AstraZeneca

Clinical Study Report Synopsis

Drug Substance	ZD4054
Study Code	D4320C00029
Edition Number	1
Date	30 January 2009

A Phase I, Randomised, Single-blind, Single-centre, Incomplete-block Crossover, Relative Bioavailability Study in Healthy Male Subjects for ZD4054 Immediate Release Tablets

Study dates: First healthy volunteer enrolled: 19 June 2008
Last healthy volunteer completed: 28 August 2008

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 objective of this study was to characterise and compare the plasma concentration-time profiles for ZD4054 when administered as a reference oral solution formulation and as 5 solid oral formulations.

The secondary objectives of this study were to characterise and compare pharmacokinetic parameters for ZD4054 when administered as an oral solution formulation and as 5 solid oral formulations, and to assure the safety of all healthy volunteers by assessment of vital signs, ECG, clinical chemistry, haematology, urinalysis and adverse events.

Study design

This was a randomised, single-blind, single-centre, incomplete-block crossover study in healthy male volunteers to assess the bioavailability of 5 variants of 10 mg tablet formulations of ZD4054 relative to a 10 mg oral solution formulation.

Target healthy volunteer population and sample size

Twenty healthy male volunteers aged 18 to 65 years were recruited to be dosed.

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

Single dose of ZD4054 10 mg oral solution formulation, followed by 3 single oral doses of five ZD4054 10 mg tablet variants (A-E).

Batch numbers: P/7575; P/5240/001; P/5240/002; P/5240/009; P/5240/010X and P/5240/005X, respectively.

Duration of treatment

Four treatment periods of 96 h duration, each separated by a washout period of at least one week.

Criteria for evaluation - pharmacokinetics (main variables)

Primary variable: Plasma concentrations of ZD4054 following administration of the ZD4054 oral solution and each of the 5 tablet variants were determined.

Secondary variable: Plasma concentrations of ZD4054 were used to determine the following pharmacokinetic parameters: maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), area under the plasma concentration-time curve from zero to infinity (AUC), area under the plasma concentration-time curve from zero to the time of the last quantifiable sample (AUC_{0-t}), terminal half-life ($t_{1/2}$), apparent clearance (CL/F), apparent

volume of distribution at steady state (Vss/F), and relative bioavailability (F_{rel}) for the tablet variants only.

Criteria for evaluation - safety (main variables)

Secondary variable: Safety and tolerability was assessed by adverse events, physical examination, electrocardiogram (ECG), heart rate (HR), blood pressure (BP) and laboratory data (clinical chemistry and haematology) and urinalysis.

Statistical methods

No formal statistical analysis was performed. Demography and baseline data have been summarised and listed using appropriate summary statistics.

Non-compartmental analysis methods have been used for the evaluation of the plasma concentration-time data obtained for the oral solution and solid oral formulations of ZD4054. All pharmacokinetic data have been listed, and summarised by treatment using standard summary statistics.

All safety data including adverse events have been summarised by means of descriptive statistics.

Subject population

Subject disposition, key demographic data, and number of subjects in each population analysed are summarised in Table S1 below. In total, 20 healthy male volunteers were enrolled into this single centre study, all of whom were randomised and received treatment, and 18 subjects completed the study (Subjects E0001003 and E0001024 discontinued prematurely). All 20 subjects were included in the safety dataset, and 19 subjects were included in the PK analysis set (Subject E0001024 excluded as he only received the oral solution formulation). The majority of subjects (60%) were of Black/African American race, and 25% were of White race; mean age was 37.2 years (range 22 – 64 years); and all subjects fulfilled the protocol eligibility criteria. No subjects received disallowed concomitant medication during the study; however subjects took analgesics for treatment of headache. Overall, the subjects who received each tablet variant were balanced with regards to demographic and other baseline characteristics.

Table S1 Subject population and disposition

	Number (%) of subjects					
	Oral solution	**A**	**B**	**C**	**D**	**E**
	N=20	**N=12**	**N=12**	**N=11**	**N=11**	**N=10**
Demographic characteristics						
Mean age (years)	37.2	38.1	34.5	36.5	38.5	36.6
Range (years)	22 - 64	24 - 64	22 - 46	22 - 49	22 - 64	24 - 64
Race:						
Black or African American	12 (60)	8 (66.7)	9 (75)	6 (54.5)	5 (45.5)	5 (50)
White	5 (25)	2 (16.7)	1 (8.3)	2 (18.2)	5 (45.5)	4 (40)
Subject Disposition						
Subjects randomised	20	12	12	12	12	12
Subjects who received treatment	20	12	12	11	11	10
Subjects who completed study:	18	12	12	10	10	10
Analysis sets						
Subjects included in Safety analysis set	20	12	12	11	11	10
Subjects included in Pharmacokinetic analysis set	19	12	12	11	11	10

Summary of pharmacokinetic results

Following administration of 5 different variants of a solid formulation of 10 mg ZD4054, the plasma concentration-time curves for each variant were similar. In general, the peak occurred between 0.5 and 4 hours post-dose, and ranged from 272 to 671 ng/mL. The oral solution resulted in a plasma concentration-time curve that peaked earlier than for the solid variants (15 to 50 minutes), and reached a higher C_{max}, 450 ng/mL to 838 ng/mL. Overall exposure in terms of AUC was unchanged across the 6 different formulations, indicating that despite the solution showing an increased rate of absorption, the extent of absorption was unchanged. This was reflected in the relative bioavailability determined for each of the solid formulations compared to the solution. The mean for each solid variant ranged from 104% to 111%. Apparent clearance, apparent volume of distribution and half-life were similar for the solution and the 5 solid formulations investigated. The mean residence time for the tablet variants was slightly longer than for the solution, due to the dissolution time for the tablets.

Summary of safety results

All formulations of ZD4054 10 mg were well tolerated by healthy volunteers. Headache was the most commonly reported AE (CTC grade 1), and occurred at a similar frequency for all formulations. There were no deaths, serious AEs, or other significant AEs reported during

this study; one subject discontinued due to AE (proteinuria). No clinically important changes were observed in any of the clinical laboratory safety parameters (haematology, clinical chemistry, urinalysis), vital signs (blood pressure and heart rate) or ECGs. Small reductions in systolic and diastolic blood pressures were noted following ZD4054 administration, although these changes were not considered to be clinically important. Overall, the safety profile was similar for all formulations tested, and the findings of this study do not raise any concerns about the safety of ZD4054 10 mg.