AstraZeneca

**Clinical Study Report Synopsis**

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| Drug Substance | AZD7325 |
| Study Code | D1140C00006 |
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# A Multi-Center, Randomized, Placebo-Controlled, Double-Blind, Parallel Group, Efficacy and Safety Study of AZD7325 in the Treatment of Generalized Anxiety Disorder (GAD)

**Study dates:** First subject enrolled: 08 December 2008
Last subject last visit: 15 May 2009

**Phase of development:** Therapeutic exploratory (II)

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

## Study centers

This study was conducted at 44 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 versus placebo in the treatment of anxiety symptoms in subjects with Generalized Anxiety Disorder (GAD) | Change in the Hamilton Rating Scale for Anxiety (HAM-A) total score from randomization to Day 28 | Efficacy |
| **Secondary** | **Secondary** | |
| To characterize the time course and effect of AZD7325 on anxiety symptoms versus placebo in subjects with GAD | At each assessment timepoint: Change from randomization in Hospital Anxiety and Depression Scale for Anxiety (HADS-A) score, Clinical Global Impression-Global Improvement (CGI-I), change from randomization in Clinical Global Impression-Severity of Illness (CGI-S) scores, remission (HAM-A ≤7,) response (≥50% decrease from randomization in HAM-A score), and change from randomization in HAM-A psychic and somatic clusters | Efficacy |
| To evaluate the effect of AZD7325 versus placebo on the health-related quality of life (QoL) of subjects with GAD | Change in each Sheehan Disability Scale (SDS) domain score of work/school, social life, and family life/home responsibilities, and SDS global total score, from randomization to each assessment timepoint | Patient-reported outcomes (PRO) (QoL) |
| To evaluate the safety and tolerability of AZD7325 in subjects with GAD | Change in physical examination results from screening, change in laboratory values, vital signs, and electrocardiogram (ECG), changes in blood glucose and lipids, adverse events (AEs), AEs related to somnolence, AEs leading to withdrawal, incidences of suicidality, changes in weight, and discontinuation symptoms as assessed by Rickels Physician Symptom Checklist (RPSC) | Safety |

| Objectives | Outcome variables | Type |
|---|---|---|
| **Exploratory** | **Exploratory** | |
| To explore the onset effect of AZD7325 on anxiety symptoms in subjects with GAD | • ≥ 30% sustained response from Day 7 defined by ≥ 30% decrease in HAM-A from randomization and maintained at Days 14, 21, and 28;<br>• ≥50% sustained response from Day 7, defined by ≥50% decrease in HAM-A from randomization and maintained at Days 14, 21, and 28;<br>• time to ≥30% sustained response,<br>• time to ≥50% sustained response | Efficacy |
| To investigate the effect of AZD7325 on symptoms of depression in subjects with GAD | Change in Montgomery-Asberg Depression Rating Scale (MADRS) total score and HADS-D total score from randomization to Days 14 and 28 | Efficacy |
| To investigate the effect of AZD7325 on sleep in subjects with GAD | Change in Pittsburgh Sleep Quality Index (PSQI) from randomization to Day 28 | PRO (QoL) |
| 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. They may also be used to study genetic factors related to GAD.To be reported separately. | PGx (optional) |

Note: The results from the exploratory objectives are not included in the Clinical Study Report (CSR) synopsis, but are presented in CSR D1140C00006.

## Study design

This was a Phase II, multi-center, double-blind, randomized, placebo-controlled, parallel group, proof-of-concept monotherapy study to determine the effect of AZD7325 on symptom improvement in subjects with GAD.

## Target subject population and sample size

Male or female subjects (18 to 65 years of age, inclusive) with a diagnosis of GAD as confirmed by the Mini-International Neuropsychiatric Interview (MINI), were randomly

assigned to receive AZD7325 at doses of 2 mg twice daily (BID) (morning and evening), 5 mg BID (morning and evening), 10 mg once daily (QD), or matching placebo tablets.

The sample size was calculated to ensure 80% power and based on an anticipated difference of 3 units from placebo and a standard deviation (SD) of 8 for the change in HAM-A total score from baseline to Day 28. Using a 1-sided test at an overall 10% significance level (corresponding to $\alpha$=0.042 for a pair-wise comparison to placebo using the Dunnett's procedure) yielded a planned sample size of 96 evaluable subjects per arm and 384 evaluable subjects in total. Assuming an approximately 6% unevaluable rate, it was estimated that 408 subjects (102 subjects per arm) would be needed to be randomized to obtain 384 evaluable subjects.

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

AZD7325 2 mg, AZD7325 5 mg, or placebo was administered twice daily (in the morning and evening). AZD7325 10 mg was administered once daily in the morning. Subjects in the AZD7325 10 mg QD treatment regimen received placebo in the evening to ensure that the number of tablets was identical for all 4 treatment regimens (each subject received 2 tablets in the morning and 2 tablets in the evening). The tablets were taken orally with water either 1 hour before or 2 hours after a meal or breakfast.

