Clinical Study Report Synopsis

Drug Substance	AZD6765
Study Code	D6702C00009
Edition Number	1.0
Date	2 September 2010

A Phase IIb, Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Efficacy and Safety Study of Adjunctive AZD6765 in Subjects with Major Depressive Disorder (MDD) with at least Moderate Symptomatology and a History of Poor Response to Antidepressants

Study dates: First subject enrolled: 31 October 2008
Last subject last visit: 4 March 2010

Phase of development: Therapeutic exploratory (IIb)

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

Study centre(s)

This study was conducted at 30 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 determine whether a superior antidepressant effect can be achieved at Week 3 with multiple infusions of AZD6765 (100 or 150 mg/infusion) versus placebo when given adjunctively with 1FDA-approved antidepressant, including SSRIs, SNRIs, bupropion or mirtazapine in patients with MDD and a history of poor response to antidepressants	Change from baseline to Week 3 in the MADRS total score	Efficacy
Secondary	**Secondary**	
To determine whether a superior antidepressant effect can be achieved at 3 days with AZD6765 (100 or 150 mg/infusion) versus placebo when given adjunctively with SSRIs, SNRIs, bupropion or mirtazapine in patients with MDD and a history of poor response	Change from baseline to 3 days in the MADRS total score	Efficacy
To evaluate the rapid antidepressant efficacy of AZD6765 at 1 day after first infusion	Change from baseline at 1 day in the QIDS-SR-16 total score	Efficacy
To determine whether AZD6765 will demonstrate a superior antidepressant efficacy compared to placebo in patients in remission (defined as MADRS total score ≤10)	Remission at each scheduled assessment and in particular at Week 3	Efficacy
To determine whether AZD6765 will demonstrate a superior response compared to placebo, in patients who are responders (defined as a ≥50% reduction from baseline in the MADRS total score)	Response at each scheduled assessment and in particular at Week 3	Efficacy
To investigate the effects of multiple infusions of AZD6765 (100 or 150 mg/infusion) on patient mood, anxiety, and perception using a battery of scales	Change from baseline at each scheduled assessment in total scores of QIDS-SR-16, MADRS, HAM-A, HAM-D, VAS and in CGI-S and CGI-I scores	Efficacy

Objectives	Outcome variables	Type
To assess the safety and tolerability of multiple infusions of AZD6765 (100 or 150 mg/infusion) via intravenous (IV) administration when administered concomitantly with other compounds used to treat depression	Incidence of adverse events (AEs), discontinuations due to AEs, serious adverse events (SAEs), death, C-SSRS; clinical laboratory test results, electrocardiogram (ECG), vital signs, weight, body mass index (BMI), physical examination; change from baseline at each scheduled assessment in total score of CADSS and BSS	Safety
Exploratory	**Exploratory**	
To evaluate the effect of adjunctive AZD6765 versus adjunctive placebo on the health-related quality of life (QoL) in patients with MDD and a history of poor response to antidepressants	Change from baseline in the QLES-Q-SF total score (sum of items 1-14) at Week 3	PRO (QoL)
To determine time to first occurrence of sustained response of AZD6765 compared to placebo	Time to first sustained response	Efficacy
To determine whether AZD6765 will demonstrate a superior sustained response compared to placebo	≥50% sustained response	Efficacy
To characterize the pharmacokinetics (PK) of AZD6765 in patients with MDD utilizing a population PK approach	AZD6765 plasma concentration levels	PK
To conduct exploratory analysis of the genes involved in the PK/PD, safety, and tolerability related to AZD6765 treatment	DNA extracted from the optional blood samples may be used to explore relationships between genetic variability and AZD6765 PK/PD, safety, tolerability, response and depression	PGx (optional)

BSS Beck Scale for Suicide Ideation; CADSS Clinician Administered Dissociative States Scale; CGI-I Clinical Global Impression-Improvement; CGI-S Clinical Global Impression-Severity of Illness; C-SSRS Columbia-Suicide Severity Rating Scale; DNA deoxyribonucleic acid; FDA Food and Drug administration; MADRS Montgomery-Åsberg Depression Rating Scale; HAM-A Hamilton Rating Scale for Anxiety; HAM-D Hamilton Depression Rating Scale for Depression; MDD major depressive disorder; PD pharmacodynamic; PGx pharmacogenetics; PRO patient reported outcome; QIDS-SR-16 Quick Inventory of Depressive Symptomatology Self-Report 16-item scale; QLES-Q-SF Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form; SNRI serotonin-norepinephrine reuptake inhibitors; SSRI selective serotonin reuptake inhibitors; VAS (Bond-Lader) Visual Analog Scale.

