AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5069
Study Code	D3550C00013
Edition Number	1
Date	02 November 2011

A Phase I, Open-Label Study to Characterise the Absorption, Distribution, Metabolism and Excretion following a Single Oral Dose of [^{14}C]AZD5069 in Healthy Male Volunteers

Study dates: First subject enrolled: 27 May 2011
Last subject last visit: 01 July 2011

Phase of development: Clinical pharmacology (I)

International 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.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To characterise the PK, routes of excretion and metabolism of a single 120 mg oral dose of [^{14}C]AZD5069 in healthy male subjects	Concentration of [^{14}C] radioactivity in plasma and whole blood, concentrations of AZD5069 (cold drug) in plasma and the resulting AUC, and $AUC_{(0-t)}$, C_{max}, t_{max}, λ_z, $t_{½}$, CL/F, and V_z/F Amount and percentage of radioactive dose recovered in both urine and faeces, amount and percentage of AZD5069 (cold drug) recovered in urine, renal clearance of [^{14}C] radioactivity and AZD5069 Whole blood:plasma radioactivity ratios for concentrations and selected pharmacokinetic parameters (AUCs and C_{max}). Plasma AZD5069 (cold): [^{14}C]AZD5069 ratios for concentrations and selected pharmacokinetic parameters (AUCs and C_{max})	Pharmacokinetic
Secondary	**Secondary**	
To further determine the safety and tolerability of a single oral administration of AZD5069 in healthy male subjects	Adverse events, vital signs, electrocardiogram, haematology, clinical chemistry, urinalysis and physical examination	Safety
Exploratory	**Exploratory**	
To perform, if required, possible exploratory analysis of significant metabolites in plasma, urine and faecal samples (Not reported in the Clinical Study Report)	Not applicable	Pharmacokinetic

λ_z: Elimination rate constant, AUC: Area under the concentration-time curve in the sampled matrix from zero (pre-dose) extrapolated to infinite time, $AUC_{(0-t)}$: Area under the concentration-time curve in the sampled matrix from zero (pre-dose) to time of last quantifiable concentration, C_{max}: Maximum plasma concentration, CL/F: Apparent oral clearance, t_{max}: Time of C_{max}, $t_{½}$: Apparent terminal elimination half-life, V_z/F: Apparent volume of distribution.

Study design

This study was a Phase I, open-label, non-comparative, single administration, single centre study. Six healthy male subjects aged 50 years and older were studied as a single group.

The study comprised 3 visits. Screening (Visit 1) within 28 days before administration Visit 2. At Visit 2 each healthy subject was admitted to the study centre on Day -1 and remained resident at the study centre until Day 8. On Day 1, subjects received a single oral administration of 120 mg (21.6 MBq) [^{14}C]AZD5069 administered as an oral solution (24 mL). Blood and urine samples (for analysis of total radioactivity, metabolite profiling, identification and bioanalysis of AZD5069) and faeces samples (for analysis of total radioactivity, metabolite profiling and identification) were collected pre-dose and at specified times up to at least 168 hours (8 days) after administration. The subjects were discharged from the study centre on Day 8 (168 hours post-dose). If significant radioactivity was still being recovered, additional 24 hour collections of urine and/or faeces were to be continued on an outpatient basis. Visit 3 was a follow-up 7 days after collection of the last sample.

Target subject population and sample size

Six (6) healthy male subjects, aged 50 years and older.

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

Table S2 Details of investigational product

Investigational product	Dosage form, strength	Manufacturer	Batch number	Expiry date
[^{14}C]AZD5069	Oral solution, 5 mg/mL (0.9 MBq/mL, 24 mL)	AstraZeneca	11-000742AZ (11-000910AZ)	29 July 2011

The nominal dose to be used for this study was 120 mg AZD5069. However, upon analysis of the dose solution it was determined that the actual dose administered was equivalent to 119 mg of AZD5069. This actual dose administered of 119 mg was used in the computation of the pharmacokinetic parameters and recovery calculations.

Duration of treatment

Single dose.

Statistical methods

No formal statistical hypothesis testing was performed in this study. The statistical analysis is descriptive and consisted of subject listings, graphs and summary statistics comprising arithmetic mean, standard deviation, median, minimum, maximum, geometric mean, and/or coefficient of variation as appropriate.

