AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9668
Study Code	D0520C00016
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An Open-Label, Single-Centre, Phase I Study to Assess the Excretion, Metabolism and Plasma Pharmacokinetics following a Single Oral Dose of 60 mg [^{14}C]AZD9668 in Healthy Male Volunteers

Study dates:	First subject enrolled: 22 June 2010 Last subject last visit: 21 July2010
Phase of development:	1

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.

Objective and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To characterise the excretion, metabolism and plasma pharmacokinetics following administration of a single oral dose of 60 mg [14C]AZD9668 in healthy male volunteers.	Percentage of radioactive dose recovered in urine and faeces and total balance, concentration of total radioactivity in blood and plasma, plasma concentrations of AZD9668 (unlabelled parent compound), metabolite profiling and identification in plasma and excreta (will be reported separately), pharmacokinetics of AZD9668 (C_{max}, t_{max}, $t_{½}$, AUC, CL/F, V_z/F, MRT, f_e, A_e, CL_R).	Pharmacokinetic
Secondary	**Secondary**	
To collect information on safety and tolerability of a single oral dose of 60 mg [14C]AZD9668 in healthy male volunteers.	Adverse events, clinical chemistry, haematology, urinalysis, vital signs, electrocardiogram, physical examination.	Safety

Study design

This study was a Phase I, open-label, single centre study. Four healthy male subjects aged 50 years and over, each received as single dose of [^{14}C]AZD9668.

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 ≥18.0 and ≤30.0 kg/m^2 and a minimum weight of 50 kg. Subjects were studies as a single group.

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

The dose was prepared at the clinical site prior the administration. The radiolabelled powder was constituted in 20 mL ethanol 95% (v/v) by using an ultrasonication bath to achieve a clear solution. It was then diluted in 80 mL commercially available apple juice. The radiolabelled product ingested contained ethanol 19% (v/v).

Each healthy volunteer received a single oral dose of 60 mg of [^{14}C]AZD9668 (corresponds to 79 mg of [14C]AZD9668 tosylate, 9 MBq) administered as a 100 mL solution followed by two 70 mL water rinses of the dosing container.

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 analyses were descriptive and consisted 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

Table S2 Summary of subject demography

Enrolment code	Race	Age (Years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
E0001002	White	52	179	82.1	25
E0001003	White	55	168	61.9	21
E0001009	White	51	180	77.5	23
E0001010	White	57	173	79.6	26

Summary of pharmacokinetic results

The geometric mean total recovery of the [^{14}C]AZD9668 dose was 92.2% with corresponding geometric mean total recovery values in urine and faeces of 63.6% and 28.5%, respectively. The excretion in urine was rapid and the major amount was excreted within the first 12 hour sampling period in all 4 subjects. The excretion rate was lower and more variable in faeces with the major amount excreted within 48 to 144 hours. Overall, the excretion was rapid with 54.3% (geometric mean) of administered dose recovered within 24 hours.

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

Parameter/Matrix	n	Min	Median	Max	Geometric mean	CV%
Recovery/Urine (%)	4	61.7	62.5	67.7	63.6	4.3
Recovery/Faeces (%)	4	26.0	29.0	30.3	28.5	7.2
Recovery/Total (%)	4	89.8	92.7	93.7	92.2	1.9

The geometric mean estimate of C_{max} was comparable for AZD9668 in plasma and for [^{14}C]-radioactivity in plasma and blood: 1300, 1490 and 1300 nmol/L, respectively. The geometric mean AUC was lower for AZD9668 in plasma than for radioactivity in plasma and blood: 7050, 13800 and 12600 h*nmol/L, respectively. Consequently CL/F decreased in the order AZD9668 in plasma (15.6 L/h) > [^{14}C]-blood (8.71 L/h) ~ [^{14}C]-plasma (7.96 L/h).

The geometric mean V_z/F was slightly larger for AZD9668 (342 L) than for radioactivity in plasma (227 L) and blood (234 L). There was a relatively large variability (CV% 67.4%) in the $t_{½}$ estimate for AZD9668 in plasma due to differences in capture of the terminal phase. For two subjects (E0001002 and E0001003) the terminal phase was captured up to 96 h resulting in a $t_{½}$ of approximately 26 h. For the other two subjects (E0001009 and E0001010) the terminal phase was captured up to 48 h with a $t_{½}$ estimate of approximately 9 h. The geometric mean $t_{½}$ estimates for radioactivity in plasma (19.8 h) and blood (18.6 h) were based on a terminal phase up to 48 or 72 h and the CV% was smaller. The MRT was shorter for AZD9668 (8.30 h) than for radioactivity in plasma (19.2 h) and blood (18.0 h).

Table S4 Summary of plasma AZD9668 and plasma or blood radioactivity PK parameters following 60 mg [^{14}C]AZD9668 oral single dose administration (n=4, PK analysis set)

Parameter[a]	AZD9668	[^{14}C]-Plasma	[^{14}C]-Blood
C_{max} (nmol/L)	1300 (29.6) (942-1890)	1490 (21.0) (1210-1990)	1300 (24.2) (1030-1810)
t_{max} (h)	1.50 (0.50-2.00)	1.50 (0.50-2.00)	1.00 (0.50-2.00)
AUC (h*nmol/L)	7050 (12.6) (5900-7930)	13800 (9.7) (12700-15800)	12600 (8.5) (11700-13600)
$AUC_{(0-24)}$ (h*nmol/L)	6590 (11.1) (5590-7140)	10200 (8.0) (9160-11000)	9580 (5.9) (8810-10000)
CL/F (L/h)	15.6 (12.7) (13.9-18.7)	7.96 (9.6) (6.98-8.65)	8.71 (8.3) (8.11-9.38)
V_z/F (L)	342 (58.6) (187-568)	227 (8.0) (212-252)	234 (30.4) (176-352)
$t_{½}$ (h)	15.2 (67.4) (8.61-25.8)	19.8 (8.9) (17.4-21.3)	18.6 (36.1) (13.0-30.1)
MRT (h)	8.30 (19.6) (7.44-11.1)	19.2 (18.1) (14.7-22.0)	18.0 (28.9) (12.4-24.7)

[a] Geometric mean, (CV%) and (range) are shown except for t_{max} where median (range) is shown

Following a dose of 60 mg [^{14}C]AZD9668 and based on geometric mean estimates, renal clearance of AZD9668 (6.70 L/h) constituted 43% of the oral clearance and 67% of the radioactivity excreted in urine was attributed to unchanged AZD9668.

Approximately half (geometric mean 51%) of the plasma exposure of drug-related material (radioactivity) in terms of AUC was accounted for by unchanged AZD9668. The blood/plasma radioactivity exposure ratio was close to unity suggesting similar distribution and binding of drug-related material in plasma and red blood cells.

Summary of safety results

There were no adverse events reported during the study. No clinically relevant abnormalities were noted in clinical laboratory, vital signs, ECG or physical examination evaluations.