AstraZeneca

**Clinical Study Report Synopsis**

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| Drug Substance | AZD7325 |
| Study Code | D1140C00014 |
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# A Multi-Center, Randomized, Placebo-Controlled, Double-Blind, Parallel Group, Phase II Study of 2 Oral Dose Groups of AZD7325, with a Lorazepam Arm, in Subjects with Generalized Anxiety Disorder (GAD)

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| **Study dates:** | First subject enrolled: 11 December 2008<br>Last subject last visit: 26 May 2009 |
| **Phase of development:** | Therapeutic exploratory (II) |
| **National Co-ordinating Investigator:** | None. |

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

## Study centre(s)

This study was conducted at 43 study centers in the United States (US).

## Publications

None at the time of writing this report.

## Objectives and criteria for evaluation

**Table S1 Primary and secondary objectives and outcome variables**

| Objectives | Outcome variables | Type |
|---|---|---|
| **Primary** | **Primary** | |
| To evaluate the efficacy of AZD7325 vs. placebo in the treatment of anxiety symptoms in subjects with generalized anxietydisorder (GAD) | Change in the Hamilton Rating Scale for Anxiety (HAM-A) total score from baseline to Day 28 | Efficacy |
| **Secondary** | **Secondary** | |
| To characterize the time course and effect of AZD7325 vs. placebo and lorazepam vs. placebo on anxiety symptoms in subjects with GAD | At each assessment timepoint: Clinical Global Impression-Global Improvement (CGI-I) and change from baseline in Clinical Global Impression-Severity of Illness (CGI-S) score, change from baseline in Hospital Anxiety and Depression Scale for Anxiety (HADS-A) score, remission (HAM-A ≤7,) response (≥50% decrease from baseline in HAM-A total score), and change from baseline in HAM-A psychic and somatic clusters | Efficacy |
| To evaluate the effect of AZD7325 vs. placebo and lorazepam vs. placebo on the health-related Quality of Life (QoL) of subjects with GAD | Change in the Quality of Life Enjoyment and Satisfaction Questionnaire (QLES-Q-SF) percent (%) maximum total score from baseline to each assessment timepoint | Patient-reported outcomes (PRO)/ (QoL) |
| To evaluate the safety and tolerability of AZD7325 and lorazepam in subjects with GAD | Change in physical examination results from screening to Visit 8 (or study termination), laboratory values, vital signs, electrocardiogram (ECG), blood glucose/lipids, adverse events (AEs), AEs related to somnolence and leading to withdrawal, incidence of suicidality, weight, Treatment Discontinuation Signs and Symptoms (TDSS) and Rickels Physician Symptom Checklist (RPSC) | Safety |
| **Exploratory** | **Exploratory** | |
| To investigate the effect of AZD7325 and lorazepam on symptoms of depression in subjects with GAD | Change in Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline to Days 14 and 28 and change in HADS-D total score from baseline to each assessment timepoint | Efficacy |

