AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1386
Study Code	D5090C00015
Edition Number	1
Date	30 June 2009

An Open, Single Dose, Phase I Study of the Excretion of Radioactivity, Metabolism and Pharmacokinetics Following Oral Administration of [^{14}C]AZD1386 to Healthy Male Volunteers

Study dates: First healthy volunteer enrolled: 22 January 2009
Last healthy volunteer completed: 26 February 2009

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)

The study was conducted in 1 centre: Clinical Pharmacology Unit (CPU), AstraZeneca R&D Alderley Park, Mereside, Alderley Park, Macclesfield, Cheshire, United Kingdom, SK10 4TG

Publications

None at the time of writing this report.

Objectives

Primary objectives

1. To investigate the rate and extent of excretion of radioactivity in urine and faeces following administration of [^{14}C]AZD1386 as an oral solution

2. To investigate the pharmacokinetics of total radioactivity in plasma and of unchanged AZD1386 in plasma

3. To investigate the metabolite profile in plasma and excreta

Secondary objectives

1. To characterise metabolites of AZD1386 in plasma and excreta if feasible

2. To assess safety and tolerability of AZD1386 after administration of a single oral dose to healthy volunteers

Furthermore, a blood sample for genotyping was collected for future, possible exploratory genetic research aimed at identifying/exploring genetic variations that may affect pharmacokinetic (PK) and pharmacodynamic (PD), safety and tolerability related to AZD1386.

Study design

This is an open, non-comparative, single centre, phase I study to evaluate the excretion of radioactivity, metabolism, pharmacokinetics, safety and tolerability following a single 95 mg oral administration of [^{14}C]AZD1386 in healthy male volunteers.

Target healthy volunteer population and sample size

In total, 6 healthy Caucasian male volunteers, 42 to 47 years inclusive, completed the study as planned. Each volunteer was given a single 95 mg oral administration of [^{14}C]AZD1386.

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

A single oral dose of [^{14}C]AZD1386 was dispensed as an oral solution (batch number 4159-1-1).

Duration of treatment

Single dose

Criteria for evaluation - pharmacokinetics (main variables)

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 AZD1386.

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.

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, pulse rate and body temperature), electrocardiogram (ECG) and laboratory variables.

Statistical methods

The determination of sample size was primarily based on previous experience with similar mass balance studies. Primary and secondary endpoints were summarised descriptively and consisted of subject listings, graphs and summary statistics.

Subject population

In total, 6 Caucasian male healthy volunteers were included and were all administered a single 95 mg dose of [^{14}C]AZD1386 during the planned treatment visit. All treated healthy volunteers completed the study.

Summary of pharmacokinetic results

Following an oral dose of [^{14}C]AZD1386 the mean total recovery of radioactive material was 101% of the dose (range 92% to 104%) within 168 h. Excretion was via urine (mean 62%, range 52% to 69%) and faeces (mean 39%, range 35% to 44%). The ratio between geometric mean (CV%) AUC for AZD1386, 15100 h*nmol/L (49%) and total radioactivity, 54800 h*nmol/L (27%) was 0.276 (24%). The corresponding ratio for C_{max} for AZD1386, 2310 nmol/L (20%) and total radioactivity, 6500 nmol/L (10%) was 0.355 (15%). The median t_{max} was 1 h both for AZD1386 and for total radioactivity. The geometric mean (CV%) $t_{½\lambda z}$ was 7.73 h (30%) for AZD1386 and 9.52 h (19%) for total radioactivity. The blood to plasma ratio of total radioactivity 1 h after dosing was 0.553 (2%). AZD1386 was extensively metabolised with only trace amounts of unchanged compound being excreted. The major metabolic pathway proceeds through oxidation of the tertiary butyl group alone or in combination with oxidations of the benzimidiazole moiety. Most oxidated metabolites exist also as their

glucuronide conjugates. The two major metabolites in plasma were characterised to be products after oxidation of the tertiary butyl group.

Summary of safety results

There were no deaths, other serious adverse events (SAEs), discontinuations due to AEs (DAEs) or other significant AEs (OAEs) in the study. There were a total of 16 adverse events (15 mild and 1 of moderate intensity for dysgeusia) reported by 6 healthy volunteers. Adverse events that were experienced post dose by 2 or more healthy volunteers were: feeling cold (n=3 healthy volunteers), dysgeusia (n=2) and hypoaesthesia oral (n=2). The AE feeling cold started within 10 to 40 min following AZD1386 administration, and had a duration of 25 to 317 min. There was an increase in body temperature ranging from 0.6°C to 1.8°C. There were no clinically relevant treatment-related changes or trends in supine blood pressure, pulse rate or laboratory variables. There were no ECG abnormalities recorded at enrolment nor follow-up.