AstraZeneca

**Clinical Study Report Synopsis**

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| Drug Substance | AZD7268 |
| Study Code | D1151C00005 |
| Edition Number | 1 |
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# A Phase IIa, Multi-center, Randomized, Double-Blind, Double-Dummy, Active and Placebo Controlled, Parallel Group Study to Assess the Efficacy and Safety of AZD7268 in Patients with Major Depressive Disorder

**Study dates:** First subject enrolled: 16 November 2009
Last subject last visit: 15 April 2010

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

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents. This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

## Study center(s)

This study was conducted at 17 centers in the US.

## Publications

None

## Objectives and criteria for evaluation

Table S1 presents objectives and criteria for evaluation.

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

| Objectives | Outcome variables | Type |
|---|---|---|
| **Primary** | **Primary** | |
| To prove the principle that AZD7268 reduces depressive symptoms in patients with MDD compared with placebo as assessed by change from baseline to Week 4 in the MADRS total score | Change in the MADRS total score from baseline to Week 4 | Efficacy |
| The following secondary assessments were also evaluated: MADRS response, MADRS remission, changes from baseline in 17-item HAM-D total, HAM-D item 1, IVRS HAM-D total, CGI-S, and QIDS-SR total scores, and CGI-I response | | Efficacy |
| **Secondary** | **Secondary** | |
| To determine if AZD7268 reduces anxiety symptoms in patients with MDD compared with placebo as assessed by the change from baseline in HAM-A total, psychic anxiety subscale, and somatic anxiety subscale scores | Change from baseline in HAM-A total, psychic anxiety subscale, and somatic anxiety subscale scores | Efficacy |
| To determine if AZD7268 reduces overall pain symptoms in patients with MDD compared with placebo as assessed by the change from baseline in VAS pain score | Change from baseline in VAS pain score | Efficacy |
| To determine if AZD7268 reduces functional impairment in patients with MDD compared with placebo as assessed by the SDS total score | SDS total score | Efficacy |
| To evaluate the safety and tolerability of AZD7268 in patients with MDD compared with placebo as assessed by vital signs measurements, weight, physical examination, clinical laboratory evaluations, ECGs, C-SSRS, and the incidence of AEs | Vital signs measurements, weight, physical examination, clinical laboratory evaluations, ECGs, C-SSRS, and the incidence of AEs | Safety |
| To investigate pharmacokinetic properties of AZD7268 in patients with MDD using a population PK analysis methodology (reported separately from the clinical study report) | | PK |

| Objectives | Outcome variables | Type |
|---|---|---|
| **Exploratory** | | |
| To determine if AZD7268 reduces depressive symptoms in MDD patients with comorbid anxiety (see Section 3.3.6.4 of the SAP for definition) compared with placebo as assessed by the change from baseline in the MADRS total score, MADRS response, MADRS remission, changes from baseline in HAM D total scores, IVRS HAM-D total scores, CGI S, and QIDS-SR total scores, and CGI-I response | To be reported separately | Efficacy |
| To determine if AZD7268 reduces anxiety symptoms in MDD patients with comorbid anxiety (see Section 3.3.6.4 of the SAP for definition) compared with placebo as assessed by the change from baseline in HAM-A total scores, psychic anxiety subscale scores, somatic anxiety subscale scores | To be reported separately | Efficacy |
| To collect and store DNA samples for future exploratory research into genes/genetic variations that may influence response to disposition, efficacy, safety, and tolerability of AZD7268 | To be reported separately | Pharmacogenetic |
| To collect samples for an exploratory study regarding the efficacy of AZD7268 in the treatment of depression using MAP | To be reported separately | PD |
| To perform exploratory analysis of AZD7268 exposure-response relationship | To be reported separately | PK |
| (Optional) To perform exploratory analysis of escitalopram exposure-response relationship | To be reported separately | PK |

