AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2066
Study Code	D0475C00005
Edition Number	1
Date	03 December 2008

A Phase I, Single-Center, Randomized, Open-Label, Two-Way Crossover, Formulation and Food Effect Study in Healthy Volunteers, to Assess the Pharmacokinetics of AZD2066 After Single Doses of a New Oral Solid Formulation and an Oral Solution

Study dates: First healthy volunteer/patient enrolled: 03 April 2008
Last healthy volunteer/patient completed: 18 June 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 the study was to investigate the PK of AZD2066 oral solid formulation in relation to the AZD2066 oral solution by assessment of drug concentrations in plasma.

The secondary objectives of the study were:

1. To investigate the effect of food on the rate and extent of absorption of AZD2066 oral solid formulation and oral solution by assessment of drug concentrations in plasma; and

2. To investigate the safety and tolerability of AZD2066 by assessment of adverse events (AEs), vital signs measurements (blood pressure and heart rate), electrocardiogram (ECG), physical examination, clinical chemistry, haematology, and urinalysis.

Furthermore, a blood sample for genotyping was collected for future, possible exploratory genetic research aimed at identifying/exploring genetic variations that may affect PK and pharmacodynamics (PD), safety and tolerability related to AZD2066.

Study design

This was a single-center, Phase I, randomized, open-label, single-dose, 2-way crossover study in 20 healthy, young male subjects, to assess the bioavailability of an AZD2066 oral solid formulation (capsule) relative to an oral solution, and to assess the effect of food on the

bioavailability of AZD2066 from the capsule and the oral solution. Each subject was randomized to 1 of 6 treatment sequences, receiving either the capsule or solution formula in either a fed or fasted state.

Target healthy volunteer population and sample size

The aim was to include healthy male and non-fertile female subjects between 20 and 45 years old with a body mass index (BMI) between 19 and 30 kg/m^2 and weight between 50 and 100 kg. The goal was to have a total of 20 evaluable subjects.

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

AZD2066 – 2 mg capsules
Single oral administration, Batch No. 4116-3-1

AZD2066 – 0.1 mg/mL oral solution
Single oral administration, Batch No. 4004-4-2

Duration of treatment

Single oral doses (solution or capsule) of the investigational product were given at approximately 0800 (8 am), under fasting or fed conditions, according to the randomization sequence. There was a 5 to 15 day washout between doses.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

AZD2066 AUC, $AUC_{(0-t)}$, and C_{max} (primary variables and secondary variables)

Criteria for evaluation - safety (main variables)

Adverse events (AEs), blood pressure and pulse rate, electrocardiography variables, physical and neurological variables, and laboratory variables.

Statistical methods

- Pharmacokinetic

Plasma concentrations of AZD2066 were summarized for each treatment using descriptive statistics. For PK analysis of AZD2066, predose samples that were <LOQ or missing were assigned a numerical value of zero for the calculation of AUC. Pharmacokinetic parameters were computed if the anomalous value was not greater than 5% of C_{max}, the PK parameters for the given subject were dropped from the PK analysis.

Statistical comparisons between treatments were made by analyzing AUC, $AUC_{(0-t)}$, and C_{max} on log scale. A linear mixed-effect analysis of variance (ANOVA) was used with period, sequence, fed/fasting condition, and formulation (capsule/solution) as fixed effects and subject within sequence as a random effect in the model. Interactions between fed/fasting condition and formulation were investigated and an interaction factor was added to the model, if needed.

The inferential targets were the contrast between fed (test) and fasting (reference) within formulation, and the contrast between capsule (test) and solution (reference) within fed/fasting condition. The least-squares estimates obtained from the ANOVA were the differences between logarithmic values. These differences were transformed back to the original scale by exponentiation to get the ratios (test/reference: capsule fed/capsule fasting, capsule fasting/solution fasting, capsule fed/solution fed, solution fed/solution fasting). The point estimates of the ratios together with 95% confidence intervals (CIs) were presented. If the between-subject variability was much greater than the within-subject variability, separate models may have been used.

It was to be concluded that there was no food effect for the capsule and solution, respectively, if the point estimates and 95% CIs for the capsule fed/capsule fasting and solution fed/solution fasting comparisons fell within the range of 80 to 125%. It was to be concluded that the capsule formulation was bioequivalent to the solution under fasting and fed conditions, respectively, if the point estimates and 95% CIs for the capsule fasting/solution fasting and capsule fed/solution fed comparisons fell within the range of 80 to 125%.

- Safety

Adverse events, laboratory variables, vitals, and ECGs are presented descriptively.

Subject population

The first subject was enrolled on 3 April 2008 and the last subject completed the study on 18 June 2008. Twenty subjects were enrolled, randomized, and received treatment. One subject was lost to follow up and did not return for follow up procedures. However, since this subject received treatment, he was included in both the PK and the safety analyses.

The safety population consisted of 20 healthy white males with a mean age of 25.8 years and a mean BMI of 24.35 kg/m^2.

Summary of pharmacokinetic results

Key AZD2066 pharmacokinetic parameters are summarized in Table 1.

