AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2423
Study Code	D2600C00008
Edition Number	1
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An Open Label, Single Dose, Phase I Study to Evaluate the Excretion of Radioactivity, the Metabolic Profile, Pharmacokinetics, Safety and Tolerability Following Single Oral Administration of [^{14}C]AZD2423 to Healthy Male Volunteers

Study dates: First subject enrolled: 16 November 2010
Last subject last visit: 22 December 2010

Phase of development: Clinical pharmacology (I)

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

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 investigate the rate, route and extent of excretion of radioactivity in urine and faeces following single oral administration of [^{14}C]AZD2423 solution	Percentage of radioactive dose recovered in urine and faeces and in total (urine+faeces)	PK
To investigate the pharmacokinetics of total radioactivity and of unchanged AZD2423 in plasma following single oral administration of [^{14}C]AZD2423 solution	Concentrations of total radioactivity in blood and plasma and of AZD2423 in plasma; pharmacokinetics of total radioactivity and of AZD2423 in plasma by means of C_{max}, t_{max}, $AUC_{(0\text{-last})}$, AUC, $t_{½}$, CL/F and V_z/F; relative exposure of AZD2423 to total radioactivity in plasma by means of $C_{max,AZD2423}/C_{max,radioactivity}$; relative exposure of total radioactivity in blood to plasma ($C_{rad,b/p}$); distribution of total radioactivity in blood cells (Cbc)	PK
Secondary	**Secondary**	
To investigate the metabolite profiles of AZD2423 in plasma and excreta	Not applicable[a]	PK
To characterise major metabolites of AZD2423 in plasma and excreta	Not applicable[a]	PK
To investigate safety and tolerability of AZD2423 following administration of a single oral dose of [^{14}C]AZD2423 solution to healthy subjects	Adverse events, clinical chemistry, haematology, urinalysis, vital signs, electrocardiogram, physical examination	Safety
Exploratory	**Exploratory**	
To investigate the concentration of unchanged AZD2423 in urine	Not determined	PK
To explore the pharmacogenetics by genotyping in blood	Not applicable[b]	Pharmaco-genetic

a These results will be reported separately from the Clinical Study Report
b These results are not reported in the Clinical Study Report

~~AUC: Area under the concentration-time curve in the sampled matrix from zero (predose) extrapolated to~~ infinity, $AUC_{(0\text{-last})}$: Area under the concentration-time curve in the sampled matrix from zero (predose) to time of last quantifiable analyte concentration, CL/F: Apparent oral clearance in the sampled matrix, C_{max}: Maximum analyte concentration in the sampled matrix, CSR: Clinical Study Report, PK: Pharmacokinetic(s), t_{max}: Time of maximum analyte concentration, $t_{1/2}$: Apparent terminal half-life, V_z/F: Apparent volume of distribution

Study design

This was an open-label, single study centre, Phase I study to evaluate the excretion of radioactivity, the metabolic profile, pharmacokinetics, safety, and tolerability following a single oral administration of [^{14}C]AZD2423 in healthy male subjects. Subjects were screened (Visit 1) within 28 days of investigational product administration and were admitted to the study centre on Day -1 of Visit 2. Subjects were administered a single oral dose of [^{14}C]AZD2423 on Day 1 of Visit 2. Subjects were to remain in the study centre until Day 8. Subjects were to attend a follow-up visit (Visit 3), 1 to 10 days after discharge from the study centre or when >90% of the radioactivity had been recovered or when radioactivity could no longer be quantified.

However insufficient radioactivity had been recovered by Day 8 (≤90% of the dose) and it was determined that prolonged monitoring was needed. Visit 2 and sample collection (urine and faeces) was extended for an additional 48 h (168 to 216 h) and the subjects were discharged 2 days later, ie, Day 10. All follow-up procedures (Visit 3 [Follow-up]) were conducted at the time of discharge from the study centre (Day 10).

Target subject population and sample size

Six (6) healthy male subjects, aged 50 to 65 years (inclusive).

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

Each subject received a single oral dose of 150 mg [^{14}C]-labelled AZD2423, containing 7.4 MBq as an oral solution (10 mL; 0.74 MBq/mL).

Table S2 Details of investigational product and any other study treatments

Investigational product	Dosage form and strength	Manufacturer	Formulation number	Batch number
[^{14}C]AZD2423	Oral solution, 15 mg/mL, 0.74 MBq/mL, 10 mL	AstraZeneca	10-005046AZ	10-005047AZ

Duration of treatment

Single doses of AZD2423 were administered. The total study duration for an individual subject was up to 50 days depending on scheduling of screening/follow-up visits and inclusion of additional collection visits.