| Objectives | Outcome variables | Type |
|---|---|---|
| To explore the onset effect of AZD7325 on anxiety symptoms in subjects with GAD | • ≥30% sustained response, defined by ≥30% decrease in HAM-A from baseline to Day 7 and maintained response at Days 14, 21 and 28.<br>• ≥50% sustained response defined by ≥50% decrease in HAM-A from baseline to Day 7 and maintained response at Days 14, 21 and 28.<br>• time to ≥30% sustained response, defined by time from baseline to first ≥30% decrease in HAM-A score and maintained response until Day 28 (Visit 8).<br>• time to ≥50% sustained response, defined by time from baseline to first ≥50% decrease in HAM-A score and maintained response until Day 28. | Efficacy |
| To investigate the effect of AZD7325 on sleep in subjects with GAD | Change in Pittsburgh Sleep Quality Index (PSQI) from baseline (Day 1) to Day 28 (Visit 8) | PRO (QoL) |
| To investigate the utility of Daily Assessment of Symptoms-Anxiety (DAS-A) scale in detecting improvement of anxiety from Day -6 to Day 7 | Change in DAS-A from baseline to post-randomization days | PRO |
| To characterize the population pharmacokinetics (PK) of AZD7325 | Blood samples taken for determining plasma concentrations of AZD7325; individual PK parameters and predictions of individual exposure (eg, maximum plasma drug concentration [$C_{max}$] and area under the curve [AUC]) | PK |
| To collect information on the abuse liability of AZD7325 | Symptom/Side-Effect Questionnaire for central nervous system (CNS)-Active Drugs (SSQCD), monitoring medication accountability/irregularities, protocol non-compliance, missing or lost medications, treatment discontinuation for potential alcohol or drug use-related reasons | Safety (Abuse liability) |
| To collect deoxyribonucleic acid (DNA) samples for retrospective genetic analyses. | Optional pharmacogenetics (PGx) sampling to study whether genetic factors explain variation in pharmacodynamic effects and PK of AZD7325, and to study genetic factors related to GAD.<br>To be reported separately | PGx (optional) |
| To validate the equivalence of an electronic patient-reported outcome interactive voice response (ePRO IVR) version of the DAS-A with the existing paper version | To validate the ePRO IVR version of the paper DAS-A | PRO |
| To explore the effect of AZD7325, lorazepam, and placebo on cognition as measured using the Digit Symbol Substitution Test (DSST) | Change in the DSST score from baseline (Day 1 prior to dosing) to each assessment timepoint | PRO |

Note: The results from the exploratory objectives are not included in the Clinical Study Report (CSR) synopsis but are presented in CSR D1140C00014.

## Study design

This was a Phase II, multi-center, double-blind, randomized, placebo-controlled, parallel group monotherapy study that compared the effect of AZD7325 on symptom improvement in subjects with GAD to that of placebo. The study also included a lorazepam arm.

## Target subject population and sample size

Eligible subjects, aged 18 to 65 years, diagnosed with GAD as assessed by the Mini-International Neuropsychiatric Interview (MINI) were enrolled.

The sample size was calculated by assuming an anticipated difference of 3 units from placebo and a standard deviation of 8 for the change in HAM-A total score from randomization to Day 28. The sample size was determined based on a 1-sided test at an overall 10% significance level and 80% power to show that at least one of the two AZD7325 doses would be better than placebo using Dunnett's procedure (the corresponding 1-sided $\alpha$=0.0575 due to the two AZD7325 doses versus placebo). Assuming an approximately 6% unevaluable rate, it was estimated that 360 subjects would be needed to be randomized to obtain 336 evaluable subjects.

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

AZD7325 5 mg twice daily (BID), AZD7325 15 mg BID, lorazepam 1 mg twice daily (BID) for 4 days followed by 2 mg BID, or placebo was administered twice daily (in the morning and the evening) during the treatment period. The tablets were taken orally with water either 1 hour before or 2 hours after a meal or breakfast. Individual batch numbers and further information are included in the CSR.

## Duration of treatment

The study consisted of a screening/washout/lead-in period of up to 28 days; a 28 day, double-blind treatment period with 1 of 4 treatment regimens (AZD7325: 5 mg BID or 15 mg BID; lorazepam 1 mg BID for 4 days, then 2 mg BID thereafter; or placebo); and a 14-day post-treatment period during the first 6 days of which subjects in the AZD7325 and placebo arms received placebo and subjects in the lorazepam arm were tapered off treatment, and followed by 8 days where no subjects in any arm received treatment. The 4 treatment regimens were assigned in a ratio of 1:1:1:1.

## Statistical methods

All statistical comparisons were based on a 1-sided significance level of $\alpha$=0.1 unless otherwise specified. For the primary analysis, Hochberg's step-up procedure was used to adjust for multiplicity (the comparison of each of the AZD7325 doses to placebo). For the secondary analyses, no multiplicity adjustments to the p-values were made, and unadjusted 2-sided 80% confidence intervals were presented where appropriate.

Descriptive statistics are used to present efficacy and safety variables. For continuous variables, n, mean, standard deviation, median, minimum, and maximum are presented. For categorical variables, n, frequency, and percentage are presented.

