AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1722
Study Code	D5611C00007
Edition Number	1
Date	4 March 2015
EudraCT Number	2013-004871-10

A Phase I, Single Centre, Open Label Study to Assess the Absorption, Distribution, Metabolism and Excretion (ADME) of a Single Oral Dose of ^{14}C-labelled AZD1722 in Healthy Male Volunteers

Study dates: First volunteer enrolled: 04 April 2014
Last subject last visit: 19 May 2014

Phase of development: Clinical pharmacology (I)

Principal Investigator: [redacted], Medical Research, Physicians

Sponsor's Responsible Medical Officer: [redacted]

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

Study centre

This was a single centre study conducted at Quintiles Drug Research Unit at Guy's Hospital, 6 Newcomen Street, London, SE1 1YR, United Kingdom, under the direction of Tim Mant.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Pharmacokinetics	To characterise the ADME of a single oral dose of [^{14}C]AZD1722 in healthy male volunteers	Percentage of total [^{14}C] radioactivity recovered in urine and faeces and the percentage of radioactive dose recovered overall; Plasma AZD1722: plasma [^{14}C]AZD1722 radioactivity and whole blood to plasma [^{14}C]AZD1722 radioactivity concentration ratios and the distribution of [^{14}C]AZD1722 radioactivity in blood cells; AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, $t_{1/2}$, λ_z, CL/F, and V_z/F for plasma AZD1722 and plasma and whole blood total [^{14}C] radioactivity; ratios of whole blood radioactivity/plasma radioactivity for AUC and C_{max}; Ae_u, cumulative Ae_u, fe_u and CL_R: total radioactivity and AZD1722, for urine; Ae_f, cumulative Ae, and fe_f for faeces Determination of the presence of AZD1722 metabolites in plasma, urine and faeces, if possible (these data are reported separately)

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Safety	Safety	To evaluate the safety and tolerability of a single oral dose of AZD1722 in healthy male volunteers by assessment of AE, vital signs (BP/pulse rate), ECG and laboratory variables (haematology, chemistry and urinalysis)	AE, vital signs, ECG, haematology, clinical chemistry, urinalysis, physical examination
Exploratory	Pharmacogenetic	To obtain optional blood samples for possible genetic research	Not applicable

ADME Absorption, distribution, metabolism and excretion; AE Adverse event; Ae_f Radioactive amount recovered in faeces during each collection interval; Ae_u Amount recovered in urine during each collection interval; AUC Area under concentration-time curve from zero (predose) extrapolated to infinity; $AUC_{(0-t)}$ Area under the concentration-time curve from zero (predose) to time of last quantifiable concentration; BP Blood pressure; CL/F Apparent oral clearance; CL_R Renal clearance of radioactivity and AZD1722; C_{max} Maximum plasma drug concentration; ECG Electrocardiogram; fe_f Percent (or fraction) of actually administered radioactivity recovered in faeces during each collection interval and overall; fe_u Percent (or fraction) of actually administered radioactivity and AZD1722 dose recovered in urine during each collection interval and overall; λ_z Apparent terminal elimination rate constant;$t_{1/2}$ Apparent terminal elimination half-life; t_{max} Time of maximum concentration; V_z/F Apparent volume of distribution

Study design

This was an open label, single dose study in 8 healthy male volunteers aged ≥50 years, who were studied as a single group. Each volunteer was admitted to the Clinical Pharmacology Unit, henceforth referred to as the study centre, in the morning of the day prior to administration of the investigational product (Day -1) and were to remain in the study centre until at least Day 8 (168 hours postdose). Screening (Visit 1) took place within 4 weeks prior to the residential stay (Visit 2) and a follow-up visit (Visit 3) took place 10 to 14 days after discharge on Day 8. Blood sampling, and pooled urine and faeces collection were obtained on a regular basis to recover the dose radioactivity. If a volunteer happened to vomit, the vomitus products were to be collected and subjected to radioactivity calculation. Safety data was collected throughout the study.

The length of the residential period was extended if deemed appropriate based on emerging data. Once the mass balance cumulative recovery of >95% had been achieved or <1% of the dose administered had been collected in urine and faeces within 2 consecutive days, volunteers were permitted to leave the study centre. If emerging data indicated that adequate dose recovery was not achieved after 7 days (ie, Day 8) then these volunteers were to be asked to continue urine and/or faecal collections for a further 3 days either on an inpatient or an outpatient basis. If adequate dose recovery was still not achieved, these volunteers were to be asked to return to the study centre approximately 7 days later, for a further 24 hour collection. For these volunteers, a final follow-up visit was to take place on the last day of urine and/or faecal collection.