AE Adverse event; CGI-I Clinical Global Impression – Improvement, CGI-S Clinical Global Impression-Severity, C-SSRS Columbia Suicide Severity Rating Scale, ECG Electrocardiogram, HAM-A Hamilton Rating Scale for Anxiety, HAM-D Hamilton Rating Scale for Depression, MAP Human Multi-Analyte Panel Version 1.6, MDD Major Depressive Disorder, MADRS Montgomery-Åsberg Depression Rating Scale, PD Pharmacodynamic; PK Pharmacokinetic; SDS Sheehan Disability Scale, QIDS-SR Quick Inventory of Depressive Symptoms-Self Report, VAS Visual Analog Scale

## Study design

This study was a multi-center, double-blind, double-dummy, randomized, parallel-group, active and placebo-controlled Phase IIa study conducted to assess the efficacy, safety, and tolerability of AZD7268 in the treatment of patients with Major Depressive Disorder (MDD). The Screening Period was up to 28 days prior to randomization into the study. Patients randomized on Day 1 (Visit 2) to 1 of 3 treatment arms returned for 4 visits at 1-week intervals during the treatment period and followed up by phone 1 week after completion of treatment.

**Target subject population and sample size**

The target population was male and female patients between the ages of 18 and 65 years old inclusive, with documented clinical diagnosis of MDD. In addition, patients were required to have a clinician-rated Hamilton Rating Scale for Depression (HAM-D) total score ≥20 and a HAM-D Item 1 (depressed mood) score ≥2 both at enrollment and randomization (Visit 2) to be eligible for the study.

Assuming a 2-sided test at an alpha level of 0.20, a sample size of 88 evaluable patients per arm would provide 90% power to detect an effect size of 0.389 between the AZD7268 and placebo groups with regard to the primary outcome variable of change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score. An effect size of 0.389 corresponds to a placebo-adjusted difference on the MADRS total score of 3.5 points with an assumed standard deviation of 9 points. By including an active control group and using a 2:2:1 randomization ratio, a total of 220 evaluable patients was required. Assuming a non-evaluability rate of 8%, 240 patients were to be randomized.

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

AstraZeneca supplied the investigational products to the investigator and were supplied as capsules (AZD7268) or tablets (encapsulated escitalopram) for oral use. Placebo was supplied as capsules matching AZD7268 and encapsulated escitalopram tablets to ensure blinding of the study.

Daily doses and treatment regimens were administered as described below:

- The AZD7268 15 mg BID arm consisted of 3 AZD7268 5 mg capsules (batch number 27264.1) dosed orally in the morning and evening. In addition, 2 placebo tablets to match encapsulated escitalopram tablets (batch number ST76062-001-FA02) were dosed orally in the morning only.

- The placebo arm consisted of 3 placebo capsules to match AZD7268 capsules (batch number 27931.1) dosed orally in the morning and evening. In addition, 2 placebos to match encapsulated escitalopram tablets (batch number ST76062-001-FA02) were dosed orally in the morning only.

- The escitalopram 20 mg QD arm consisted of 3 placebo to match AZD7268 capsules (batch number 27931.1) dosed orally in the morning and evening. In addition, during Week 1, one encapsulated 10-mg escitalopram tablet (batch number 27795.1) and 1 placebo to match encapsulated escitalopram tablet (batch number ST76062-001-FA02) were dosed orally in the morning only. During Weeks 2 through 4, two encapsulated 10-mg escitalopram tablets were dosed orally in the morning only.

On Day 1, patients were asked to take only the evening dose. Study drug was taken with approximately 240 mL of water.

**Duration of treatment**

The duration of the patient's participation was up to 64 days including a screening period of up to 28 days, 28 days of treatment, and a follow-up phone contact, 7-days after the completion of the treatment period. At Visit 2, after a washout period of 7 to 28 days, patients were randomized to receive 1 of the 3 treatment arms: AZD7268 15 mg BID, placebo, or escitalopram 20 mg QD at a randomization ratio of 2:2:1 for 28 days. If the patient was currently not being administered medications requiring washout, the patient was randomized once the inclusion/exclusion criteria had been met.

