AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD7325
Study Code	D1140C00005
Edition Number	1
Date	29 January 2009

A phase I open-label, fixed sequence study to determine the effect of multiple doses of AZD7325 on the pharmacokinetics of midazolam (CYP3A4) and caffeine (CYP1A2)

Study dates: First healthy volunteer/patient enrolled: 04 July 2008
Last healthy volunteer/patient completed: 10 September 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)

This study was conducted in the

The first healthy volunteer was enrolled on 4th July 2008 and the last healthy volunteer completed the study on 10th September 2008.

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to determine the effects of repeated doses of AZD7325 on the pharmacokinetic profile of a CYP3A4 substrate (midazolam and its 1' hydroxy metabolite) and a CYP1A2 substrate (caffeine and its paraxanthine [3-desmethyl] metabolite).

Secondary objectives were:

To evaluate the safety and tolerability of repeated doses of AZD7325 in combination with midazolam and caffeine.

To evaluate the pharmacokinetics of AZD7325 on Days 1, 11 and 12.

To evaluate the pharmacodynamic effects of AZD7325 in combination with midazolam on selected psychometric assessments using a Visual Analogue Scale (VAS).

Study design

The indication for AZD7325 is generalized anxiety disorder (GAD). This was a single centre, open label, fixed sequence, non-randomized study in a single cohort of 24 healthy male subjects to determine the effects of repeated doses of AZD7325 on a CYP3A4 substrate (midazolam) and a CYP1A2 substrate (caffeine).

All subjects were to receive a single dose of midazolam (5 mg) on Day -2 and Day 11 and a single dose of caffeine (200 mg) on Day -1 and Day 12. Subjects received a single daily dose of AZD7325 (10 mg) on Days 1-12.

Target healthy volunteer population and sample size

Twenty-four healthy male subjects were enrolled onto the study. Subjects were to be healthy male subjects aged between 18 and 45 years (inclusive) of age, current non-smokers with a Body Mass Index (BMI) of $\geq$19 to $\leq$30 kg/m^2.

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

Investigational product: AZD7325 10 mg oral capsule batch number ST76095-001-FA02.

Non-investigational products: Midazolam 2 mg/mL oral solution, caffeine 50 mg tablet.

Duration of treatment

All subjects were to receive a single dose of midazolam (5 mg) on Day -2 and Day 11 and a single dose of caffeine (200 mg) on Day -1 and Day 12. Subjects received a single daily dose of AZD7325 (10 mg) on Days 1-12.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

The following PK parameters were estimated for midazolam, midazolam 1'-hydroxy metabolite, caffeine, caffeine metabolite paraxanthine (3-desmethyl) and AZD7325: AUC, $AUC_{(0-t)}$, $AUC_{(0-24)}$, AUC_{τ}, C_{max}, t_{max}, $t_{½\lambda z}$.

Pharmacodynamics for midazolam were assessed by Visual Analogue Scales (VAS) and a Structured Verbal Questionnaire.

Criteria for evaluation - safety (main variables)

Safety and tolerability were assessed by the incidence and severity of adverse events (collected throughout the study), abnormalities in vital sign assessments, clinical laboratory parameters, physical examination and ECGs.

Statistical methods

There was no formal statistical analysis of the safety variables; safety variables were described by descriptive statistical methods.

The pharmacokinetic concentrations and parameters were described by descriptive statistical methods and plotted if appropriate.

There was no formal statistical analysis of the pharmacodynamic variables; pharmacodynamic variables were described by descriptive statistical methods and plotted if appropriate.

Subject population

Twenty-four young healthy males were enrolled onto the study. Twenty-three subjects completed the study as planned. One subject withdrew his consent prior to dosing with AZD7325 and was therefore withdrawn from the study. The subject received 1 dose of midazolam 2 mg. The subject was not replaced.

Subjects were 24 young healthy males, aged between 20 and 41 years and with BMIs between 21 and 30 kg/m^2. Some subjects had out-of-range values at baseline for laboratory safety tests, vital signs or ECG parameters, but upon review of the data the Investigator considered that these values were not clinically significant and that the subjects were healthy and eligible to participate in the study.

Summary of pharmacokinetic results

The mean plasma exposure of midazolam and midazolam 1´-hydroxy in terms of AUC and $AUC_{(0-t)}$ was slightly lower while C_{max} was similar after a 5 mg single dose of midazolam administered in combination with a 10 mg steady-state administration of AZD7325 as compared to a single dose of midazolam alone.

The 90% confidence intervals of the geometric mean ratios comparing AUC and $AUC_{(0-t)}$ of midazolam after steady-state administration of AZD7325 vs. midazolam alone were not contained within the pre-defined range of 0.8-1.25. The lower limits of the 90% CIs were below 0.8 indicating AUC and $AUC_{(0-t)}$ of midazolam to be 19% lower in combination with the AZD7325 treatment. The 90% CI of C_{max} was however contained within the range 0.80-1.25. The corresponding CIs for AUC, $AUC_{(0-t)}$ and C_{max} of the midazolam 1´-hydroxy metabolite indicated that AZD7325 had no significant effect on the exposure of midazolam 1´-hydroxy.

