Clinical Study Report Synopsis

Drug Substance	AZD6765
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A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase IIb Efficacy and Safety Study of Adjunctive AZD6765 in Patients with Major Depressive Disorder (MDD) and a History of Inadequate Response to Antidepressants

Study dates:	First subject enrolled: 16 December 2011
	Last subject last visit: 26 August 2013
Phase of development:	Therapeutic exploratory (IIb)

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

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To evaluate the efficacy of AZD6765iv (50 mg or 100 mg/infusion) as adjunct to current antidepressant medication versus antidepressant medication + placebo as assessed by the change from baseline to Week 6 in the MADRS total score in patients with MDD (DSM IV TR 296.2x or 296.3x) who exhibited an inadequate response to 3 or more different antidepressant treatments by history.	Primary: Change from baseline to Week 6 in the MADRS total score
Secondary	Efficacy	To evaluate the efficacy of 50 mg and 100 mg AZD6765 as adjunct to current antidepressant medication versus antidepressant medication + placebo in patients with MDD who exhibited an inadequate response to 3 or more different antidepressant treatments by history.	Key Secondary: Change from baseline to Week 12 in MADRS total score Key Secondary: Percentage of patients with sustained response from Week 6 to 12 Change from baseline in MADRS total score Percentage of patients who are responders (defined as a ≥50% reduction from baseline on the MADRS total score) Percentage of patients who are remitted (defined as a ≤10 on the MADRS total score) Change from baseline in functional impairment as measured by the SDS total score

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
			Change from baseline in severity of depressive symptoms as measured by CGI-S scale
			Improvement of depressive symptoms as measured by CGI-I scale
			Change from baseline in severity of depressive symptoms as measured by QIDS-SR-16 total score
Safety	Safety	To assess the safety and tolerability of AZD6765 as adjunct to current antidepressant medication versus antidepressant medication + placebo in the treatment of patients with inadequate response to antidepressant treatments as assessed by AEs, vital signs, ECG, laboratory measures, the C-SSRS, and the CADSS total scores	AEs/SAEs, including their severity
			AEs leading to treatment discontinuation or study withdrawal
			Suicidality as measured by AEs of suicidality, suicidal ideation, suicide attempts, and suicide completion
			OAEs, other AEs of special interest
			Change from baseline in physical examination results, weight, BMI, vital signs, clinical laboratory test results, and ECG results
			Suicidality as assessed by C-SSRS
			Dissociative symptoms after infusion as assessed by the percentages of patients with CADSS total scores in the following categories: low (0 to 2), medium (3 to 10), high (11 to 25) and very high (≥26), after infusion
Safety	Safety	To assess any changes from baseline in cognition via CogState testing	Change from baseline in cognition as measured by a composite test score based on the following CogState test battery tasks: Detection, Identification, One-card Learning, and One-back
Exploratory[a]	Pharmacogenetic	To conduct an exploratory analysis of whether family history of alcohol abuse and the GABRA2 genes are involved in the efficacy of AZD6765 treatment	DNA extracted from the optional blood samples may be used to explore whether family history of alcohol abuse and the GABRA2 genes are involved in the efficacy of AZD6765 treatment

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory [a]	Safety	To conduct an exploratory analysis of whether AZD6765, as adjunct to current antidepressant medication versus antidepressant medication + placebo:	Change from baseline in the HAM-A total score
		- improves anxiety as measured by HAM-A total score	Reduced suicidal ideation measured by S-STS
		- reduces suicidal ideation as measured by S-STS	

[a] Results are reported separately from the CSR.

AEs adverse events; BMI body mass index; CADSS Clinician Administered Dissociative States Scale; CGI-I Clinical Global Impression-Improvement; CGI S Clinical Global Impression-Severity; CSP clinical study protocol; CSR clinical study report; C-SSRS Columbia-Suicide Severity Rating Scale; DSM-IV-TR Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; ECG electrocardiogram; GABRA2 GABA A receptor alpha 2; HAM-A Hamilton Depression Rating Scale for Anxiety; MADRS Montgomery-Åsberg Depression Rating Scale; MDD major depressive disorder; OAEs other significant AEs; PK pharmacokinetic; QIDS-SR-16 Quick Inventory of Depressive Symptomology Self-Report 16-item scale; SAEs serious adverse events; SDS Sheehan Disability Scale; S-STS Sheehan Suicidality Tracking Scale.

