AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5672
Study Code	D1710C00010
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An Open-Label, Phase I Study to Assess the Excretion of Radioactivity, Metabolic Profiles and Pharmacokinetics following a Single Oral Dose of [^{14}C]AZD5672 in Healthy Male Volunteers

Study dates: First healthy volunteer enrolled: 13 June 2008
Last healthy volunteer completed: 15 July 2008

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

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 of this study was to characterise the metabolism, excretion and pharmacokinetics of a single oral dose of 200 mg [^{14}C]AZD5672 in healthy male volunteers.

The secondary objective was to collect information on the safety and tolerability of a single oral dose of 200 mg [^{14}C]AZD5672 in healthy male volunteers.

Study design

This was an open-label, Phase I, single-centre 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 AZD5672 200 mg (300 μCi/11.1 MBq) was administered as an oral solution (4 mg/mL). Batch number P7567 - Clinicopia Lot ID 08-013363AZ.

Duration of treatment

Single dose.

Criteria for evaluation - pharmacokinetics (main variables)

AZD5672 PK:

- Plasma concentrations
- Area under the plasma concentration-time curve, AUC, $AUC_{(0-t)}$, $AUC_{(0-24)}$
- Maximum plasma concentration, observed C_{max}, and the time at which this occurs, t_{max}
- Oral clearance, CL/F
- Apparent volume of distribution, V_z/F
- Terminal half life, $t_{½}$

Total radioactivity:

- Plasma and blood concentration, and the resulting AUC, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, t_{max}, $t_{½}$
- Amount and % dose recovered in urine and faeces over time
- Identification and quantification of 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 analysis was 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 as planned; all received the dose of [^{14}C]AZD5672 and all completed the study.

All 4 subjects were male Caucasians with age range 52 to 58 years, height range 175 to 185 cm, weight range 88 to 93 kg. 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]AZD5672.

Summary of pharmacokinetic results

Following oral administration of a [^{14}C]AZD5672 solution (200 mg, 11.1 MBq) to 4 healthy male volunteers, radioactive recovery was high over the 240 h sampling period (mean ±SD 92.8% ±21.6 of dose recovered). A total of 17.9% ±4.72 of the dose was recovered in urine (approximately 5% being AZD5672) and 74.9% ±21.9 in faeces (approximately 33% being AZD5672).

Over the first 12 h following dosing, the shape of the plasma concentration-time profile of total radioactivity was similar to that for AZD5672, but the radioactive concentrations were higher than that for AZD5672. No radioactivity was quantifiable from 24 h post-dose, even though very low concentrations of AZD5672 were measured.

AZD5672 was rapidly absorbed, (median AZD5672 plasma t_{max} approximately 1 h, range 0.75 to 1 h). The terminal elimination $t_{1/2}$, (starting from approximately 48 to 144 h post-dose), was approximately 64 h, and was associated with low AZD5672 concentrations, which may be sub-therapeutic.

The major circulating component was AZD5672, representing 53.2% of the total radioactivity $AUC_{(0\text{-}24h)}$. Four major radioactive metabolite peaks were present. The largest of these were identified as an ethylamide fragment (AZ13218397), 34.7% of the parent AUC and *N*-dealkylated amine cleavage product (AZ11905989), 30.7% of the parent AUC. The other metabolites were identified as α-OH AZD5672 (11.5% of parent AUC) and an oxidised AZD5672 metabolite (4.0% parent AUC).

Due to the cleavage of the molecule in the formation of the *N*-dealkylated amine, the remainder of the molecule was not radiolabelled and could not be fully quantified. Three metabolites of this portion of the molecule were identified by LC/MS in plasma. These were identified as AZ12555874, AZ13210291 and AZ12565486 + glucuronide.

All of the circulating metabolites were identified in urine samples, the major metabolites being *N*-dealkylated amine and α-OH AZD5672. The latter was a major metabolite in faeces extracts. Other faecal metabolites were identified as AZD5672 + H_2O, oxidised and di-oxidised AZD5672.

Summary of safety results

Four subjects experienced 15 AEs, none were considered a serious or significant adverse event, and none caused discontinuation of the study drug or death.

Eleven AEs reported were of mild intensity. Three AEs of moderate intensity were recorded, these were neck pain (Subject E0001991) and low back pain (Subjects E0001995 and E0001999). Only one AE of severe intensity was reported, this was severe muscle cramps in Subject E0001995.

Subject E0001995 reported AEs of muscle spasm in the calf muscles on 5 occasions during the study (between Day 4 and Day 8). These events were mainly mild in intensity and transient although one episode was reported as severe intensity. This subject also reported an AE of back pain (moderate intensity) on Day 10 and musculoskeletal stiffness (mild intensity) on Day 11. These AEs were not considered to be related to study treatment by the Investigator.

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