**Subject population**

A total of 369 (54.5%) subjects were randomly assigned to treatment at 43 study centers in the US. Of the 369 subjects randomized, 78.0% (288/369 subjects) completed the treatment period and 76.4% (282/369) completed the treatment and the follow-up period. In general, baseline demographic data were similar across treatment groups. Most subjects enrolled in this study were White (76.9%) with a mean age of 39.7 years and between 40 and 65 years old (52.4%).

**Summary of efficacy results**

Primary efficacy

The primary efficacy variable was the change from baseline to Week 4 (Day 28) in HAM-A total score. The change from baseline was compared between each of the two AZD7325 doses and placebo with last observation carried forward (LOCF) in the modified intent-to-treat (mITT) analysis set using an analysis of covariance (ANCOVA) model. The mITT population included all randomized subjects, classified according to the assigned treatment, who took investigational product (IP) and who had a HAM-A total score assessment at randomization and at least one HAM-A total score post-randomization. At Week 4, the mean change in HAM-A total score from baseline was negative for all treatment groups and placebo, indicating improvement in all groups. The primary efficacy analysis of the change from baseline to Week 4 in the HAM-A total score showed that both AZD7325 doses were numerically better than placebo (-0.6 for AZD7325 5 mg BID vs. placebo and -1.0 for AZD7325 15 mg BID vs. placebo), but neither dose reached statistical significance at the 1-sided significance level of 0.1 (1-sided adjusted p=0.273 for each dose vs. placebo). Subjects treated with AZD7325 5 or 15 mg BID did not exhibit significantly greater improvement in anxiety symptom severity than the placebo-treated subjects after 4 weeks of treatment.

Lorazepam 2 mg BID was statistically significantly better than placebo at the 1-sided significance level of 0.1 (1-sided p=0.084), with a difference in mean change in HAM-A total score from baseline (lorazepam 2 mg BID – placebo) of -1.4 after 4 weeks of treatment.

Secondary efficacy

In the HAM-A observed case (OC) analysis, AZD7325 at both doses showed a statistically significant difference compared to placebo at Week 2 at the 1-sided significance level of 0.1. For lorazepam, the difference compared to placebo was statistically significant at Day 4 and Week 2. Similar results were seen in other secondary efficacy measures where only 1 or 2 of the time points showed a statistically significant result compared to placebo for AZD7325 and lorazepam.

Neither AZD7325 doses improved the quality of life and sleep during the study. Lorazepam did not improve the quality of life but improved sleep quality during the study.

**Summary of PK results**

The PK exposure of AZD7325 at steady-state was assessed in GAD subjects using single timepoint plasma-concentration data. The results indicated plasma exposure of AZD7325 increased with doses.

A significant number of plasma samples had AZD7325 levels below limit of quantification in both dose groups in this study. Even though this increased the overall variability, plasma exposure in GAD subjects when their plasma concentrations were detectable were comparable to those data found in the healthy volunteers (by comparing the results from previous single and multiple ascending dose studies), and maintained steady state over a 28-day dosing period.

**Summary of safety results**

There were no SAEs or deaths in this study. Adverse events were the most common reason for discontinuation from the studies. The highest rate of AE-related discontinuations was seen in the AZD7325 15 mg BID dose group (13%). The CNS-related AEs were the most common adverse class associated with AZD7325. Dizziness was the most common single AE with AZD7325 with rates up to 30% in the 15 mg BID dose groups. Somnolence was the second most common AE and was seen in the AZD7325-treated groups at higher rates than in the placebo group. The rate of somnolence was 12% in the placebo group, 17% in the 5 mg BID group, 19% in the 15 mg BID group and 32% in the lorazepam group. These data suggest that AZD7325 is not placebo-like in terms of causing somnolence, yet causes less sedation than lorazepam.

Discontinuation of AZD7325 treatment did not result in withdrawal symptoms. Adverse event frequency during the first week after discontinuation was 18.7% in placebo, 18.3% in 5 mg BID, 20.7% in 15 mg BID and 18.5 % in the lorazepam groups. The RPSC and TDSS results support this conclusion.

There were no significant trends in laboratory evaluations, ECG, or vital signs. Seven subjects had either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations above 3x upper limit normal. However, these subjects were equally distributed across the AZD7325, lorazepam and placebo groups. The highest ALT level in these studies was 504 IU/L, which was seen in the lorazepam group.