Statistical methods

Statistical analysis was carried out by using the SAS® software, version 9.2. Given the exploratory nature, no formal statistical hypothesis testing was performed in this study. The statistical analysis of the primary and secondary endpoints was descriptive and consisted of subject listings, graphs and summary statistics comprising geometric mean, coefficient of

variation, arithmetic mean, standard deviation, median, minimum and maximum values or frequency tables as appropriate.

Subject population

All 6 enrolled subjects were included in the safety analysis set and the pharmacokinetic analysis set. All 6 subjects completed the study. All enrolled subjects (100%) were males aged from 50 to 64 years, with a mean weight of 86.1 kg and a mean body mass index of 27 kg/m^2.

Summary of pharmacokinetic results

The geometric mean total recovery of the [^{14}C]AZD2423 dose was 85.4% (individual range 81.7 to 88.3%) and included a single 24 h sample between 360 h and 384 h postdose (the urine sampling terminated at 216 h and the faeces sampling was interrupted between 240 h and 360 h). The geometric mean total recovery in urine and faeces was 21.7% and 63.0% of the dose, respectively. The excretion in urine was rapid with the major amount excreted within 24 h. The excretion was slower in faeces with the major amount excreted within 72 h. Overall, the excretion rate was moderate with the major part of the administered dose recovered within 72 h.

Table S3 Summary of total recovery (% of dose) in urine, faeces and total (urine+faeces)

Parameter/Matrix	n	Geometric mean	CV%	Min	Median	Max
Recovery/Urine (%)	6	21.7	25.6	14.8	21.9	32.0
Recovery/Faeces (%)	6	63.0	8.4	56.3	63.6	71.3
Recovery/Total (%)	6	85.4	2.8	81.7	86.2	88.3

CV%: Coefficient of variation, Min: Minimum, Max: Maximum

A minor fraction of the radioactivity plasma exposure was accounted for by unchanged AZD2423. The geometric mean ratio AZD2423/total radioactivity in plasma was not constant over time. At the first sampling timepoint (0.33 h) the ratio was 69%, while thereafter decreasing to 2.2% at the last sampling timepoint (168 h). The inter-individual variability in the exposure parameters was low to moderate (<50%). The geometric mean apparent terminal half-life ($t_{½}$) estimate was longer for radioactivity than for AZD2423 and, while obtained with good precision, exceeded the actual PK sample collection time. The geometric mean blood/plasma radioactivity concentration ratio ($C_{rad,b/p}$), measured at different timepoints up to 48 h postdose were 70 to 96%. The geometric mean distribution of radioactivity into blood cells (Cbc) was moderate (<50%).

Table S3 Summary of plasma AZD2423 and plasma radioactivity PK parameters following 150 mg [^{14}C]AZD2423 oral single dose administration (n=6, PK analysis set)

Parameter[a]	AZD2423	[^{14}C]-Plasma
C_{max} (nmol/L)	351 (32.7)	591 (34.2)
t_{max} (h)	0.52 (0.33-1.00)	1.01 (0.67-4.05)
AUC (h*nmol/L)	2620 (35.1)	ND
$AUC_{(0\text{-}last)}$ (h*nmol/L)	2370 (38.3)	24400 (13.9)
CL/F (L/h)	134 (35.2)	ND
V_z/F (L)	10600 (44.5)	ND
$t_{½}$ (h)	54.9 (43.6)	195 (65.0)

a Geometric mean and (CV%) are shown except for t_{max} where median and (range) is shown
ND: Not determined

The major metabolic pathways of AZD2423 detected in urine and faeces were oxidation and dealkylation reactions at the N-*tert*-Butylpiperazine moiety and formation of a reactive intermediate in the same piperazine ring leading to conjugation with glutathione and subsequent breakdown products thereof. AZD2423 and 3 oxidation products, a dealkylation product, a glucuronic acid conjugate, and a series of glutathione adduct breakdown products were detected and characterized in the plasma samples.

Summary of safety results

No deaths, serious adverse events or discontinuations were reported during the study. From the 4 subjects who reported at least 1 adverse event, 3 subjects had adverse events considered causally related to the investigational product (dyspepsia, tachycardia, supraventricular extrasystoles and dysgeusia) by the Investigator. These AEs were all considered mild in intensity. No clinically relevant changes were identified for clinical chemistry, haematology, urinalysis, vital signs or electrocardiograms.