AstraZeneca

Clinical Study Synopsis

Drug Substance	AZD1386
Study Code	D5090C00007
Edition Number	1
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A Phase I, Single-centre, Randomised, Open-label, Five-way Cross-over Formulation- and Food-effect Study in Healthy Volunteers to Assess the Pharmacokinetics of AZD1386 after Single Doses of Two Oral Solid Formulations and an Oral Solution

Study dates: First healthy volunteer enrolled: 17 June 2008
Last healthy volunteer completed: 12 August 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)

PAREXEL Clinical Pharmacology Research Unit, Northwick Park Hospital, Harrow, Middlesex, United Kingdom.

Study dates		**Phase of development**
First subject enrolled	17 June 2008	Clinical pharmacology (I)
Last subject completed	12 August 2008	

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to investigate the pharmacokinetics (PK) of two oral solid formulations of AZD1386 in relation to the AZD1386 oral solution by assessment of drug concentration in plasma.

The secondary objectives of the study were:

1. To investigate the effect of food on the rate and extent of absorption of AZD1386 oral solid formulations by assessment of drug concentration in plasma

2. To investigate the safety and tolerability of AZD1386 by assessment of adverse events, vital signs measurements (blood pressure, pulse and body temperature), electrocardiogram (ECG), physical examination, clinical chemistry, haematology, and urinalysis.

Study design

The study was designed as a five-way cross-over, open-label, randomised, single centre study to investigate the pharmacokinetics of AZD1386 after single dose administration of a maximum dose of 90 mg of an oral solution in the fasted state and two oral solid formulations both in the fed and the fasted state. It could be decided to evaluate a lower than a 90 mg dose of AZD1386 following evaluation of the results of the multiple ascending dose (MAD) study.

Target healthy volunteer population and sample size

A total of 12 healthy male and female (of non-childbearing potential) subjects aged 20 to 45 years.

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

Drug: AZD1386
Formulation: oral solution
Strength: 2.5 mg/mL
Single dose: 90 mg in the fasted state
Batch number: 4059-4-2

Drug: AZD1386
Formulation: capsule for oral use
Strength: 30 mg
Single dose: 90 mg in the fasted and in the fed state
Batch number: 4128-1-1

Drug: AZD1386
Formulation: tablet for oral use
Strength: 15 mg
Single dose: 90 mg in the fasted and in the fed state
Batch number: 4127-1-1

Duration of treatment

The study comprised of five investigational periods which were separated each by a wash-out period of at least seven days. An investigational period lasted for about 3 days. Considering a Screening period of 28 days and Follow-up visit between seven to 14 days after final administration of the investigational product the total duration of this study for a subject was about 70 days with all wash-out periods in between.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Primary:
For AZD1386 in plasma: AUC and C_{max}

Secondary:
For AZD1386 in plasma: $AUC_{(0-t)}$, t_{max}, t_{lag}, $t_{1/2}$, CL/F and MRT

Criteria for evaluation - safety (main variables)

Vital signs including body temperature, clinical chemistry, haematology, urinalysis, ECG parameters, telemetry abnormalities and adverse events (AE)

Statistical methods

The log (AUC) and log (C_{max}) were analyzed by an analysis of variance (ANOVA) model. The model included period, treatment (solution fasted, tablet fasted, capsule fasted, tablet fed or capsule fed) as fixed effects and subject as random effect. The 90% confidence intervals were calculated for the contrast between fed and fasting within each oral solid formulation,

and the pair-wise contrasts between oral solution, tablet fasted and capsule fasted. These estimates were transformed back to the original scale to get estimates for the ratios (tablet or capsule fed/ tablet or capsule fasted, tablet or capsule fasted/ oral solution fasted, tablet fasted/ capsule fasted). The point estimates of the ratios together with confidence intervals were presented.

Descriptive statistics including geometric mean values and geometric coefficients of variation were calculated for each treatment for all pharmacokinetic parameters.

Subject population

In total, 12 healthy male volunteers between the age of 21 and 45 were enrolled into the study and randomised, all of them received treatment, and 11 healthy volunteers completed the study as per protocol. One subject was discontinued from the study due to AEs considered causally not related to treatment. All volunteers were healthy based on the screening examination, complied with the inclusion criteria and none met any exclusion criteria. The 12 subjects were all included in the safety and in the PK analysis set. No major protocol deviations were recorded.

Summary of pharmacokinetic results

The results of the statistical analysis of the primary endpoints of the study are summarised in Table S1. The main PK parameters of AZD1386 derived for all treatments are shown in Table S2.