Study design

This was a global, multicenter, randomized, double-blind, parallel group, placebo-controlled, Phase IIb efficacy and safety study of 2 dose groups conducted at approximately 60 sites in patients with major depressive disorder (MDD) who had a lifetime history of inadequate response to 3 or more antidepressant treatments, 1 of which must include a current antidepressant medication.

The study consisted of a screening period of up to 42 days (or ≤6 weeks). Patients were then randomized to a 12-week, double-blind, placebo-controlled, outpatient infusion treatment period of AZD6765 50 mg, 100 mg, or placebo, followed by a 14-day follow-up visit.

Target subject population and sample size

The target population consisted of male and female patients (aged 18 to 70 years inclusive) currently meeting criteria for a major depressive episode and meeting lifetime criteria of MDD (single episode or recurrent), as confirmed by the Mini-International Neuropsychiatric Interview (MINI).

At screening, a patient had to be taking at least 1 antidepressant medication for a minimum of 4 weeks, and meet minimum scores of Hamilton Rating Scale for Depression (HAM-D-17) ≥24, CGI-S ≥5, and QIDS-SR ≥19. The patient also had to meet these minimum ratings on the day of randomization. Randomization could not occur until the treatment with the current antidepressant medication was a minimum of 6 weeks.

Previous antidepressant treatments were defined as any of the following:

1. Antidepressant medications

2. Electroconvulsive therapy (ECT)

3. Transcranial Magnetic Stimulation (TMS)

4. Vagal Nerve Stimulation (VNS)

Inadequate response was defined as treatment with 1 of the above listed treatment options sustained for adequate dose and duration, after which the patient continued to meet DSM-IV-TR criteria for a major depressive episode. The 3 or more different protocol-required inadequate responses could have occurred anytime during the life of the patient.

The sample size calculation in this study was done to ensure 90% power to show that at least 1 of the 2 AZD6765 doses was statistically significantly better than placebo with regard to the primary outcome variable, change from baseline to Week 6 in MADRS total score. The sample size was calculated by assuming a difference of 5.5 units from placebo and a standard deviation (SD) of 10 for the change from baseline to Week 6 in MADRS total score. Based on the Bonferroni multiplicity adjustment, the one-sided significance level was planned at 1.25%. Then, a sample size of 84 patients per arm was required for the primary analysis (at Week 6) to provide 90% power for each comparison. Assuming approximately 10% of information would be lost at Week 6 due to dropouts, it was estimated that a total of 282 patients (94 patients per arm) needed to be randomized.

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

All treatments were given over 60 minutes and given once per day on non-consecutive days:

- 50 mg AZD6765 infusions were given at a final volume of 100 mL at an infusion rate of 1.67 mL/min (0.833 mg/min)

- 100 mg AZD6765 infusions were given at a final volume of 100 mL at an infusion rate of 1.67 mL/min (1.667 mg/min)

- Placebo infusions were given at a final volume of 100 mL at an infusion rate of 1.67 mL/min.

Patients received multiple infusions of AZD6765 or placebo during the treatment period. There were 3 infusions administered per week during Weeks 1 through 3 (1 per day on non-consecutive days), 1 infusion per week during Weeks 4 through 6, and 1 infusion every other week during Weeks 7 through 12 (ie, infusion to occur during Week 8, Week 10, and Week 12). Patients remained on the same dose of all of their background psychoactive medication during the study, including the 14-day follow-up period. Individual batch numbers and further information are included in the clinical study report (CSR) appendix.

Duration of treatment

Eligible patients had a screening period of up to 6 weeks. Following the screening period, patients entered a 12-week double-blind treatment period followed by a 14-day follow-up period.

