AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2066
Study Code	D0475C00008
Edition Number	1
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An Open label, Single dose, Phase I study of the Excretion of Radioactivity, Metabolism and Pharmacokinetics following Oral administration of [^{14}C]AZD2066 to Healthy Male Subjects

Study dates: First healthy volunteer enrolled: 19 January 2009
Last healthy volunteer last visit: 19 February 2009

Phase of development: Clinical Pharmacology (I)

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.

Objectives

The primary objectives were:

1. to investigate the rate and extent of excretion of radioactivity in urine and faeces following administration of [^{14}C]AZD2066 as an oral solution.

2. to investigate the pharmacokinetics of total radioactivity and of unchanged AZD2066 in plasma.

3. to investigate the metabolite profile in plasma and excreta.

The secondary objectives were:

1. to characterise metabolites of AZD2066 in plasma and excreta.

2. to assess safety and tolerability of AZD2066 after administration of a single oral dose to healthy male volunteers.

Furthermore, a blood sample for genotyping was collected for future, possible exploratory genetic research aimed at identifying/exploring genetic variations that may affect the pharmacokinetics, pharmacodynamics, safety and tolerability related to AZD2066. The pharmacogenetic part of the study was optional for all healthy volunteers.

Study design

This was an open label, non-comparative, single centre, phase I study to evaluate the excretion of radioactivity, metabolism, pharmacokinetics, safety and tolerability of a single oral dose of [^{14}C]AZD2066.

Target healthy volunteer population and sample size

In total, 6 healthy male volunteers between the ages of 35 to 50 years inclusive were to participate in the study.

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

Each healthy volunteer received a single 13.5 mg oral dose of [^{14}C]AZD2066 (1 mg/mL oral solution + 0.192 MBq/mL (5.19 μCi/mL) (batch number 4157-1-1)).

Duration of treatment

Single dose

Criteria for evaluation - pharmacokinetics (main variables)

The amounts of total radioactivity expressed as % of the dose in urine (A^*_{urine}), faeces (A^*_{faeces}) and the sum of the total radioactivity in urine and faeces (A^*_{total}). The cumulative amount excreted during the entire collection period was also calculated. In addition, the total radioactivity in whole blood at selected time-points was determined.

Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), terminal plasma half-life ($t_{½\lambda z}$), area under the plasma concentration-time curve from zero to infinity (AUC), oral plasma clearance (CL/F), oral volume of distribution during terminal phase (V_z/F), mean residence time (MRT) for AZD2066.

The identification and profile of metabolites of AZD2066 in plasma, urine and faeces

Criteria for evaluation - safety (main variables)

Adverse events (AEs), vital signs (supine blood pressure and pulse rate), electrocardiogram (ECG) and laboratory variables.

Statistical methods

The determination of sample size was primarily based on previous experience with similar mass balance studies. No formal power calculation was performed and descriptive statistics have been primarily used to summarize pharmacokinetic data.

Subject population

In total, 6 healthy volunteers completed the study as planned. All healthy volunteers were males between the ages of 40 and 47 years. One healthy volunteer was black (or African American) and the other healthy volunteers were white. The safety and PK analysis sets included all healthy volunteers. There were no important protocol deviations.

Summary of pharmacokinetic results

Radiolabelled material was measured in urine and faeces for up to 216 h after the oral administration of [^{14}C]AZD2066. During this period, the mean total recovery of radioactive material in urine and faeces was 92% of the dose. Excretion of radioactivity was predominantly via the faeces, with 40% to 65% (mean ± sd of 57% ± 10%) of the administered dose recovered by 216 h post dose. The excretion of the radioactivity in urine was 28% to 50% (mean ± sd of 35% ± 8%).

Mean $AUC_{AZD2066}$ /$AUC_{radioactivity}$ and $C_{max,AZD2066}$ /$C_{max,radioactivity}$ were 0.70 and 0.92, respectively, demonstrating that AZD2066 contributed to the majority of total radioactivity exposure. The $t_{1/2\lambda z}$ of total radioactivity was slightly longer than for AZD2066, indicating that there is a metabolite (or metabolites) with slightly longer $t_{1/2\lambda z}$ than AZD2066.

The major metabolites were characterised to be one dihydroxylated metabolite (oxidation on the benzene moiety) excreted in faeces represented up to 14% of the administered dose and one *O*-dealkylation product excreted in both urine and faeces represented up to 10% of the administered dose. In plasma the major circulating species were AZD2066 and 1 metabolite characterised as an *N*-oxide (oxidation on the pyridine moiety). This metabolite (M12) represented between 4 to 21% of the total peak area in the radiochromatograms.

Summary of safety results

There were no deaths, other Serious Adverse Events (SAEs), Discontinuation of investigational product due to adverse events (DAEs) nor Other significant adverse events (OAEs) in the study. All AEs (8 AEs in total reported by 4 volunteers) were mild in intensity. There were no clinically relevant treatment related changes nor trends in laboratory values and vital signs. There were no ECG abnormalities recorded at enrolment nor follow-up.