AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD8566
Study Code	D1320C00011
Edition Number	1
Date	10 December 2009

An Open, Randomised, Phase I, 2-Period Crossover Trial to Investigate the Absolute Bioavailability and the Effect of Food on the Oral Bioavailability of AZD8566 in Healthy Volunteers

Study dates: First healthy volunteer enrolled: 17 March 2009
Last healthy volunteer last visit: 24 April 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)

One study centre in the UK.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Study objectives and variables

Objective			Variable
Priority[a]	**Type**	**Description**	**Title and description**
Primary	Pharmacokinetic	To investigate the effect of food on AZD8566 pharmacokinetic (PK) parameters following single oral 6 mg doses of AZD8566 in healthy volunteers.	Fed and fasted: AUC, $AUC_{(0-24)}$, $AUC_{(0-t)}$, C_{max}, $t_{½}$, t_{max}, MRT, CL/F, Vz/F
Secondary	Safety	To investigate the safety and tolerability of single oral 6 mg doses of AZD8566 in healthy volunteers in the fed and fasted state.	Adverse events, clinical chemistry, haematology, urinalysis, 12-lead ECG, blood pressure (supine and orthostatic), pulse
	Pharmacokinetic	To determine the bioavailability of an oral solution formulation of AZD8566 in the fasted state compared with a 10 µg intravenous carbon-14 [^{14}C] microtracer dose.	Percent bioavailability (F)
		To define the intravenous pharmacokinetics of AZD8566.	AUC, $AUC_{(0-24)}$, $AUC_{(0-t)}$, C_{max}, $t_{½}$, t_{max}, MRT, CL, Vz, total radioactivity AUC

[a] Exploratory objectives are shown in the Clinical Study Protocol and Clinical Study Report, but the data did not form part of the Clinical Study Report or this Clinical Study Report Synopsis.

AUC: area under the plasma-concentration time curve from zero to infinity; $AUC_{(0-t)}$: area under the plasma concentration-time curve from zero to time t; $AUC_{(0-24)}$: area under the plasma concentration-time curve from zero to time 24 h; CL: total body clearance of drug from plasma; CL/F: total body clearance of drug from plasma following oral dosing/fraction of administered dose systemically available; C_{max}: maximum plasma drug concentration after single dose administration; CSP: clinical study protocol; $t_{½}$: half-life of drug in plasma; F: fraction of administered dose systemically available; MRT: mean residence time; t_{max}: time to reach peak or maximum plasma concentration following drug administration; Vz: volume of distribution (apparent) during terminal phase; V_Z/F: volume of distribution (apparent) during terminal phase/fraction of administered dose systemically available.

Study design

This was an open-label, randomised, Phase I, 2-period crossover study performed in 10 healthy volunteers at a single centre. The study investigated the pharmacokinetics, safety and tolerability of AZD8566 in the fed and fasted state. Healthy volunteers were randomly allocated to receive 2 of the following treatments.

Regimen A: Oral dose of 6 mg AZD8566 in a fasted state followed by a single intravenous microtracer dose (10 µg) containing no more than 5 kBq (135 nCi) [^{14}C]-AZD8566 administered by infusion over 15 minutes, 1 hour 45 minutes after the oral dose.

Regimen B: Oral dose of 6 mg AZD8566 in a fed state.

Regimen C: Oral dose of 6 mg AZD8566 in a fasted state.

During the first study period, 5 volunteers received regimen A (single oral dose of 6 mg AZD8566 in a fasted state followed by a single intravenous microtracer dose, 10 µg) and 5 volunteers received regimen B (single oral dose of 6 mg AZD8566) in a fed state. During the second study period, 5 volunteers received regimen B and 5 volunteers were to receive regimen C (single oral dose of 6 mg AZD8566 in a fasted state); all volunteers were to cross over and receive the oral dose of AZD8566 under the opposite conditions (fed or fasted state) from the first study period.

Target subject population and sample size

The study included healthy male and female (permanently or surgically sterile or postmenopausal) volunteers aged 18 to 55 years, who provided written informed consent and had clinically normal physical findings, laboratory values and ECGs. Healthy volunteers were not to take any medication (except hormone replacement therapy or occasional paracetamol) within 3 weeks before first administration of study drug. They were to have no history of convulsions or seizures and no history of infection or risk of infection due to recent surgery or trauma. They were to have no history or presence of conditions known to interfere with the absorption, distribution, metabolism or excretion of the study drug.

The study was exploratory in nature and not statistically powered. Ten volunteers were considered to provide sufficient data to provide an indication of whether food affects the pharmacokinetics of AZD8566, and provide estimates to allow statistical powering of a future definitive study. In addition, 5 out of the 10 volunteers were also dosed with an intravenous microtracer dose in order to explore the absolute bioavailability of AZD8566. This was intended to gain a better understanding of its routes of elimination and to provide information that would enable the design of any future drug interaction and formulation development studies.