Table 1 Summary Statistics for Key AZD2066 Pharmacokinetic Parameters by Treatment

Parameter	Treatment	n	Geometric LS Mean	95% CI
AUC (nmol*h/L)	Capsule Fasted	15	4069	(3439, 4815)
	Capsule Fed	11	3850	(3254, 4556)
	Solution Fasted	7	4229	(3434, 5210)
	Solution Fed	4	3988	(3160, 5033)
$AUC_{(0-t)}$ (nmol*h/L)	Capsule Fasted	15	3866	(3288, 4545)
	Capsule Fed	12	3714	(3186, 4329)
	Solution Fasted	8	4029	(3302, 4916)
	Solution Fed	4	3962	(3164, 4962)
C_{max} (nmol/L)	Capsule Fasted	15	195.8	(169.8, 225.9)
	Capsule Fed	12	172.6	(152.6, 195.3)
	Solution Fasted	8	213.0	(172.5, 262.9)
	Solution Fed	4	168.5	(131.0, 216.8)
t_{max} (h) [a]	Capsule Fasted	15	1.0	(0.75, 3.0)
	Capsule Fed	12	4.0	(1.5, 9.0)
	Solution Fasted	8	0.63	(0.50, 1.0)
	Solution Fed	4	4.0	(4.0, 4.0)

Note: Geometric LS means and 95% CIs for AUC, $AUC_{(0-t)}$, and C_{max} are based on a linear mixed model with fixed effects for treatment (4 levels), period (2 levels), and sequence (6 levels) and a random effect for subject within sequence.
Note: Subject E0001034 received an unscheduled treatment of Capsule Fed during Period 1. Data from this period are not included in this analysis.
a Data presented for t_{max} are median (minimum, maximum).
CI – confidence interval; LS – least-squares; n – number of observations.
Source: Tables 11.2.2 and 11.2.3.1

The results of statistical comparisons of AZD2066 exposure parameters (AUC, $AUC_{(0-t)}$, and C_{max}) between treatments are presented in Table 2.

Table 2 Results of Statistical Comparisons of Key AZD2066 Pharmacokinetic Parameters

CAPSULE / SOLUTION Fasted			CAPSULE / SOLUTION Fed		
Parameter	**Ratio (%)**	**95% CI (%)**	**Parameter**	**Ratio (%)**	**95% CI (%)**
AUC	96.22	(82.22, 112.59)	AUC	96.56	(78.41, 118.90) [a]
$AUC_{(0-t)}$	95.95	(83.08, 110.81)	$AUC_{(0-t)}$	93.72	(76.45, 114.89) [a]
C_{max}	91.95	(76.45, 110.60) [a]	C_{max}	102.44	(78.90, 133.02) [a]

FED / FASTED Capsule			FED / FASTED Solution		
Parameter	**Ratio (%)**	**95% CI (%)**	**Parameter**	**Ratio (%)**	**95% CI (%)**
AUC	94.62	(80.79, 110.82)	AUC	94.28	(69.55, 127.82) [a]
$AUC_{(0-t)}$	96.06	(82.31, 112.12)	$AUC_{(0-t)}$	98.35	(73.34, 131.88) [a]
C_{max}	88.16	(72.31, 107.48) [a]	C_{max}	79.13	(54.31, 115.28) [a]

Note: Results presented are the geometric least-squares mean ratios and 95% confidence interval (CIs), based on a linear mixed model with fixed effects for treatment (4 levels), period (2 levels), and sequence (6 levels) and a random effect for subject within sequence.
Note: Subject E0001034 received an unscheduled treatment of Capsule Fed during Period 1. Data from this period are not included in this analysis.
a 95% CI is outside the 80% to 125% limit for bioequivalence.
Source: Table 11.2.3.1

The results of this study showed that the bioavailability of the capsule was very similar to the solution. Overall AZD2066 exposure (AUC and $AUC_{(0-t)}$) was comparable, and only a small decrease (8% mean decrease) was seen in C_{max} for the capsule compared to the solution when both were administered under fasted conditions.

Administration with a high-fat breakfast slowed the rate of absorption of AZD2066 (t_{max} delayed by approximately 3 hours), which caused a modest decrease (12% mean decrease) in C_{max}, but no change in overall exposure (AUC and $AUC_{(0-t)}$) for the capsule. In the case of the solution, a similar effect was seen (21% mean decrease in C_{max}, no real decrease in mean AUC and $AUC_{(0-t)}$), but subject numbers were small for this comparison for the solution, which resulted in wider 90% CIs.

Summary of safety results

In this population of healthy male subjects, AZD2066 2 mg oral solution and AZD2066 2 mg capsule were well tolerated during both fed and fasted states. A total of 16 AEs, 4 of which were predose, were reported by 10 subjects in the study. Subjects in all treatment groups (capsule, solution, fasted, or fed) experienced AEs; however, subjects in the capsule fasted treatment group reported the most AEs.

No deaths, serious adverse events, discontinuations due to AEs, or other significant AEs were reported during study conduct.

The most common AEs during active treatment were headache and nasal congestion, each reported by 2 subjects.

There were no significant changes in laboratory safety values, vital signs, ECG findings, physical examination findings, or neurological examination findings during study conduct.