AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD6280
Study Code	D0850C00014
Edition Number	1
Date	14 May 2009

A phase 1, single centre, single dose, double-blind, double-dummy, four-way crossover, placebo-controlled, randomized study to investigate the effects of AZD6280 on sedation, cognition and EEG in comparison with lorazepam in healthy male volunteers.

Study dates:	First healthy volunteer enrolled: 3 September 2008 Last healthy volunteer completed: 8 December 2008
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 was a single centre study.

Study period		Phase of development
Date of first subject enrolled	3 September 2008	Phase 1
Date of last subject completed	8 December 2008	

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to investigate the pharmacodynamic (PD) effects of single oral doses of AZD6280 on sedation and cognition in comparison with placebo, and lorazepam, a widely used non-selective GABAA modulator for anxiolysis.

The secondary objectives were:

- To evaluate the safety and tolerability of AZD6280 by assessing adverse events (AEs), vital signs, laboratory parameters, and electrocardiograms (ECGs).
- To measure the effects of single oral doses of AZD6280 with electroencephalograms (EEGs) and to assess whether the EEG power spectral changes seen in animal studies of AZD6280 are observed in humans.
- To determine the effects of single oral doses of AZD6280 on body sway and to compare these effects to those of lorazepam.
- To investigate the pharmacokinetic (PK) profile of AZD6280 after single oral dose administration. Mathematical PK/PD modelling to correlate the relationships between plasma concentration and effects for changes in central nervous system (CNS) measurements was to be attempted.

Study design

This was a single centre, single dose, 4-way cross over, double blind, double-dummy, placebo controlled, randomised study.

Sixteen subjects completed the study. They were randomized to 16 different treatment sequences. The sequences were balanced across these subjects.

The washout period was at least 1 week. Dropouts were to be replaced by subjects receiving the same order of treatments.

The order of the treatments was based on the Williams Latin Square design leading to a 4-way crossover design.

Target healthy volunteer population and sample size

Sixteen healthy male subjects between the ages of 18 and 55 years, both inclusive, were enrolled into the study.

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

AZD6280 immediate release oral capsules of 5 mg and 20 mg strength were supplied to the by AstraZeneca. The low dose treatment was 10 mg, and the high dose treatment was 40 mg.

Lorazepam 1 mg tablets and matching placebo tablets were supplied to the The administered dose was 2 mg.

All treatments were dosed orally.

Each treatment consisted of 2 capsules (AZD6280 and/or its placebo capsules) and 2 tablets (lorazepam 2 x 1 mg or matching placebo tablets).

Individual batch numbers are included in the CSR.

Duration of treatment

The duration of subject participation included a screening period of maximally 21 days, four 24-hour stays in the clinical pharmacological unit, 3 washout periods of at least 7 days, and a follow-up period of at least 7 days.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

PK parameters that were assessed included the following:

- C_{max} - Maximum plasma concentration
- t_{max} - Time to reach maximum plasma concentration following drug administration
- 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
- $t_{½\lambda z}$ - Elimination half-life in plasma
- CL/F - Apparent oral clearance of AZD6280

PD parameters were also assessed. The following CNS function tests were performed to assess drug effects (the abbreviations/terms in the parentheses are their short names):

Sedation

- Bond & Lader Visual Analogue Scale for subjective alertness (VAS alertness)

Cognitive functions (CogState test)

- International shopping list task (ISL)
- International shopping list delayed recall (ISLR)
- Timed chase test (Chase)
- Groton maze learning test (GMLT)
- Detection task (DET)
- Identification task (IDN)
- One card learning task (OCL)

Other CNS functions

- Saccadic eye movement (SEM)
- Smooth pursuit eye movement (Smooth)
- Bond & Lader Visual Analogue Scale for subjective feelings (VAS calmness, VAS mood)
- Bowdle Visual Analogue Scale for "feeling high," internal perception, and external perception (VAS "feeling high," VAS internal, VAS external)
- Body sway (Sway)
- Electroencephalogram (EEG)
- Adaptive tracking (Tracker)

Criteria for evaluation - safety (main variables)

Safety and tolerability were assessed by the incidence and severity of AEs, abnormalities in vital sign assessments, clinical laboratory parameters, and ECGs.

Statistical methods

Mixed model analyses of variance (using SAS PROC MIXED) was performed to analyse the PD data. The appropriate factors were entered into the model which typically includes treatment, period, time, and treatment by time as fixed effects, with subject, subject by time,

and subject by treatment as random effects, and with the baseline value as covariate, where baseline was defined as the average of the available values obtained prior to dosing. Treatment effects were reported as the contrasts between active treatment and placebo, along with 95% confidence intervals.