**Statistical methods**

Except for the primary efficacy variable (as noted below), all hypotheses were tested with two-sided tests at the 0.05 level of significance. No adjustments to the reported p-values were made for analyses of multiple secondary variables. Where appropriate, model-based point estimates were presented together with 2-sided 95% confidence intervals (CIs). Missing data were handled using the last observation carried forward (LOCF) approach, as appropriate.

The primary efficacy variable, change from baseline to Week 4 in MADRS total score, was analyzed using a mixed effects repeated measures model (MMRM) including treatment group, visit and treatment-by-visit interaction as fixed factors, center as a random factor and baseline MADRS total score as a covariate. The primary comparison was the difference between the AZD7268 and placebo groups at Week 4. Proof of principle was declared if the difference was less than zero and the 2-sided p-value was significant at the 0.20 level. Analysis of covariance (ANCOVA) methods were used for the analysis of the LOCF change from baseline in MADRS total score. The ANCOVA model included baseline score as a covariate, treatment group as a fixed factor, and center as a random factor. The comparison of interest was the difference between the AZD7268 and placebo groups at the end of treatment (ie, the LOCF value).

Methods similar to the MMRM methods described above were used for the analyses of the following variables: change from baseline in HAM-D total, HAM-D Item 1, Clinical Global Impression - Severity (CGI-S), Interactive Voice Response System (IVRS) HAM-D total, Quick Inventory of Depressive Symptoms-Self Report (QIDS-SR) total, Hamilton Rating Scale for Anxiety (HAM-A) total, HAM-A psychic anxiety subscale, HAM-A somatic anxiety subscale, Visual Analog Scale (VAS) pain, and SDS total scores. For each model, the comparison of interest was the difference between the AZD7268 and placebo groups at Week 4. Methods similar to the ANCOVA methods described above were used for the analysis of the following LOCF variables: change from baseline in HAM-D total, CGI-S, IVRS HAM-D total, and HAM-A total scores.

A MADRS response was defined as a decrease from baseline in MADRS total score of 50% or greater. A MADRS remission was defined as a MADRS total score of 10 or less. A Clinical Global Impression - Improvement (CGI-I) response was defined as a CGI-I score equal to 1 ("very much improved") or 2 ("much improved"). The presence of comorbid anxiety was defined as a HAM-A total score of 16 or greater. Logistic regression methods were used for the analysis of the LOCF MADRS response indicator. The logistic regression

model for MADRS response and remission included terms for center, treatment group and baseline MADRS total score. The model for CGI-I response included the CGI-S baseline score. The comparison of interest was the difference between the AZD7268 and placebo groups at the end of treatment.

Exploratory analyses were conducted using MMRM methods to determine if AZD7268 reduced depressive symptoms in MDD patients with comorbid anxiety (as defined above) compared with placebo, as assessed by the following variables: change from baseline in the MADRS total score, MADRS response, MADRS remission, changes from baseline in HAM-D total, IVRS HAM-D total, CGI S, and QIDS-SR total scores and CGI-I response. Exploratory analyses were also conducted using MMRM methods to determine if AZD7268 reduced anxiety symptoms in MDD patients with comorbid anxiety compared with placebo as assessed by the change from baseline in HAM-A total score, psychic anxiety subscale and somatic anxiety subscale scores.

Efficacy analyses were conducted using the full analysis set (FAS) and the pharmacokinetic compliant analysis set (PKCAS). The PK fully compliant analysis set (PKFCAS) was used for a limited set of analyses. Safety data were analyzed using the safety analysis set. The PK analyses were conducted using the PK analysis set.

**Subject population**

As planned in the protocol, patients were randomized in a ratio of approximately 2:2:1 to AZD7268, placebo, and escitalopram. The percentages of patients completing the study were comparable across study groups. Furthermore, the distributions of gender, race, and age, and the average baseline MADRS total score, as well as concomitant medication use and treatment compliance, were similar across the 3 treatment groups. Overall, the study population evaluated in this study was typical of patients in other clinical studies evaluating the safety and efficacy of antidepressant treatment.