Median t_{max} of midazolam and midazolam 1´-hydroxy was similar between treatments (0.50 h). The geometric mean CL/F of midazolam increased from 62 L/h (midazolam alone) to 76 L/h when administered during AZD7325 steady-state administration. Median $t_{½\lambda z}$ of midazolam decreased from 5.2 h (midazolam) to 3.6 h (midazolam+AZD7325) while median $t_{½\lambda z}$ of midazolam 1´-hydroxy (2.3-2.4 h) was similar between treatments.

The mean plasma exposure in terms of AUC and $AUC_{(0-t)}$ was slightly higher for caffeine while the exposure was similar for paraxanthine (3-desmethyl) following a 200 mg single dose caffeine administered in combination with a steady-state administration of 10 mg AZD7325 as compared to a single dose of caffeine alone.

For both caffeine and its metabolite paraxanthine (3-desmethyl) the 90% CIs of the geometric mean ratios comparing AUC, $AUC_{(0-t)}$ and C_{max} after a single dose of caffeine in combination with steady-state administration of AZD7325 vs. administration of caffeine alone were contained within the pre-defined range of 0.8-1.25.

Median t_{max} of caffeine (1.0 h) was similar between treatments while a slight increase in median t_{max} of paraxanthine 3-desmethyl was observed; 6.0 h (caffeine alone) vs. 9.0 h (caffeine+AZD7325). The geometric mean CL/F of caffeine decreased from 5.8 L/h (caffeine alone) to 5.0 L/h when administered during AZD7325 steady-state administration. Median $t_{½\lambda z}$ of caffeine (6.3-7.0 h) and paraxanthine (3-desmethyl) (7.4-8.0 h) was similar between treatments.

On Day 1 the geometric mean C_{max}, $AUC_{(0-24)}$ and AUC were 57 ng/mL, 210 ng*h/mL and 261 ng*h/mL, respectively. On Day 11 (in combination of midazolam) the geometric mean C_{max} was 69 ng/mL and on Day 12 (in combination with caffeine) the C_{max} was 72 ng/mL. The AUC_{τ} on Day 11 and Day 12 were 285 ng*h/mL and 327 ng*h/mL, respectively. Any possible time-dependency in the pharmacokinetics of AZD7325 was not further evaluated due to the concomitant administration of midazolam on Day 11 and caffeine on Day 12.

The geometric mean CL/F of AZD7325 was 38 L/h on Day 1 and slightly lower on Day 11 and Day 12, 35 L/h and 31 L/h, respectively. Median t_{max} was similar between observations (0.80-1.0 h) and median $t_{½\lambda z}$ ranged between 14-18 h.

Summary of pharmacodynamic results

Visual analogue scale changes from baseline are summarised in Table S1. Positive numbers indicate a decrease in alertness from baseline, a decrease in calmness from baseline and a decrease in mood from baseline. Negative numbers indicate an increase in alertness from baseline, an increase in calmness from baseline and an increase in mood from baseline.

The greatest mean change from baseline on Day -2 was a 23% increase in drowsiness at 2 hours post-dose (5.3% increase on Day 11, 2 hours post-dose). The greatest mean change from baseline on Day 11 was an 18.4% decrease in clear-headedness at 0.5 hours post-dose (-15.6% decrease on Day -2, 0.5 hours post-dose).

A decrease in alertness was observed at 0.5 hours post-dose and 2 hours post-dose on both Day -2 (midazolam only) and Day 11 (midazolam and AZD7325). There was a slight increase in calmness post-dose on both Day 2 and Day 11, and there was a reduction in mood at 0.5 hours post-dose and 2 hours post-dose on both Day -2 and Day 11.

Table S1 Visual Analogue Scale (change from baseline)*

		Alertness	Calmness	Mood
Day -2	0.5 hours post-dose	12.6	0.0	5.1
	2 hours post-dose	14.1	-2.0	3.7
	6 hours post-dose	-1.3	-1.4	-0.4
	12 hours post-dose	1.9	-0.6	0.8
Day 11	0.5 hours post-dose	13.4	-3.3	5.8
	2 hours post-dose	5.1	-2.7	2.0
	6 hours post-dose	-4.2	-3.3	-1.2
	12 hours post-dose	-1.6	-3.3	1.0

Baseline is defined as the pre-dose measurement on that day.
Source: Table 11.2.33

Summary of safety results

AZD7325 administered in combination with caffeine and midazolam was well tolerated by subjects.

A total of 68 TEAEs were reported by 20/24 (83%) subjects. The most commonly reported TEAE during the study was somnolence. The TEAE most commonly reported by subjects receiving AZD7325 was dizziness.

After dosing with just midazolam, 12 TEAEs were reported, the most common of which was somnolence. Following dosing with just caffeine, only 3 events were reported.

After dosing with just AZD7325, 42 TEAEs were reported, the most common of which were dizziness, somnolence, vision blurred, feeling abnormal and irritability.

After dosing with midazolam and AZD7325, 1 TEAE (somnolence) was reported. Following dosing with caffeine and AZD7325, 10 TEAEs were reported, the most common of which was procedural site reaction.

The system organ class with the greatest frequency of TEAEs was nervous system disorders.

There was 1 moderate intensity TEAE during the study (rash vesicular), which was considered by the Investigator to be not related to any treatment.

The majority of TEAEs (44/68) were considered to be related to AZD7325, 10/68 TEAEs were considered related to midazolam and 5/68 were considered to be related to caffeine.

There were no clinically significant changes in laboratory values, vital signs or ECG during the study. Visual inspection of the mean data did not reveal any trends.

Date of the report

29 January 2009