Subject population

A total number of 17 male subjects were included, of which 16 subjects completed the study per protocol. Due to a positive pre-dose urine screen test for THC, one subject was excluded from the study without dosing on his 2nd study day and was replaced by a newly recruited subject. The latter subject took the study medication in the same order as the discontinued subject.

Summary of pharmacokinetic results

The PK results of this study were consistent with previous findings in healthy male volunteers (refer to the AZD6280 Investigator's Brochure Addendum). The results indicated fast absorption and dose proportionality following oral administration of AZD6280. Moderate to high inter-subject variability was observed in C_{max} and AUC.

Summary of pharmacodynamic results

The study demonstrated the effects of single oral doses of AZD6280 10 mg, AZD6280 40 mg, and lorazepam 2 mg on different PD parameters. The effects of AZD6280 10 mg, AZD6280 40 mg, and lorazepam 2 mg were first compared to placebo. Subsequently, comparisons were made between each dose of AZD6280 and lorazepam, as well as between the 2 doses of AZD6280.

- AZD6280 10 mg caused statistically significant reductions in saccadic peak velocity, EEG Alpha Fz-Cz, and Theta Fz-Cz. All of these effects were statistically significantly less robust than those of lorazepam 2 mg. The effect on saccadic peak velocity (SPV) was lower than AZD6280 40 mg in a dose-proportional manner, while the effects on EEG parameters were comparable to those of the higher dose. On the other hand, AZD6280 10 mg was devoid of effects on a wide range of PD variables measuring subjective sedation, cognition, postural balance, neurophysiologic function, visuo-motor coordination, subjective feelings, or psychomimetic symptoms.

- AZD6280 40 mg produced statistically significant effects on SPV, smooth pursuit, tracker, and body sway. These effects were all statistically significantly less robust than after lorazepam 2 mg, but overall higher (statistically significantly or not) than the effects of AZD6280 10 mg. AZD6280 40 mg induced an isolated statistically significant increase in VAS "feeling high." Although the maximal increase was comparable to that of lorazepam 2 mg, the effect lasted considerably shorter. Contrary to lorazepam, AZD6280 40 mg did not distort either internal or external perceptions. AZD6280 had no effects on VAS alertness, which showed clear reductions with lorazepam 2 mg.

- AZD6280 40 mg was associated with a clear EEG power reduction in Delta, Theta, and Alpha bands and with an increase in Beta power. The effects of AZD6280 40 mg on the Fz-Cz leads of Theta and Alpha bands were comparable to those of AZD6280 10 mg. Lorazepam 2 mg had similar albeit usually larger effects, but in contrast to the decreases observed with AZD6280 40 mg, lorazepam 2 mg caused statistically significant increases in EEG power on the Delta and Gamma bands.

The PD effects of each active treatment compared to placebo are summarised in Table S1 and Table S2.

Table S1 Summary of analysis results on primary and secondary PD variables after single doses of lorazepam 2 mg, AZD6280 10 mg, and AZD6280 40 mg

Variables[a]	Lorazepam 2 mg	AZD6280 10 mg	AZD6280 40 mg	Relationship of effect [b]	Interpretation
Primary					
VAS alertness	↓	=	=	Lora>A-10 Lora≈A-40 A-40≈A-10	Lorazepam reduced subjective alertness.
Secondary					
Sway	↑↑	=	↑	Lora>A-40>A-10	Lorazepam and AZD6280 40 mg impaired postural balance.
SPV	↓↓	↓↓	↓↓	Lora>A-40>A-10	Lorazepam, AZD6280 40 mg, and AZD6280 10 mg reduced neurophysiologic response.
SacRT	↓↓	=	=	Lora>A-40≈A-10	Lorazepam reduced neurophysiologic response.
SacInacc	↓	=	=	Lora>A-40≈A-10	Lorazepam reduced neurophysiologic response.
Smooth	↓↓	=	↓	Lora>A-40≈A-10	Lorazepam and AZD6280 40 mg reduced neurophysiologic response.
Tracker	↓↓	=	↓	Lora>A-40≈A-10	Lorazepam and AZD6280 40 mg impaired visuo-motor coordination and vigilance.
VAS external	↑	=	=	Lora>A-40≈A-10	Lorazepam induced psychomimetic symptom regarding external perception.
VAS internal	↑↑	=	=	Lora>A-40≈A-10	Lorazepam induced psychomimetic symptom regarding internal perception.