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

Table S2 Details of investigational product

Investigational product	Dosage form and strength	Manufacturer	Formulation number
Oral AZD8566	Solution 20 mg/mL	AstraZeneca	F13634
Radiolabelled intravenous AZD8566	Solution 2 µg/mL	Pharmaceutical Profiles Ltd	not applicable

Duration of treatment

In regimens A and B in the first study period, and in regimens C and B in the second study period, AZD8566 was administered as a single oral dose; intravenous microtracer dosing was included in regimen A only. The recommended washout period between doses and between second dose and follow-up was a minimum of 7 days. Healthy volunteers were admitted to the clinical in the morning of the day prior to dosing; those who received regimen A remained in the clinic for 96 hours following dosing, and those who received regimens B and C were discharged home at 48 hours and attended for 72- and 96-hour assessments as an outpatient.

Statistical methods

The plasma PK parameters of AUC, $AUC_{(0-24)}$, $t_{½}$ and C_{max} of oral dosing were formally statistically analysed. These variables were logarithmically transformed prior to analysis. For the analysis of AUC, $AUC_{(0-24)}$, $t_{½}$ and C_{max}, an analysis of variance model (ANOVA) was used, fitting for the effects of subject, period and state (fed or fasted). The results of the analysis were presented in terms of the geometric least squares means for each treatment (fed or fasted), the ratio of the geometric least squares means for fed:fasted, and its corresponding 90% confidence interval (CI). For the assessment of absolute bioavailability, the values of F were summarised using a 90% CI (calculated on the log scale and then back-transformed). While this study was not powered to show bioequivalence statistically, AUC, $AUC_{(0-24)}$, $t_{½}$ and C_{max} were analysed to provide the ratio (or difference) of the geometric least squares mean for fed:fasted, and the corresponding 90% CIs. Interpretation of these results were aided by reference to the standard bioequivalence limits (80%, 125%), to assess whether there appeared to be a trend for a difference in that parameter in the fed and fasted state. The t_{max} following oral dosing was also examined using a non-parametric analysis on untransformed data. The food effect on t_{max}, as measured by subject differences (fed minus fasted), was analysed using a Wilcoxon signed rank test. The Hodges-Lehman estimator of median food effect was calculated and corresponding 90% CIs constructed.

Subject population

Ten healthy male volunteers were enrolled and randomised into the study. The 10 male volunteers enrolled into this study were representative of a healthy male population and were appropriate for this Phase I study investigating the effect of food on the pharmacokinetics of

AZD8566. Demographic and baseline characteristics were similar across each of the 2 treatment sequences: fed/fasted (mean age 35.4 years) and fasted/fed (mean age 39.8 years).

There were no discontinuations from the study. One healthy volunteer was considered ineligible (ECG at rest not normal) for the second, fasted, period of the study and was not dosed in this period, but a final, post-study assessment was carried out for this healthy volunteer. The data for this subject were included in the analysis of all available data (ie, analysis of intravenous microtracer dose PK [n=5], bioavailability estimates [n=5], and safety results [n=10], but not in the summary of oral PK parameters [n=9] or the statistical analysis of the effect of food on the oral pharmacokinetics of AZD8566 [n=9]).

Summary of pharmacokinetic results

(a) Oral pharmacokinetics of AZD8566

Inspection of individual healthy volunteer data, and fed and fasted group data, showed slightly higher values for PK parameters for the fed state than those observed for the fasted state as follows:

- The t_{max} varied between 2 h and 4 h for fed volunteers and between 1 h and 3 h for fasted volunteers.
- The geometric mean C_{max} was 32.5 nmol/L (range 25.1 to 48.8 nmol/L) for fed volunteers and 31.6 nmol/L (range 23.4 to 43.0 nmol/L) for fasted volunteers.
- The geometric mean AUC was 702 nmol.h/L (range 438 to 991 nmol.h/L) for fed volunteers and 605 nmol.h/L (range 377 to 910 nmol.h/L) for fasted volunteers.
- The geometric mean $t_{½}$ was 15.9 h (range 10.5 to 21.0 h) for fed volunteers and 15.3 h (range 11.1 to 19.3 h) for fasted volunteers.

(b) Statistical analysis of the effect of food on the oral pharmacokinetics of AZD8566

This study was not powered to show bioequivalence statistically, but bioequivalence CI limits (0.80, 1.25) were used as to aid interpretation of CIs for AUC, $AUC_{(0-24)}$ and C_{max}. The 90% CI for C_{max} (0.94, 1.15) lay within the standard bioequivalence limits (0.80, 1.25) and contained 1.00 showing no difference between fed and fasted states; the CIs for AUC (1.11, 1.21) and $AUC_{(0-24)}$ (1.08, 1.18) also lay within the bioequivalence limits showing no difference in the extent of absorption of AZD8566 when administered with or without food. Similarly the CI for $t_{½}$ (1.00, 1.08) indicated no difference in half-lives between fed and fasting states. The value for t_{max} appeared to increase when AZD8566 was administered with food: median t_{max} was 2.0 h for the fasted state and 3.0 h for the fed state. However, the Hodges-Lehman estimator for the difference in t_{max} (fed minus fasted) was 1.00 h (90% CI 0.00, 1.00), indicating no statistical difference in absorption times between the fed and fasted states. Together these results showed no overall change in exposure was observed when AZD8566 was administered with food when compared to administration without food.