Subject population

Six subjects were enrolled in the study as planned. All 6 subjects completed the study. All 6 enrolled subjects (100.0%) were white males with ages ranging from 50 to 65 years, a mean weight of 82.6 kg and a mean body mass index of 25.6 kg/m^2. All demographic parameters were in accordance with the inclusion criteria.

Summary of pharmacokinetic results

Mean recovery of total radioactivity in urine and faeces combined as percent of dose was 100% and ranged from 98.1% to 103% of the dose. Most of the recovered radioactivity was found in urine (65.1%) with 34.6% found in faeces. The average percentage of AZD5069 dose recovered in urine was 6.66% indicating that the majority of radioactivity in urine may be attributed to AZD5069 metabolites.

Key pharmacokinetic parameters for AZD5069 in plasma, radioactivity in plasma, and radioactivity in whole blood are summarised in Table S3.

AZD5069 appeared to be rapidly absorbed with peak concentrations being achieved at a median time of 0.5 hour for plasma AZD5069 and 1 hour for radioactivity in plasma and whole blood. Mean plasma radioactivity equivalent concentrations were greater than mean AZD5069 plasma concentrations at all sampling times indicating the presence of metabolic products in the systemic circulation. The ratio of AZD5069 to plasma radioactivity equivalent concentrations was time dependent and decreased during the time-course from an average of approximately 80% at 0.25 hour to 7% at 48 hours. This suggests that metabolite(s) with a slower elimination than that of the parent compound may be formed.

Table S3 Summary of key AZD5069 and total radioactivity pharmacokinetic parameters

Parameter	N	Statistic	AZD5069 plasma	[^{14}C] Plasma	[^{14}C] Blood
AUC [a] (nmol·h/L)	6	Geo. mean (Geo. CV%)	45000 (36.0)	105000 (24.0)	55100 (28.0)
C_{max} [a] (nmol/L)	6	Geo. mean (Geo. CV%)	17400 (10.0)	22100 (13.4)	11600 (10.1)
t_{max} (h)	6	Median (min, max)	0.5 (0.5, 2.52)	1.0 (0.5, 2.52)	1.0 (0.5, 2.52)
$t_{1/2}$ (h)	6	Geo. mean (Geo. CV%)	9.77 (49.9)	33.7 (18.1)	18.2 (48.7)
C_{maxPL}/ C_{maxPR}	6	Geo. mean (Geo. CV%)	0.787 (7.2)	-	-
AUC_p/AUC_{pr}	6	Geo. mean (Geo. CV%)	0.429 (20.0)	-	-
$C_{max\ br}/C_{max\ pr}$	6	Geo. mean (Geo. CV%)	-	-	0.526 (8.6)
AUC_{br}/AUC_{pr}	6	Geo. mean (Geo. CV%)	-	-	0.526 (8.0)

AUC: area under the concentration-time curve in the sampled matrix from zero (pre-dose) extrapolated to infinite time, br: whole blood radioactivity, C_{max}: maximum plasma concentration, Geo. CV%: geometric coefficient of variation in percent, Geo. mean: geometric mean, max: maximum, min: minimum, p: plasma; pr: plasma radioactivity, t_{max}: Time of C_{max}, $t_{½}$: Apparent terminal elimination half-life.

[a] For radioactivity AUC units are: nmolEq·h/L and C_{max} units are: nmolEq/L.

Summary of safety results

There were no deaths, serious adverse events or withdrawals due to adverse events reported in the study. Four (4) subjects reported 6 adverse events. The adverse event reported by the most subjects was headache of which all events were considered causally (possibly) related to the investigational product by the Investigator. No clinically significant findings were reported for the vital signs, electrocardiogram, physical examinations, haematology or clinical chemistry (except for low neutrophil plasma concentrations that were quickly restored).

A decrease in the neutrophil plasma concentrations following administration of the investigational product was expected. The observed changes in neutrophil plasma concentrations were consistent with previous studies with AZD5069 and were not considered to be clinically relevant in the healthy subjects participating in this study. The lowest mean neutrophil value was observed at 12 hours post-dose, which was later than the observed maximum plasma concentration.

Conclusion(s)