Table S1 **Summary of analysis results on primary and secondary PD variables after single doses of lorazepam 2 mg, AZD6280 10 mg, and AZD6280 40 mg**

Variables[a]	Lorazepam 2 mg	AZD6280 10 mg	AZD6280 40 mg	Relationship of effect [b]	Interpretation
VAS "feeling high"	↑	=	↑	Lora≈A-40>A-10	Both lorazepam and AZD6280 40 mg induced euphoric mood.

[a] EEG results are presented in Table S2.
[b] The effect relationship refers to the statistical comparison between the treatments. A statistically more robust effect is presented as ">,"while a non-statistically significant comparison is expressed as "≈."
Note: ↑↑ indicates a very significant increase [p<0.001], ↑ indicates a significant increase [0.001<p<0.05], = indicates no statistically significant change [p>0.05], ↓ indicates a significant decrease [0.001<p<0.05], and ↓↓ indicates a very significant decrease [p<0.001].
A-10 AZD6280 10 mg; A-40 AZD6280 40 mg; EEG Electroencephalogram; Lora Lorazepam 2 mg; PD Pharmacodynamic; SacInacc Saccadic inaccuracy; SacRT Saccadic reaction time; SPV Saccadic peak velocity; VAS Visual Analogue Scale.

Table S2 summarises the alteration of EEG spectral power under each active treatment in comparison with placebo.

Table S2 **Summary of analysis results on EEG parameters after single doses of lorazepam 2 mg, AZD6280 10 mg, and AZD6280 40 mg**

EEG band	EEG lead	Lorazepam 2 mg	AZD6280 10 mg	AZD6280 40 mg	Relationship of effect [a]
Delta (2-4 Hz)	Fz-Cz	↑	=	↓	Lora≠A-40>A-10
	Pz-Oz	=	=	=	Lora≈A-40≈A-10
Theta (4-7.5 Hz)	Fz-Cz	↓	↓	↓	Lora≈A-40≈A-10
	Pz-Oz	↓	=	=	Lora> [b]A-40≈A-10
Alpha (7.5-13.5 Hz)	Fz-Cz	↓↓	↓	↓	Lora>A-40≈A-10
	Pz-Oz	↓↓	=	↓	Lora>A-40≈A-10
Beta (13.5-35 Hz)	Fz-Cz	↑	=	↑	Lora≈A-40>A-10
	Pz-Oz	↓	=	=	Lora>A-40≈A-10
Gamma (35-48 Hz)	Fz-Cz	↑↑	=	=	Lora>A-40≈A-10
	Pz-Oz	=	=	=	Lora≈A-40≈A-10

Table S2 Summary of analysis results on EEG parameters after single doses of lorazepam 2 mg, AZD6280 10 mg, and AZD6280 40 mg

EEG band	EEG lead	Lorazepam 2 mg	AZD6280 10 mg	AZD6280 40 mg	Relationship of effect [a]

[a] The effect relationship refers to the statistical comparison between the treatments. A statistically more robust effect is presented as ">," while a non-statistically significant comparison is expressed as "≈." The mark "≠" indicates effects of opposite directions.

[b] The difference between lorazepam and AZD6280 40 mg was nearly significant, p=0.0654.

Note: ↑↑ indicates a very significant increase [p<0.001], ↑ indicates a significant increase [0.001<p<0.05], = indicates no statistically significant change [p>0.05], ↓ indicates a significant decrease [0.001<p<0.05], and ↓↓ indicates a very significant decrease [p<0.001].

A-10 AZD6280 10 mg; A-40 AZD6280 40 mg; EEG Electroencephalogram; Lora Lorazepam 2 mg.

Summary of safety results

- The administration of single dose AZD6280 10 mg or 40 mg were safe and well tolerated in the selected study population of 17 healthy male volunteers.
- In general, AEs occurred more frequently with AZD6280 40 mg than with AZD6280 10 mg, but were milder and less frequent than with lorazepam 2 mg.
- Compared to lorazepam 2 mg, AZD6280 40 mg caused fewer gastrointestinal and less frequent and intensive CNS-effects (particularly indicative of sedation). AZD6280 caused some high feeling, which lasted a shorter time and was accompanied by fewer psychomimetic effects as compared to lorazepam 2 mg,.
- The AE frequency and severity of AZD6280 10 mg were comparable to placebo.
- No changes or individual abnormalities of blood pressure, heart rate, respiratory rate, or auricular temperature were judged as clinically significant by the investigator.
- No clinically significant abnormalities in laboratory or ECG results were identified.