Table S1 Point estimates of mean and 90% CI for ratios of the capsule or tablet formulation and the oral solution of AZD1386 (PK analysis set)

Parameter [unit]	Comparison		Ratio	90% CI	p-value
C_{max} [nmol/L]					
	OS fasted	vs. CAP fasted	1.82	1.56; 2.12	<0.0001
	OS fasted	vs. TAB fasted	1.33	1.15; 1.55	0.003
	CAP fasted	vs. TAB fasted	0.73	0.63; 0.85	0.001
AUC [nmol*h/L]					
	OS fasted	vs. CAP fasted	0.87	0.79; 0.95	0.026
	OS fasted	vs. TAB fasted	0.84	0.77; 0.92	0.003
	CAP fasted	vs. TAB fasted	0.97	0.88; 1.06	0.541

CAP fasted/fed = capsule formulation fasted/fed state, CI = confidence interval, OS fasted = oral solution fasted state, TAB fasted/fed = tablet formulation fasted/fed state.

Maximum plasma concentration of AZD1386 was highest for the oral solution, ie, about 82% and 33% higher compared with the capsule and the tablet formulation, respectively. A significant difference in C_{max} was also determined between both solid formulations, peak exposure for the capsule formulations was about 17% lower compared to the tablet formulation.

Under fasted conditions, the total exposure (AUC) to AZD1386 by the oral solution was significantly lower of about 13% and 16% compared with the capsule and the tablet formulation, respectively. No significant difference in AUC was determined between fasted administration of the capsule and the tablet formulations.

Table S2 Pharmacokinetic parameters of AZD1386 (PK analysis set)

Parameter	**Summary statistic**	**CAP fasted**	**CAP fed**	**OS fasted**	**TAB fasted**	**TAB fed**
[unit]		**N=12**	**N=12**	**N=12**	**N=12**	**N=12**
C_{max}	Gmean (CV%)	1112 (29.3)	1674 (19.4)	1993 (25.2)	1496 (32.4)	1738 (22.7)
[nmol/L]	n	11	12	11	12	12
AUC	Gmean (CV%)	13943 (19.6)	16235 (24.3)	12102 (35.0)	13918 (26.5)	16880 (25.1)
[nmol*h/L]	n	11	12	11	12	12
t_{max}	Median (range)	2.00 (1.00-3.98)	3.76 (2.01-5.00)	1.00 (0.51-1.11)	2.00 (0.99-3.50)	3.75 (1.00-5.08)
[h]	n	11	12	11	12	12
$t_{1/2}$	Gmean (CV%)	10.55 (32.9)	6.99 (25.4)	6.94 (22.1)	8.83 (20.5)	7.10 (23.4)
[h]	n	11	12	11	12	12

CAP fasted/fed = capsule formulation fasted/fed state, CV = coefficient of variation, Gmean = geometric mean, , OS fasted = oral solution fasted state, TAB fasted/fed = tablet formulation fasted/fed state.

The statistical analysis of the effect of food on the exposure to AZD1386 for the capsule and tablet formulation is shown in Table S3.

Table S3 Point estimate of mean and 90% CI for ratio of the capsule or tablet formulation of AZD1386 in the fasted versus fed state (PK analysis set)

Parameter [unit]	Comparison		Ratio	90% CI	p-value
C_{max} [nmol/L]					
	CAP fed	vs. CAP fasted	1.55	1.34; 1.81	<0.0001
	TAB fed	vs. TAB fasted	1.16	1.01; 1.34	0.089
AUC [nmol*h/L]					
	CAP fed	vs. CAP fasted	1.21	1.10; 1.33	0.001
	TAB fed	vs. TAB fasted	1.21	1.11; 1.33	0.001

CAP fasted/fed = capsule formulation fasted/fed state, CI = confidence interval, OS fasted = oral solution fasted state, TAB fasted/fed = tablet formulation fasted/fed state.

Intake of a high fat meal increased total AZD1386 exposure (AUC) for both oral solid formulations to the same extent by about 21%. A significant increase in peak exposure (C_{max}) was observed for the capsule formulation.

Summary of safety results

Overall, 11 (91.7%) subjects reported 56 AEs of mild to moderate intensity. Dysgeusia, headache and symptoms related to the sensation of a change of the body temperature including feeling hot, pyrexia, feeling cold, and a sensation of body temperature change were the most common and relevant AEs. No severe, serious or other significant AEs occurred during the study.

Mean body temperature was slightly elevated upon dosing across all treatments; most evident between 3 and 6 hours post-dose and the highest individual body temperature observed did not exceed 38.2°C.

There were no significant treatment related effects on laboratory safety variables, 12-lead ECG, blood pressure, pulse, telemetry, and physical examination.