AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD6280
Study Code	D0850C00015
Edition Number	1
Date	06 November 2009

A phase I, single center, open-label, fixed sequence study to determine the effect of multiple doses of AZD6280 on the pharmacokinetics of midazolam (CYP3A4) and caffeine (CYP1A2)

Study dates:	First healthy volunteer/patient enrolled: 12 January 2009 Last healthy volunteer/patient completed: 03 March 2009
Phase of development:	Clinical pharmacology (I)
International Co-ordinating Investigator:	
Sponsor's Responsible Medical Officer:	

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 first healthy volunteer was enrolled on 12th January 2009 and the last healthy volunteer completed the study on 3rd March 2009.

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 AZD6280 on the pharmacokinetic profile of a CYP3A4 substrate (midazolam and its 1' hydroxy metabolite) and a CYP1A2 substrate (caffeine and its 3-desmethyl paraxanthine metabolite).

Secondary objectives were:

To evaluate the safety and tolerability of repeated doses of AZD6280 in combination with midazolam and caffeine.

To evaluate the pharmacodynamic effects of AZD6280 in combination with midazolam on selected psychometric assessments using a Visual Analogue Scale (VAS).

Study design

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 AZD6280 on a CYP3A4 substrate (midazolam) and a CYP1A2 substrate (caffeine).

All subjects received a single dose of midazolam (5 mg) on Day -2 and Day 13 and a single dose of caffeine (200 mg) on Day -1 and Day 14. Subjects received a single daily dose of AZD6280 (30 mg) on Days 1-14.

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: AZD6280 20 mg oral capsule batch number PO10056345; AZD6280 5 mg oral capsule batch number PO10056347.

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 13 and a single dose of caffeine (200 mg) on Day -1 and Day 14. Subjects received a single daily dose of AZD6280 (30 mg) on Days 1-14.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

The following PK parameters were estimated for midazolam, midazolam 1'-hydroxy metabolite, caffeine, paraxanthine (3-desmethyl metabolite of caffeine) and AZD6280: AUC, $AUC_{(0-t)}$, CL/F, C_{max}, t_{max}, $t_{½\lambda z}$. For AZD6280 only, steady state was verified from trough (C_{min}) samples collected Days 10-14.

Pharmacodynamics for midazolam were assessed by Visual Analogue Scales (VAS).

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. The development of AZD6280 dependency was monitored for using a physician symptom questionnaire.

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

Subjects were 24 young healthy males, aged between 21 and 31 years and with BMIs between 19 and 30 kg/m^2. Some subjects had out-of-range values at baseline for laboratory safety tests, vital signs or ECG parameters; 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.

Twenty-three subjects completed the study as planned. One subject was withdrawn on Day 13, after Day 13 dosing with AZD6280 but prior to Day 13 dosing with midazolam, due to a moderate adverse event of drowsiness. The subject received 1 dose of midazolam 5 mg; 1 dose of caffeine 200 mg and 13 doses of AZD6280. The subject was not replaced.

Summary of pharmacokinetic results

Levels of midazolam were in general comparable between the 2 treatment periods but with a slightly higher peak concentration during combination treatment. The levels of the metabolite 1´ hydroxy midazolam were lower when midazolam was given with AZD6280. The caffeine plasma concentration versus time curves appeared similar regardless of AZD6280 co-administration and the paraxanthine (3-desmethyl metabolite of caffeine) concentrations were in general comparable but with a slightly lower peak concentration during combination treatment.

Steady state for AZD6280 was verified by trough samples collected Days 10 to 14. The inter-individual variability was high (C_{trough} range: 1.71-99.2 ng/mL; CV% Day 10-14: 99.3-118.7%) but the intra-individual variability was low.

The individual data generally showed comparable values in AUC for midazolam during both treatments while AUC for 1´-hydroxy midazolam was comparable or slightly lower during midazolam+AZD6280 treatment. There was no clear trend for C_{max} when comparing the 2 treatments.

The mean values of AUC, $AUC_{(0-t)}$ and C_{max} for midazolam were 85.9 ng*h/mL, 80.5 ng*h/mL and 32.9 ng/mL (midazolam alone) and 85.0 ng*h/mL, 81.5 ng*h/mL and 36.3 ng/mL (midazolam+AZD6280). The corresponding values for 1´-hydroxy midazolam were 22.5 ng*h/mL, 21.3 ng*h/mL and 11.8 ng/mL (midazolam alone) and 18.4 ng*h/mL, 17.0 ng*h/mL and 10.2 ng/mL (midazolam+AZD6280) (Table 11.2.6 and Table 11.2.7). The variability (CV%) in AUC, $AUC_{(0-t)}$ and C_{max} was comparable between the AZD6280 and AZD6280+midazolam treatments for both midazolam and 1´-hydroxy midazolam.

The mean AUC ratio for 1´-hydroxy midazolam to midazolam was slightly lower (approximately 20%) during AZD6280 co-administration.

The 90% CIs of the geometric mean ratios comparing AUC, $AUC_{(0-t)}$ and C_{max} after steady-state administration of AZD6280 vs. midazolam alone were contained within the pre-defined range of 0.8-1.25 for midazolam indicating that AZD6280 had no significant effect on the exposure of midazolam. The lower limits of the 90% CIs were below 0.8 for 1´-hydroxy midazolam suggesting a lower exposure (18, 20 and 15% lower, for AUC, $AUC_{(0-t)}$ and C_{max}, respectively), when midazolam was given in combination with AZD6280.

The mean CL/F of midazolam was unaffected by prolonged administration of AZD6280 (74.9 L/h during midazolam alone treatment and 72.9 L/h during midazolam+AZD6280 treatment). Median midazolam t_{max} and mean $t_{½λz}$ were comparable between treatments (t_{max} was 0.5 hours for both treatments and $t_{½λz}$ was 3.4 hours during midazolam alone treatment and 3.3 hours during midazolam+AZD6280 treatment).