(c) Intravenous microtracer dose pharmacokinetics and bioavailability estimates

The absolute bioavailability data suggest complete absorption of AZD8566 following oral dosing, and are supported by CL, V_Z and $t_{½}$ data for intravenous dosing that were found to be similar to those following an oral dose. The results obtained for mean clearance following intravenous dosing of AZD8566 were as follows: mean CL=22.1 L/h, range 16.4 to 29.5 L/h; mean volume of distribution V_Z=333 L, range 252 to 405 L; mean $t_{½}$ =10.6 h, range 6.72 to 15.9 h. The results obtained for mean clearance following a single oral dose of AZD8566 were as follows: mean CL/F=18.5 L/h; range 11.8 to 28.5 L/h; mean Vz/F=396 L; range 290 to 468 L; mean $t_{½}$ =15.3 h; range 11.1 to 19.3 h.

Percentage bioavailability of AZD8566 for individuals was high (between 77.5 and 101.3%); F=92.2% (90% CI 83.3, 102.0). This was suggestive of complete absorption following an oral dose. Together these data were evidence of similar PK characteristics for AZD8566 following either oral or intravenous dosing.

Summary of safety results

There were no deaths, serious adverse events (SAEs) or discontinuations from the study due to adverse events (AEs).

One healthy volunteer reported a mild AE (headache) during the study. This event occurred predose before the first study period (fasted state). A further healthy volunteer reported mild sunburn on the same day (time unknown) as dosing in the fasted state (ie, 8 days after dosing in the fed state). The AE was still ongoing at the end of the study, but thought by the investigator not to be related to treatment. Apart from this single AE, there were no other treatment-emergent AEs reported during the study.

Haematology results showed there were no trends or individual abnormalities associated with administration of AZD8566 under fasted or fed conditions that raised any safety concerns for the haematology parameters measured (including the parameters activated partial thromboplastin time, prothrombin time, or platelet aggregation).

Clinical chemistry results showed minor elevations in ALT, AST and total bilirubin. All ALT elevations were <1.4 x upper limit of normal range (ULN); all AST elevations were <1.75 x ULN (<1.2 x ULN for post-dose values); total bilirubin values were <1.25 x ULN. One healthy volunteer had raised random plasma glucose levels during the second study period, 48 h after dosing in the fed state: 8.1 mmol/L (upper limit of normal 7.8 mmol/L); by post-study follow-up random glucose levels had returned to 4.8 mmol/L, which was within the normal range. There were no individual abnormalities associated with administration of AZD8566 under fasted or fed conditions that raised any safety concerns for the clinical chemistry parameters measured (including liver function parameters).

Urinalysis results showed that one healthy volunteer was positive for urinary glucose 24 hours after dosing with AZD8566 in the fed state, and 24 and 48 hours after dosing with AZD8566 in the fasted state. This volunteer had normal plasma glucose levels at all visits, was negative

for urinary glucose at other timepoints, and negative for urinary protein and blood at all timepoints. All other healthy volunteers were negative for urinary glucose, protein and blood at all timepoints after dosing in both fed and fasted states, and all healthy volunteers were negative for all parameters at the post-study follow-up. There were no clinically relevant changes in urinalysis over time for any urinalysis parameter, and no clinically important individual abnormalities.

Vital signs results showed that 2 healthy volunteers experienced 3 occurrences of postural hypotension (ie, drop in BP ≥25 mmHg and/or diastolic ≥15 mmHg from supine). All occurrences of postural hypotension were asymptomatic and were observed at different timepoints throughout the fed period. There was no evidence of an increase or decrease in supine blood pressure (individual values or group means) throughout the study. There were no clinically significant changes from baseline in any other vital signs parameters.

ECG findings showed that there were no healthy volunteers with QTcF >450 ms. Two healthy volunteers had changes from baseline in QTcF of >30 ms duration. One of these healthy volunteers had an abnormal ECG (incomplete right bundle branch block) at entry to the study, which was assessed as not clinically significant by the investigator, and showed a reduction from baseline (-40 ms) in QTcF 24 hours post-dose in the fed state. The second healthy volunteer had an ECG abnormality at screening at the start of the study. This abnormality was a nonspecific intraventricular conduction delay, which was assessed as not clinically significant by the investigator, and the subject entered the study and was dosed in the first, fed, period. At the start of the second, fasted, period with a further ECG, however, the subject showed an increase from baseline (+39 ms) in QTcF and the non-specific intraventricular block seen on this occasion was considered to be clinically significant by the investigator and the subject was not dosed in this period because he did not qualify in terms of an inclusion criterion concerning normal ECG. There were no significant changes from baseline in any other ECG parameters.

There were no significant changes from baseline in any physical finding during the study.