**Summary of efficacy results**

Overall efficacy

The primary efficacy analysis was an MMRM analysis for the FAS and PKCAS for the change in MADRS total score from baseline to Week 4. No significant treatment effect was observed for the AZD7268 group compared to the placebo group or for the escitalopram group compared to the placebo group.

Overall, across multiple secondary efficacy analyses, neither the AZD7268 group nor the escitalopram group showed marked separation from the placebo group.

Efficacy in patients with comorbid anxiety

In the sub-population of patients with comorbid anxiety, defined as those with a baseline HAM-A score ≥16, numerically greater reductions in the primary efficacy variable were observed for AZD7268 versus placebo for FAS and for PKCAS.

In the secondary efficacy analyses for patients with comorbid anxiety, the AZD7268 group showed numerically greater reductions as compared to placebo in HAM-D total, CGI-S, QIDS-SR, HAM-A total, VAS, and SDS total scores. In addition, AZD7268 patients had numerically higher proportions of patients achieving criteria for MADRS response, MADRS remission, and CGI-I response.

**Summary of safety results**

The overall incidence of AEs was higher in the escitalopram group (72.0%) than the AZD7268 group (54.2%) and the placebo group (50.5%). There were no deaths or non-fatal SAEs in the study. Across treatment groups, most AEs were mild or moderate. The following severe AEs were each reported once in the placebo group: blood creatinine phosphokinase increased, headache, irritability, and nasopharyngitis. The following severe AEs were each reported once in the escitalopram group: gastroenteritis, headache, and sedation. No severe AEs were reported in the AZD7268 group.

The number of patients with AEs considered by the investigator to be related to treatment was higher in the escitalopram group (54.0%) than in the AZD7268 group (41.7%) or placebo group (34.3%). Dry mouth, fatigue, diarrhea, dizziness, somnolence, headache, libido decreased, and nausea were among the most common treatment-related AEs. The following common treatment-related AEs occurred most frequently in the AZD7268 treatment group: dry mouth (AZD7268: 13.5%; placebo: 9.1%; escitalopram: 6.0%), fatigue (AZD7268: 5.2%; placebo: 1.0%; escitalopram: 2.0%), and dizziness (AZD7268: 4.2%; placebo: 1.0%; escitalopram: 4.0%). The following common treatment-related AEs occurred most frequently in the escitalopram treatment group: diarrhea (AZD7268: 4.2%; placebo: 4.0%; escitalopram 10.0%), nausea (AZD7268: 3.1%; placebo: 4.0%; escitalopram: 12.0%), and somnolence (AZD7268: 4.2%; placebo: 3.0%; escitalopram: 6.0%), and libido decreased (AZD7268: 0%; placebo: 1.0%; escitalopram: 6.0%). Treatment-related headache occurred most frequently in the placebo group (AZD7268: 6.3%; placebo: 13.1%; escitalopram: 12.0%).

The percentage of subjects withdrawing from the study due to AEs was small in each treatment group (4.2% in the AZD7268, 3.0% in the placebo group, and 4.0% in the escitalopram group). Of 234 subjects treated, the IP was discontinued due to AEs for only 9 subjects (4 treated with AZD7268, 3 with placebo, and 2 with escitalopram). The 9 subjects experienced a total of 23 AEs, all non-serious. The majority of these AEs (14 of 23) were mild, 8 were moderate, and 1 (irritability) was severe. The AEs experienced were from the following SOCs: Psychiatric Disorders (7 AEs), Gastrointestinal Disorders (5), General Disorders and Administrative Site Conditions (5), Nervous System Disorders (4), and Skin and Subcutaneous System Disorders (2). At study completion, all AEs had resolved, except for subject E1015013, whose AEs (apathy, confusional state, dry mouth, initial insomnia, and

thirst) remained ongoing.

No clinically meaningful changes in laboratory parameters, ECG, or physical examination results were observed.

Overall, AZD7268 was generally safe and well tolerated.

**Summary of pharmacokinetic results**

Not applicable

**Summary of pharmacodynamic results**

Not applicable

**Summary of pharmacokinetic/pharmacodynamic relationships**

Not applicable

**Summary of pharmacogenetic results**

Not applicable