AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1981
Study Code	D9830C00006
Edition Number	1
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An Open, Single-dose, Single-Centre, Phase I Study to Assess the Metabolism, Excretion and Pharmacokinetics of [^{14}C]AZD1981 in Healthy Male Volunteers

Study dates: First subject enrolled: 16 February 2010
Last subject last visit: 25 March 2010

Phase of development: Clinical pharmacology (I)

Principal Investigator:

Sponsor's Responsible Medical Officer:

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

Study centre(s)

Publications

None at the time of writing this report.

Objective and criteria for evaluation

The primary objective was to characterise the absorption, distribution, metabolism and excretion (ADME) of a single oral dose of 250 mg [^{14}C]AZD1981 in healthy male subjects.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To characterise the ADME of a single oral dose of 250 mg [^{14}C]AZD1981 in healthy male subjects.	Radioactive dose recovered in urine and faeces and total (urine+faeces): Recovery (Ae or Af, % of dose) Pharmacokinetics of total radioactivity in blood, plasma and urine and of AZD1981 in plasma and urine: C_{max} (µmol/L), t_{max} (h), AUC_{0-t} (h*µmol/L), AUC (h*µmol/L), λ_z (h^{-1}), $t_{½}$ (h), CL/F (L/h), V_z/F (L), Ae (µmol) and CLr (L/h) Distribution of radioactivity in red blood cells: Cbc (%) Urine excretion of AZD1981 in relation to [^{14}C] radioactivity (%) Metabolite profiles generated from pooled plasma (representative individual time points, AUC_{0-5h}, and AUC_{0-12h}), urine (0-12h), and faeces (individually assigned fractions).	Pharmacokinetic

Study design

AZD1981 is being developed by AstraZeneca as an oral treatment for asthma. This study was a phase-I, open-label, single-centre study. Four healthy male subjects aged 50 to 65 years (inclusive) each received as single dose of [^{14}C]AZD1981.

Target subject population and sample size

Subjects were to be four healthy, non-smoking, male subjects aged 50 to 65 years (inclusive). They were to have a body mass index (BMI) ≥18.0 and ≤30.0 kg/m^2 and a minimum weight of 50 kg. Subjects were studied as a single group.

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

Subjects received a single dose of 150 mL [^{14}C]AZD1981 oral solution 1.67 mg/mL, batch number 10-000080AZ, containing 250 mg [^{14}C]AZD1981.

Duration of treatment

Single dose.

Statistical methods

Statistical analysis was carried out by using the SAS® software. Given the exploratory nature, no formal statistical hypothesis testing was performed in this study. The statistical analysis were descriptive and consist of subject listings, graphs and summary statistics comprising geometric mean, coefficient of variation, arithmetic mean, standard deviation, minimum, median and maximum values as appropriate.

Subject population

The demographic and key baseline characteristics of study subjects are summarised in Table S2 below.

Table S2 Summary of subject demography

Enrolment code	Race	Age (Years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
E0001001[a]	White	51	181	87.3	26.0
E0001002	White	51	176	89.3	28.0
E0001004	White	60	173	68.3	22.0
E0001006	Black or African American	50	173	81.1	27.0
Mean	NA	53	176	82	26

[a] Subject E0001001 was included in the PK analysis set but excluded from the summary statistics of AZD1981 and [^{14}C] radioactivity in urine and total (urine+faeces) recovery as he accidentally discarded approximately 150 to 200 mL urine at 1 hour and 8 minutes post dose. Urine from all 4 subjects was used for the metabolite profiling and characterization.

Source: Table 11.1.4 and Listing 12.2.4.1.

Summary of pharmacokinetic results

The geometric mean total recovery of the [^{14}C]AZD1981 dose was 95.1% (range 94.4% to 95.6%) with corresponding geometric mean recovery values in urine and faeces of 52.7% and 41.9%, respectively. The excretion in urine was rapid and the major amount was excreted within the first 6-hour sampling period. The excretion was slower in faeces with the major amount excreted within 72 hours.

More than 80% of the radioactivity excreted into urine was accounted for by unchanged AZD1981. The geometric mean half-life in urine was comparable between AZD1981 and radioactivity (14 hours). Renal clearance was slightly higher for AZD1981 (6.90 L/h) than for drug related material (AZD1981 and metabolites/reaction products), ie, radioactivity (5.12 L/h).

The geometric mean exposure (C_{max}, AUC_{0-t} and AUC) decreased in the order [^{14}C]-plasma > AZD1981 in plasma > [^{14}C]-blood and consequently CL/F increased in the order [^{14}C]-plasma (10.7 L/h) < AZD1981 in plasma (17.8 L/h) < [^{14}C]-blood (22.2 L/h). The variability in the exposure parameters was low to moderate (CV% range of 19.9% to 35.0%). Estimates of terminal half-life based on plasma and blood data were shorter than those based on urinary excretion data; geometric mean values for radioactivity and AZD1981 in plasma and for radioactivity in blood were 7.42 h and 4.93 h and 3.58 h, respectively. The geometric mean V_z/F was in the same range for AZD1981 in plasma and radioactivity in plasma and blood (114 L to 127 L).

The major part (60%) of the plasma exposure of drug-related material (radioactivity) in terms of AUC was accounted for by unchanged AZD1981. The blood/plasma exposure ratios were <1 and there was a negligible distribution of radioactivity in blood cells.

Metabolite characterization quantified 2 metabolites in plasma: N-deacylated (AZ111811203; 4.15%) and acyl glucoronide (AZ12455398; 2.86%). In urine, the major metabolites were identified as acylglucuronide (AZ12453389; 11.1%) and S-oxide (AZ12300270; 9.55%). In faeces, no metabolite exceeded 5% of the excreted dose.

Summary of safety results

AZD1981 was well tolerated by subjects during the study. There were no deaths, serious adverse events or withdrawals due to adverse events (AEs).

During the study AEs were experienced by 2/4 subjects.

During the study 1 subject experienced 3 headaches (1 moderate, 2 mild) and 1 event of nausea (moderate), and 1 subject experienced 1 event of headache (mild). All AEs except 1 event of mild headache were considered to be related to AZD1981.

There were no clinically relevant findings in clinical laboratory tests, vital signs, ECG or physical examination during the study.