**Duration of treatment**

The study consisted of a screening/washout/lead-in period of between 7 and 28 days; a 28-day double-blind treatment period with 1 of 4 treatment regimens (AZD7325: 2 mg BID, 5 mg BID, and 10 mg QD, or placebo); and a 7-day post-treatment period. Subjects were assigned to 1 of the 4 treatment regimens in a 1:1:1:1 ratio.

**Statistical methods**

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

The statistical analysis focused on the comparisons between each of the AZD7325 doses and placebo. No statistical comparisons were made between the three AZD7325 doses.

Descriptive statistics are used to present efficacy and safety variables. For continuous variables, n, mean, SD, median, minimum (min), and maximum (max) are presented. For categorical variables, n, frequency, and percentage are presented.

**Subject population**

A total of 424 subjects were randomized. Of these, 83.5% (354/424 subjects) completed the study (both the treatment and follow-up periods) and 70 subjects (70/424, 16.5%) withdrew

early (all during the treatment period). The most common reason for discontinuation was due to an AE (27/70 subjects, 38.6%). In general, baseline demographic data were balanced across treatment groups. Most subjects enrolled in this study were White (69.2%) and between 40 and 65 years old (56.1%); the average age was 41.5 years.

**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 to Week 4 in HAM-A score was compared between each of the 3 AZD7325 groups and placebo, with last observation carried forward (LOCF) in the modified intent-to-treat (mITT) population. 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, including placebo, indicating improvement in all groups. The AZD7325 10 mg QD and 5 mg BID treatment groups showed the greatest mean change from baseline to Week 4 (-11.5 and -11.1, respectively). However, for all AZD7325 groups, the mean change in HAM-A total score from baseline for was not statistically significantly superior to that for placebo at the 1-sided significance level of 0.1—the Dunnett's adjusted 1-sided p-values were 0.734, 0.681, and 0.490, respectively, for the 2 mg BID, 5 mg BID, and 10 mg QD groups.

Secondary efficacy

The time course and effect of AZD7325 on anxiety symptoms in subjects with GAD were assessed by the secondary efficacy variables from baseline to each assessment point.

At all doses tested in this study, AZD7325 was not effective at treating anxiety symptoms in subjects with GAD as assessed by the HAM-A total score change from baseline to Day 28. In a selected secondary analysis of the primary endpoint (HAM-A Observed Cases), AZD7325 showed a statistically significant difference compared to placebo at week 2, 3 and 4 in the 10 mg QD dose group.

At Week 4, the mean change from baseline in MADRS total score was statistically superior to placebo. However, this finding was not supported by the results of HADS-D, a self-reported measure of depression.

**Summary of PK results**

The PK exposure of AZD7325 at steady-state was assessed in GAD subjects using single timepoint plasma-concentration data at each visit. Results indicated that there was a dose-dependent increase in plasma exposure between 2 mg and 5 mg BID. The concentration ranges within the dosing interval (ie, 12 hours post the last dosing for BID and 24 hours for

QD) for 2 mg BID, 5 mg BID, and 10 mg QD were 0 to 37.4, 0 to 125, and 0 to161 ng/mL, respectively. Their median values were 4.04, 8.23, and 5.54 ng/mL, respectively.

A large portion of plasma samples and subjects from all dose cohorts exhibited AZD7325 plasma concentrations below limit of quantification in this trial. Even though this increased the measurement variability, plasma concentrations in GAD subjects when their plasma concentrations were detectable were, in most cases, comparable (visually) to those found in healthy volunteers (results adopted from previous multiple ascending dose [MAD] studies) and maintained steady state over a 28-day period of dosing.

**Summary of safety results**

Overall, 73.2% of subjects experienced at least 1 AE during the study. The number of subjects experiencing any AE was similar across all treatment groups. No deaths were reported in this study.

Four subjects (0.9%) experienced serious (SAEs) during the study (2 each in the 2 mg BID and 5 mg BID groups). No SAEs were reported in the placebo and 10 mg QD groups. The number of subjects who experienced at least 1 AE related to the IP was higher in the 10 mg QD group (71/105, 67.6%) than in the 2 mg BID (58/106, 54.7%), 5 mg BID (66/106, 62.3%) or placebo (57/105, 54.3%) group.

Twenty-eight subjects (6.6%) experienced AEs leading to discontinuation of IP. A slightly higher number of subjects discontinued IP due to an AE in the 10 mg QD group than in the placebo, 2 mg BID and 5 mg BID groups.

Twenty-seven subjects (6.4%) had AEs leading to withdrawal from the study. The most frequently reported AEs leading to discontinuation from the study were dizziness and mental impairment, followed by sedation and somnolence.

One suicide attempt was observed during the post-treatment period. This event occurred after the study was completed and was therefore considered unrelated to the IP.

There were no notable changes over time in vital signs, hematology, clinical chemistry or ECG findings in any treatment group.

No subjects in any treatment group had a MADRS item 10 score of $\geq$4.

There were no notable differences among treatment groups in discontinuation symptoms as assessed by the change from baseline RPSC total score during the follow-up period.