AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD7325
Study Code	D1140C00003
Edition Number	Final
Date	10 June 2009

A phase 1, single centre, single dose, double-blind, double-dummy, four-way crossover, placebo-controlled, randomized study to investigate the effects of AZD7325 on sedation, cognition and EEG in comparison with lorazepam in healthy male volunteers.

Study dates: First healthy volunteer enrolled: 2 June 2008
Last healthy volunteer 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 was a single centre study. Sixteen healthy male subjects between the ages of 18 and 55 years, both inclusive, were enrolled into the study.

Study period		Phase of development
Date of first subject enrolled	2 June 2008	Phase 1
Date of last subject completed	10 September 2008	

Publications

None at the time of writing this report.

Objectives

The primary objective was to investigate the pharmacodynamic (PD) effects of single oral doses of AZD7325 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 AZD7325 by assessing adverse events (AEs), vital signs, laboratory parameters, and electrocardiograms (ECGs)
- To measure the effects of single oral doses of AZD7325 with encephalogram (EEG) and to assess whether the EEG power spectral changes seen in animal studies of AZD7325 are observed in humans
- To determine the effects of single oral doses of AZD7325 on body sway and to compare its effects to those of lorazepam.
- To investigate the pharmacokinetic (PK) profile of AZD7325 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

A single centre, single dose, 4-way cross over, double blind, double-dummy, placebo controlled, randomized study to investigate the effects of AZD7325 on sedation, cognition, and EEG, and to compare these effects to those of lorazepam in healthy male volunteers.

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

The washout period was at least 1 week. Dropouts were replaced by subjects with 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

The study aimed to complete the investigation in 16 healthy male volunteers, who aged 18 to 55 years and had a Body Mass Index (BMI) between 18 and ≤ 30 kg/m^2 (all extremes inclusive).

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

AZD7325 immediate release oral capsules of 1-mg and 10-mg strength were supplied to the Leiden University Medical Centre (LUMC) pharmacy by AstraZeneca. The low dose treatment was 2 mg, and the high dose treatment was 10 mg.

Lorazepam 1-mg tablets and matching placebo tablets were supplied to the LUMC pharmacy by Katwijk Farma BV.

All treatments were dosed orally.

Each treatment consisted of 2 capsules (AZD7325 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 AZD7325

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 analyze 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 18 male subjects were included, of which 16 subjects completed the study per protocol. Due to personal reasons, two subjects withdrew their informed consents after completion of their 1st study day and were replaced by two newly recruited subjects. The latter subjects took the study medication in the same order as the discontinued subjects.

Summary of pharmacokinetic results

The PK results of this study were consistent with previous findings in healthy male volunteers (refer to AZD7325 Investigator's Brochure Addendum). The results indicated fast absorption and dose proportionality following oral administration of AZD7325. Pharmacogenetic studies might be informative for the moderate to high inter-subject variability observed in C_{max} and AUC.

Summary of pharmacodynamic results

The study evaluated the effects of single oral doses of AZD7325 2 mg, AZD7325 10 mg, and lorazepam 2 mg on different PD parameters. The effects of AZD7325 2 mg, AZD7325 10 mg, and lorazepam 2 mg were first compared to placebo, and then the effects of AZD7325 were compared to lorazepam.

- AZD7325 2 mg did not have statistically significant effects on any PD variables measuring sedation, cognition, neurophysiologic function, postural balance, visuo-motor coordination, subjective feelings, or psychomimetic symptoms.

- AZD7325 10 mg did not have statistically significant effects on PD variables measuring sedation, cognition, postural balance, or visuo-motor coordination. However, AZD7325 10 mg induced an isolated statistically significant increase in VAS "feeling high". Although this increase was quantitatively comparable to that of lorazepam 2 mg, inspection of the time profiles showed that the effect lasted considerably shorter. Contrary to lorazepam, AZD7325 10 mg was devoid of distortion of either internal or external perceptions. In addition, AZD7325 10 mg was associated with clear EEG power reduction in Delta and Theta bands. These reductions differed from the characteristic benzodiazepine EEG signature induced by lorazepam. If confirmed, such specific effects on EEG mapping by AZD7325

and lorazepam may reflect distinct neuropharmacological properties of partial α2,3-selective and non-selective GABAA-agonists.