Median t_{max} and mean $t_{½λz}$ of 1´-hydroxy midazolam was comparable between treatments (t_{max} was 0.5 hours for both treatments and $t_{½λz}$ was 2.6 hours during midazolam alone treatment and 2.5 hours during midazolam+AZD6280 treatment).

The variability in CL/F and $t_{½\lambda z}$ was comparable between treatments.

The individual data generally showed similar values in AUC and C_{max} for caffeine and paraxanthine (3-desmethyl metabolite of caffeine) between the treatments caffeine vs. caffeine+AZD6280.

The mean values of AUC, $AUC_{(0-t)}$ and C_{max} for caffeine were 33094 ng*h/mL, 31588 ng*h/mL and 4151 ng/mL (caffeine alone) and 36579 ng*h/mL, 35406 ng*h/mL and 4350 ng/mL (caffeine+AZD6280). The corresponding values for paraxanthine (3-desmethyl metabolite of caffeine) were 22312 ng*h/mL, 21282 ng*h/mL and 1208 ng/mL (caffeine alone) and 22811 ng*h/mL, 21460 ng*h/mL and 1125 ng/mL (caffeine+AZD6280) (Table 11.2.8 and Table 11.2.9). The variability (CV%) in AUC and $AUC_{(0-t)}$ was comparable between the AZD6280 and AZD6280+caffeine treatments for both caffeine and paraxanthine (3-desmethyl metabolite of caffeine). The variability in C_{max} was slightly higher during AZD6280+caffeine treatments (16.9 vs 12.4% for caffeine and 16.1 vs 12.6% for paraxanthine (3-desmethyl metabolite of caffeine).

The mean AUC ratio for paraxanthine (3-desmethyl metabolite of caffeine) to caffeine remained relatively unchanged despite AZD6280 co-administration.

For both caffeine and its metabolite paraxanthine (3-desmethyl metabolite of caffeine) 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 AZD6280 vs. administration of caffeine alone were contained within the pre-defined range of 0.8-1.25. Thus, non existence of a relevant effect, defined as -20 or +25 %, was shown, even if for caffeine some effect seems to be present, as the 90 % C.I. do not include 1 for AUC and AUC(0-t).

The mean CL/F of caffeine was unaffected by prolonged administration of AZD6280 (6.6 L/h for caffeine alone and 6.2 L/h when administered during AZD6280 steady-state treatment). Median t_{max} and mean $t_{½\lambda z}$ of caffeine were comparable between treatments (t_{max} was 1.0 hour for both treatments and $t_{½\lambda z}$ was 5.6 hours during caffeine alone treatment and 6.0 hours during caffeine+AZD6280 treatment).

Median t_{max} and mean $t_{½\lambda z}$ of paraxanthine (3-desmethyl metabolite of caffeine) was comparable between treatments (t_{max} was 6.0 hours for both treatments and $t_{½\lambda z}$ was 7.4 hours during caffeine alone treatment and 8.3 hours during caffeine+AZD6280 treatment).

The variability in CL/F and $t_{½\lambda z}$ was comparable between treatments.

Summary of pharmacodynamic results

Pharmacodynamics were assessed using VAS after administration of midazolam alone (Day -2) and after midazolam in combination with AZD6280 (Day 13). The greatest mean change from baseline on Day -2 was a 12.3% decrease in attentiveness at 0.5 and 2 hours post dose (10.1% decrease on Day 13, 0.5 hours post-dose; 10.0% decrease on Day 13, 2 hours

post dose). The greatest mean change from baseline in this parameter on Day 13 was a 19.1% decrease in alertness at 0.5 hours post-dose (10.0% decrease on Day -2, 2 hours post dose).

During the study, greater than 10% mean changes from baseline were recorded for alert/drowsy (maximum change: 19.1% increase in alertness on Day 13, 2 hours post dose), fuzzy/clear-headed (maximum change: 15.0% decrease in clear-headedness on Day 13, 0.5 hours post dose), well-coordinated/clumsy (maximum change: 10.5% increase in clumsiness on Day 13 at 0.5 and 2 hours post dose) and attentive/dreamy (maximum change: 10.1% decrease in attentiveness on Day 13 at 0.5 hours post dose).

There were no overall factors (alertness, calmness or contendedness) that had a greater than 10% mean change from baseline recorded during the study. However, visual inspection of the data revealed a mean decrease in alertness from baseline at 0.5 hours and 2 hours post dose on both Day -2 (6.5% at 0.5 hours post dose and 8.1% at 2 hours post dose) and Day 13 (9.3% at 0.5 hours post dose and 9.5% at 2 hours post dose). At 6 and 12 hours post dose, there was no mean decrease in alertness from baseline.

Summary of safety results

There were no deaths or serious adverse events during the study. Generally AZD6280 was well tolerated by subjects.

One subject was withdrawn from the study due to an AE of moderate somnolence. The AE was considered to be related to AZD6280. It was the only moderate intensity TEAE reported during the study.

A total of 48 TEAEs were reported by 21/24 (87.5%) subjects.

The most common TEAEs were of the system organ class nervous system disorders. The most common TEAEs were dizziness and somnolence.

After dosing with midazolam alone, 4 events were reported by 3/24 subjects; after dosing with caffeine alone 2 events were reported by 2/24 subjects; after dosing with AZD6280 alone 34 events were reported by 18/24 subjects.

After dosing with midazolam and AZD6280, 3 events were reported by 3/23 subjects; after dosing with caffeine and AZD6280, 5 events were reported by 3/23 subjects.

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.