AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9056 hydrochloride
Study Code	D1520C00010
Edition Number	1
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A Phase I, Open-Label, Single-Centre Study to Assess the Metabolism, Excretion and Pharmacokinetics of a Single Oral Dose of [^{14}C]AZD9056 in Healthy Male Volunteers

Study dates: First healthy volunteer enrolled: 21 February 2008
Last healthy volunteer completed: 27 March 2008

Phase of development: Clinical pharmacology (I)

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

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Study centre

This study was conducted at 1 centre in the UK (AstraZeneca Clinical Pharmacology Unit, Alderley Park).

Publications

None at the time of writing this report.

Objectives

The primary objective was to characterise the metabolism, excretion and pharmacokinetics of a single oral dose of 400 mg [^{14}C]AZD9056 in healthy male volunteers.

The secondary objective was to collect information on the safety and tolerability of a single oral dose of 400 mg [^{14}C]AZD9056 in healthy male volunteers.

Study design

This was an open-label, single dose, radiolabel study.

Target healthy volunteer population and sample size

It was planned that 4 healthy male volunteers aged ≥50 years would complete the study.

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

[^{14}C]-labelled AZD9056 400 mg (containing 200 µCi/7.4 MBq) was administered as an oral solution (5 mg/mL). Batch number 08-012925AZ.

Duration of treatment

Single dose.

Criteria for evaluation - pharmacokinetics (main variables)

- AZD9056, AZ11705294 and AZ10620023 derived pharmacokinetics: plasma concentration, AUC, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, t_{max}, CL/F, V_z/F, $t_{1/2}$
- Total radioactivity: plasma and blood concentration, AUC, C_{max}, t_{max}, $t_{1/2}$
- Percent dose recovered in urine and faeces over time, where dose received is calculated by subtracting any residual from the straw or dose vessel from the planned dose.
- Identification of significant additional metabolites in plasma and excreta.

Criteria for evaluation - safety (main variables)

Adverse events, clinical chemistry, haematology, urinalysis, vital signs, electrocardiogram (ECG), physical examination.

Statistical methods

No formal statistical analyses were performed on the pharmacokinetic or safety data from this study. All data were listed and pharmacokinetic variables were summarised using standard summary statistics.

Subject population

Four healthy male volunteers were enrolled into the study; all received the dose of [^{14}C]AZD9056 and all completed the study.

All 4 subjects were male Caucasians with age range 50 to 60 years, height range 168 to 184 cm, weight range 78 to 95 kg and BMI 26.2 to 29.4 kg/m^2. Medical and surgical histories and physical examination data were as expected for healthy volunteers in this age group.

Overall, the volunteers recruited for this study were appropriate for this Phase I study investigating the ADME of [^{14}C]AZD9056.

Summary of pharmacokinetic results

Following oral administration of a solution dose of [^{14}C]AZD9056 (400 mg, 7.4 MBq) to 4 healthy male volunteers, the recovery of radioactivity was good with a mean ±SD of 95.7% ±1.3 of dose recovered over the 240 h sampling period. A total of 40.3% ±4.6 of the dose was recovered in urine and 54.3% ±3.3 in faeces. The majority of the radioactivity excreted in urine was recovered by 72 h after dosing, and that in faeces by 96 h. Recoveries by time, based on total radioactivity, were consistent across the 4 subjects.

One subject (E0001992) vomited after receiving his dose of [^{14}C]AZD9056. Analysis of the small volume of vomit revealed that the subject had only lost 4.2% of the radioactivity dosed. This was not considered to have affected the overall analysis, and so the subject was not excluded from the PK analysis set.

Samples from each subject for metabolite profiling were taken from specific timepoints and pooled. Plasma samples were pooled from 1, 4, 12 and 24 h samples, urine samples were pooled from the 0 to 72 h period, while faeces were pooled for the 24 to 48h and the 48 to 72 h sampling periods.

Plasma samples showed the presence of 3 major components. In terms of total radioactivity these were identified as AZD9056 (54.3%), AZ10620023 (23.4%), and AZ10626013, a benzoic acid metabolite (11.0%). The metabolites AZ10620023 and AZ10626013 correspond to 43.1 and 20.3% of the parent $AUC_{(0\text{-}24h)}$, respectively. Other minor metabolites present included AZ11705294 and 3 isomers of adamantane hydroxylated parent compound (AZ12967158, AZ12874355 and AZ12954089).

The major urinary metabolite in terms of total radioactivity, was identified as a hydroxylated benzoic acid metabolite (15.6%). Also present was AZD9056 and a number of isomers of hydroxylated adamatane products of AZD9056. The major radioactive components in faeces in terms of total radioactivity, were identified as AZD9056 (11.3%) and AZ11705294 (10.1%). Minor metabolites present included hydroxylated metabolites of AZD9056, AZ10620023, AZ11705294 and N-dealkylated AZD9056. A number of isomers were present. A total of 16.7% of the dose was excreted as AZD9056, 11.3% in faeces and 5.4% in urine.

Pharmacokinetic analysis showed a terminal half life of total radioactivity of 48.0 h and that for AZD9056 of 24.4 h. Quantifiable concentrations of total radioactivity were detected up to 240 h after dosing in 2 of the 4 subjects. The half-life of total radioactivity is longer than accounted for by the half-lives of AZD9056 and the 2 metabolites measured suggesting the presence of a minor metabolite of longer half-life.

Summary of safety results

Three subjects experienced 9 AEs, none were considered a serious adverse event or significant adverse event, and none caused discontinuation of the study drug or death.

Subject E0001995 reported abdominal discomfort 10 h after the dosing. Contact dermatitis on the wrist and arm were also reported by this subject, but were not considered to be related to the study drug by the Investigator.

Epistaxis was experienced by subject E0001999 at Day 4 after the dosing, the opinion of the Investigator was that this was unrelated to the study treatment.

Subject E0001992 reported dysgeusia, nausea and vomiting. The dysguesia appeared soon after the dosing and lasted approximately 1 h. This subject experienced nausea 10 min after dosing, this persisted for around 3 h during which time the intensity varied from mild to moderate then back to mild. At 33 min post-dose the subject vomited a small volume (less than 10 mL).

There were no haematology, clinical chemistry, urinalysis, vital signs or ECG findings of clinical concern in the study.