- Lorazepam 2 mg showed robust effects on various PD parameters, which indicated general CNS depression and multi-domain cognitive impairment.

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

Table S1 Summary of analysis results on primary and secondary PD variables under treatment of lorazepam 2 mg, AZD7325 2 mg, and AZD7325 10 mg

Variables[a]	Lorazepam 2 mg	AZD7325 2 mg	AZD7325 10 mg	Interpretation
Primary				
VAS alertness	↓↓	=	=	Lorazepam increased subjective sedation.
Secondary				
VAS calmness	↑	=	=	Lorazepam increased subjective calmness.
Sway	↑↑	=	=	Lorazepam impaired postural balance.
SPV	↓↓	=	=	Lorazepam impaired neurophysiologic function.
Smooth	↓↓	=	=	Lorazepam impaired neurophysiologic function.
Tracker	↓↓	=	=	Lorazepam impaired visuo-motor coordination and vigilance.
VAS external	↑	=	=	Lorazepam induced psychomimetic symptom regarding external perception.
VAS internal	↑	=	=	Lorazepam induced psychomimetic symptom regarding internal perception.
VAS feeling high	↑	=	↑	Both lorazepam and AZD7325 10 mg induced a comparable euphoric mood.

[a] EEG results are presented in Table 2.

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

PD Pharmacodynamic; SPV Saccadic peak velocity; VAS Visual Analogue Scale.

Table 2 summarises the alteration of EEG spectral power under each active treatment in comparison with placebo.

Table 2 Summary of analysis results on EEG parameters under treatment of lorazepam 2 mg, AZD7325 2 mg, and AZD7325 10 mg

EEG band	EEG lead	Lorazepam 2 mg	AZD7325 2 mg	AZD7325 10 mg
Delta (2-4 Hz)	Fz-Cz	↑	=	↓↓
	Pz-Oz	=	=	↓
Theta (4-7.5 Hz)	Fz-Cz	↓	=	↓↓
	Pz-Oz	↓	=	↑
Alpha (7.5-13.5 Hz)	Fz-Cz	↓↓	=	=
	Pz-Oz	↓	=	=
Beta (13.5-35 Hz)	Fz-Cz	↑	=	=
	Pz-Oz	↓	=	=
Gamma (35-48 Hz)	Fz-Cz	↑	=	=
	Pz-Oz	=	=	=

Note: ↑↑ indicates a very significant increase [P<0.001]; ↑ indicates a significant increase [0.001<P<0.05]; = indicates no change [P>0.05]; ↓ indicates a significant decrease [0.001<P<0.05]; and ↓↓ indicates a very significant decrease [P<0.001].
EEG Electroencephalogram.

Summary of safety results

- The administration of single dose AZD7325 2 mg or 10 mg were safe and well tolerated in the selected study population of 18 healthy male volunteers, including 16 study completers and 2 prematurely discontinued subjects.
- In general, AEs occurred more frequently with AZD7325 10 mg than with AZD7325 2 mg, but less frequently than with lorazepam 2 mg.
- The AEs of lorazepam 2 mg reflected a wide range of CNS effects induced by non-selective GABAA amplification, including sedation, cognitive impairment, mood alteration, and psychomotor disturbance.
- Compared to lorazepam 2 mg, AZD7325 10 mg caused fewer gastrointestinal and less frequent and intensive CNS-effects (particularly indicative of sedation). AZD7325 caused some high feeling, which compared to lorazepam 2 mg lasted shorter and was accompanied by fewer psychomimetic effects.
- The AE frequency and severity of AZD7325 2 mg were comparable to placebo.
- No changes or individual abnormalities of blood pressure, heart rate, or auricular temperature were judged as clinically significant by the investigator, despite the statistically significant increase of heart rate following lorazepam 2 mg.

- No clinically significant abnormalities in laboratory or ECG results were identified.

Date of the report

10 June 2009