Statistical methods

Efficacy analyses were based on the modified intent-to-treat (mITT) analysis set that included all randomized patients who received at least 1 dose of investigational product (IP) and who have a baseline MADRS total score assessment and at least 1 post-baseline MADRS total score classified according to their randomized treatment.

Safety and tolerability assessments were based on the safety analysis set, which included all randomized patients who were given the IP, and for whom any post-dose data were available, classified according to the treatment actually received.

The primary efficacy variable, change from baseline to Week 6 in the MADRS total score, was analyzed using a Mixed Model Repeated Measures (MMRM) analysis of all of the post-baseline MADRS total scores through the end of the study (Week 14). The model included treatment, visit, treatment by visit interaction, and the baseline MADRS total score by visit as fixed effects, and site as a random effect. Restricted Maximum Likelihood (REML) with an unstructured variance-covariance matrix was used for estimation in the MMRM analysis. Each AZD6765 dose was compared with placebo.

The MMRM analysis of the primary efficacy variable, change from baseline to Week 6 in the MADRS total score, was repeated on the Per-protocol (PP) analysis set to assess the robustness of the results. This PP analysis set included only those mITT patients who had no significant protocol deviations and who received the treatment to which they were randomized.

Change from baseline in the MADRS total score at Week 12 and at the other scheduled visits was assessed using the MMRM analysis for the primary efficacy variable.

For the other continuous secondary efficacy variables (change from baseline in the CGI-S score, the SDS total score, the HAM-A total score, and the QIDS-SR-16 total score at each scheduled assessment), the same MMRM approach as for the primary efficacy variable was used for the analyses.

For the binary secondary efficacy variable with only a single post-baseline assessment (Sustained Response), the analysis was performed using logistic regression with independent variables of treatment and the baseline MADRS total score.

For the binary secondary efficacy variables with multiple post-baseline assessments (Response, Remission, and CGI-I response), the analysis was performed using a generalized linear model of the repeated measures. A logit link function was used and the statistical inferences were based on Generalized Estimating Equations. The independent variables were

treatment, visit, treatment by visit interaction term, and a baseline measurement related to the dependent analysis variable. For Response and Remission, the baseline MADRS total score was used as the baseline measurement; for CGI-I response, the baseline CGI-S score was used.

For demonstration of superiority for the primary efficacy variable (change from baseline to Week 6 in the MADRS total score) and the 2 key secondary efficacy variables (change from baseline to Week 12 in the MADRS total score and Sustained Response), a gate-keeping procedure with recycling approach was used to control the overall family-wise error rate for comparisons of the 2 AZD6765 doses with placebo and over the 3 endpoints (the primary endpoint and the 2 key secondary endpoints). Superiority of AZD6765 over placebo was shown if, following the gate-keeping procedure, either the 50 mg or 100 mg dose group demonstrated significantly better efficacy than the placebo group for at least the primary efficacy variable. No multiplicity adjustments were made for the other secondary efficacy variables.

Descriptive statistics were used to present the safety outcomes including incidences and severity of AEs and SAEs; incidences of AEs leading to treatment discontinuation and study withdrawal, incidences of AEs associated with suicidality, and incidences of OAEs; changes from baseline in physical examination results, weight, BMI, vital signs, clinical laboratory test results, and ECG results; suicidality as assessed by C-SSRS; and changes from baseline in the CADSS total scores.

Subject population

A total of 542 patients were enrolled in the study and of these, 302 patients were randomized and entered the double-blind treatment period. Of the 302 randomized patients, 99.7% received treatment, 79.5% completed treatment, and 78.8% completed the study. For patients who were not randomized, the most common reason for non-randomization was eligibility criteria not fulfilled (89.6%).

Of the 302 randomized patients, 20.2% discontinued treatment. The most common reason for discontinuation of treatment was subject decision (9.6%). The percentage of patients who discontinued treatment due to subject decision was 9.9% in the 50 mg AZD6765 group, 7.9% in the 100 mg AZD6765 group, and 11.0% in the placebo group. A higher percentage of patients in the 100 mg AZD6765 group (8.9%) discontinued treatment due to AE compared with the 50 mg AZD6765 group (2.0%) and the placebo group (4.0%).

