasma is a suitable matrix for PK sampling of AZD6765.

On average, 95.9% of the administered dose was recovered as radioactivity in urine and faeces within 240 hours, of which 93.8% was recovered in urine and 1.93% in faeces. Parent drug (AZD6765) accounted for 37.0% of the dose excreted in urine. Most of the radioactive dose

was excreted within 72 hours (ie, similar to the excretion profile of parent drug) and less than 1% of the dose was excreted after 120 hours.

There was evidence for the slow formation and subsequent elimination of metabolic product(s) based on the time-dependent decrease in the plasma AZD6765/plasma radioactivity concentration ratio and the large percent of non-AZD6765 radioactive recovery in urine. However, the systemic contribution of the metabolic product(s) is minor, as evidenced by the large exposure ratios (maximum concentration in the sampled matrix [C_{max}] and area under the concentration-time curve in the sampled matrix from zero (pre-dose) extrapolated to infinity [AUC]) for plasma AZD6765 to plasma radioactivity.

Summary of safety results

AZD6765 can be considered tolerated in 5 of the 6 treated subjects when administered as a single 150 mg [^{14}C]AZD6765 intravenous infusion in healthy males. Subject E0001015 (one of the 2 Asian subjects) did not tolerate the 150 mg infusion and reported moderate nausea and dizziness after the start and moderate headache after the end of the infusion, which were treated with paracetamol. No deaths, serious adverse events (SAEs), discontinuation of the investigational product (IP) due to an AE (DAE) or severe AEs were reported.

Four of the 6 subjects (67%) reported 15 treatment-emergent adverse events (TEAEs), all except 1 (hypoaesthesia), considered causally related to the IP. The most frequently (3 subjects [50%]) reported Preferred Term was headache, in the System Organ Class Nervous system disorders. Most of the TEAEs reported by subjects on Visit 2 (Day 1) were considered moderate namely, headache, nausea, dizziness, feeling drunk and sensation of heaviness. The only mild TEAEs reported by subjects on Visit 2 (Day 1) were rhinitis and lethargy. All other TEAEs reported by subjects after Visit 2 (Day 1) were considered to be mild.

No clinically relevant changes or values were observed in clinical chemistry, haematology or urinalysis variables, in vital signs measurements, physical examination findings and neurological examinations. None of the 6 subjects showed any suicidal intentions and no clinically significant ECG abnormalities were reported.