Each healthy volunteer received a nominal 15 mg single oral dose of the investigational product which was administered as an oral solution to the volunteers after an overnight fast of at least 8 hours. Pharmacokinetic and safety data were collected for approximately 7 days after administration of the investigational product as described above.

Target subject population and sample size

A total of 8 healthy male volunteers aged ≥50 years with regular daily bowel movements, had a body mass index between 18 and 32 kg/m^2 (inclusive) and weighed at least 50 kg and no more than 110 kg were enrolled in the study and all the volunteers completed the study.

Investigational product: dosage, mode of administration and batch numbers

Table S2 Details of investigational product

Investigational product	Dosage form and strength	Manufacturer	Batch number
[^{14}C]AZD1722	Oral solution; 15 mg AZD1722 incorporating 11.1 MBq (300 µCi) of ^{14}C (20 mL)	AstraZeneca, Sweden	140000625AZ

Duration of treatment

Healthy volunteers received a single administration of [^{14}C]AZD1722 on Day 1.

Study duration was approximately 7 weeks and entailed a screening, treatment and follow-up visit. Screening took place within 4 weeks prior to the residential period and a follow-up took place 10 to 14 days after the scheduled discharge (17 to 21 days after administration of the IP). The treatment period was scheduled for approximately 7 days following dose administration which was to be modified based on emerging dose recovery results.

Statistical methods

No formal statistical hypothesis testing was performed in this study. The statistical analysis for pharmacokinetic and safety data was descriptive and consist of volunteer listings, graphs and summary statistics comprising arithmetic mean, standard deviation, median, minimum (min), maximum (max), geometric mean, and/or coefficient of variation or frequency distribution summaries as appropriate.

Subject population

A total of 8 volunteers were enrolled in the study and all of them received a single dose of the investigational product and completed the study. Of the 8 volunteers enrolled in the study, for 5 volunteers urine and faecal samples were collected up to Day 11, for 1 volunteer up to Day 10 and for 2 volunteers up to Day 7.

Summary of pharmacokinetic results

Concentrations for parent drug AZD1722 were not quantifiable in all of the urine and plasma.

Radioactivity appeared to be rapidly absorbed systemically with peak nmol concentrations achieved at a median time of 2 hours in plasma and 4 hours in whole blood.

In all 8 volunteers, plasma and whole blood radioactivity concentrations remained above the LLOQ up to the last sampling time of 120 hours postdose. Mean whole blood radioactivity concentrations appeared to decline in a monophasic manner over time, and the mean plasma radioactivity concentrations appeared to decline in a multiphasic manner. This observation supports the idea of metabolic products of the parent drug to be bound to or within the blood cells.

Radioactivity in plasma geometric mean for $AUC_{(0-t)}$ was 1040 nmolEQ*h/L and 5.0-fold higher in whole blood of 5240 nmolEQ*h/L. Geometric mean radioactivity in plasma C_{max} was 41.4 nmolEQ/L and 1.8-fold higher in whole blood (C_{max} 74.5 nmol EQ/L). The geometric mean $t_{1/2}$ of radioactivity in plasma was 35.7 hours and 70.7 hours in whole blood.

By the end of sample collection (240 hours) mean total cumulative recovery of radioactivity in urine and faeces combined was 89.2% of dose delivered. Greater than 85% of the dose in total radioactivity was recovered by 144 hours post dose. Geometric mean cumulative recovery of dose of total radioactivity in urine (Cum fe_u) was 8.99% (range 4.81% to 19.9%) of dose and 79.3% (range 69.2% to 84.7%) in faeces (Cum fe_f). This indicates the primary route of elimination of radioactivity was by faecal elimination.

Summary of safety results

- AZD1722 was considered generally safe and well-tolerated in the population studied. No deaths, SAEs or DAEs were reported
- Two volunteers reported at least one AE ie, headache and device failure
- Variations, with no trends over time in mean and median laboratory values and vital signs measurements were observed. Abnormal laboratory values and ECG reading were reported, however none were considered as clinically significant by the Investigator and were not reported as AEs. No abnormal vital signs measurements and physical examination findings were reported

Conclusions

- [redacted]

- [redacted]

[redacted]