Treatment groups were similar with regard to disposition, demographics, and baseline characteristics. The patient population recruited to the study was considered representative of the treatment-refractory target population for the AZD6765 program and was appropriate for this study. Compliance was generally high and similar for all treatment groups. The use of concomitant medications was similar across treatment groups.

Summary of efficacy results

Primary efficacy

The primary efficacy outcome variable was the change in the MADRS total score from baseline to Week 6. Higher MADRS scores indicate higher levels of depressive symptoms; thus, a negative change from baseline indicates a reduction (or improvement) in depressive symptoms.

AZD6765 (50 mg or 100 mg/infusion) as an adjunct to current antidepressant medication was not superior to antidepressant medication + placebo in reducing depressive symptoms as assessed by change in MADRS total score at 6 weeks of treatment for MDD in patients who exhibited an inadequate response to 3 or more different antidepressant treatments by history.

Mean MADRS total scores decreased from baseline to Week 6 for the AZD6765 and placebo groups, indicating a reduction in depressive symptoms in all groups. The LS mean change in MADRS total score was -14.37 for the 50 mg AZD6765 group, -14.40 for the 100 mg AZD6765 group, and -13.18 for the placebo group. Neither of the AZD6765 treatment groups had a statistically significant difference relative to placebo.

Secondary efficacy

AZD6765 was not superior to placebo for any of the secondary efficacy variables as described in Table S1.

Summary of safety results

AZD6765 at doses of 50 mg and 100 mg was safe and generally well tolerated as an adjunct to current antidepressant medication over 12 weeks of treatment for MDD in patients who exhibited an inadequate response to 3 or more different antidepressant treatments by history:

- The percentage of patients experiencing at least 1 AE during the randomized treatment or follow-up periods was 77.1% in patients who received AZD6765 and 70.0% in the placebo group. Dizziness (35.8% vs 10.0%) was the most common AE occurring at a higher incidence in patients who received AZD6765 compared with the placebo group during the randomized treatment period. Most AEs were mild or moderate in intensity. The incidence of patients experiencing AEs that resulted in discontinuation of IP was 5.5% in patients who received AZD6765 and 4.0% in the placebo group.

- During the study, 6 patients who received AZD6765 (3.0%) and 4 patients in the placebo group (4.0%) experienced SAEs. No deaths occurred in the study.

- An increase in the incidence of AEs in the prespecified categories of dizziness and abuse liability (based on FDA guidance) were noted in patients who received

AZD6765, particularly for the preferred term of dizziness. Most events were mild, and none resulted in the discontinuation of IP.

- The incidence of events of special interest was higher in patients treated with AZD6765 compared with placebo within the following prespecified AE categories: extrapyramidal syndrome and depression/anxiety AEs.

- There were no clinically meaningful differences between AZD6765 and placebo with respect to the incidence of AEs prespecified in the following safety areas of special interest: suicide/self-injury, agitation/aggression, mania/hypomania/bipolar disorders, somnolence, other sleep-related, sexual dysfunction, and rash.

- There were no clinically meaningful differences between AZD6765 and placebo in the incidence of cognitive or psychotomimetic AEs.

- The incidence of dissociative AEs was higher in patients who received AZD6765 compared with placebo. Furthermore, the incidence of dissociative AEs was higher in patients who received 100 mg AZD6765 compared with patients who received 50 mg AZD6765 or placebo.

- There were no clinically meaningful differences between AZD6765 and placebo with respect to change from randomization in physical examination results, clinical laboratory test results, vital signs, or ECG results.

- There were no clinically meaningful differences between AZD6765 and placebo in the proportion of patients developing hypertension.

- As assessed by the C-SSRS, there were no clinically meaningful differences between AZD6765 and placebo in the incidence of suicidal behavior and suicidal ideation after randomization.

- There was no clinically meaningful difference between AZD6765 and placebo with respect to cognitive decline, as assessed by CogState.

- There were no clinically meaningful differences between AZD6765 and placebo with respect to dissociative states, as assessed by CADSS.