Note: The results of the exploratory objective for QLES-Q-SF are not included in the Clinical Study Report (CSR) synopsis but are presented in CSR D6702C00009. The PK results are not included in the CSR but will be reported as a separate population PK report. There is currently no plan to conduct PGx exploratory analyses.

Study design

This was a Phase IIb, multicenter, double-blind, randomized, placebo-controlled, parallel group, outpatient study to determine the effect of AZD6765 on symptom improvement in patients with MDD who had a history of poor response to antidepressants. History of poor response was defined as treatment failure on 1 or more antidepressants (in addition to the antidepressant the patient was taking at enrollment) after exposure at adequate doses or maximum tolerated doses for ≥4 weeks.

Target subject population and sample size

Pre-amendment criteria: Prior to Amendment 3, a baseline HAM-D score of ≥26, CGI-S score of ≥5, and QIDS-SR-16 score of ≥21 was required. Amendment 3 refined the study design to allow greater enrollment but also clarified both the schedule of infusions as well as use of other medications. The study population was no longer restricted to patients with severe MDD. MDD with a history of poor response remained an inclusion criterion. The inclusion criteria was loosened to include patients with baseline HAM-D ≥20, CGI-S ≥4, and QIDS-SR-16 ≥16 and to permit entry for less severe disease. Patients who were considered screening failures under the entrance criteria outlined in the previous version of the protocol, but would have qualified under the revised criteria, were to be considered for re-screening.

Post-amendment criteria: Eligible patients (male or female patients 18 to 65 years of age, inclusive), with a clinically established diagnosis of MDD, single episode or MDD, recurrent as confirmed by the Mini-International Neuropsychiatric Interview (MINI) and with baseline HAM-D ≥20, CGI-S ≥4, and QIDS-SR-16 ≥16) were enrolled.

The patient population in this study had far more severe MDD compared to other studies based on the baseline HAM-D score, despite taking multiple antidepressants/psychotropics, and allowing of some suicidal ideation (HAM-D item 3 ≤2).

The sample size was calculated by assuming a treatment difference of 6 units between each AZD6765 dose and placebo, and a standard deviation (SD) of 9 for the change of MADRS total score from baseline to 3 weeks. Using a 2-sided test with α=0.05 (80% power with a multiplicity adjustment using Dunnett's procedure) yielded an overall planned sample size of 45 evaluable patients per treatment group and 135 to 140 evaluable patients in total. Assuming a 10% early withdrawal rate, it was estimated that 150 patients (50 patients per treatment group) would need to be randomized to obtain 135 to 140 evaluable patients.

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

The IP, AZD6765 or placebo (0.9% saline solution), was administered intravenously at the study center. The IP was administered under the supervision of the study personnel during the 3-week treatment period after the patient was randomized to 1 of the 3 treatment arms: 1) AZD6765 100 or 150 mg, and 2) placebo. Individual batch numbers and further information are included in the CSR appendix.

Duration of treatment

The study consisted of an up to 30-day screening and enrollment period, a 3-day placebo run-in period, a 3-week outpatient treatment period where patients were randomized to AZD6765 (100 or 150 mg) or placebo, and a 5-week outpatient follow-up maintenance period. Patients received 3 infusions per week of AZD6765 or placebo while on their current antidepressants.

Statistical methods

In general, all efficacy and safety variables are presented using descriptive statistics and graphs as appropriate. Continuous variables are presented with descriptive statistics (n, mean, standard deviation [SD], median, min, max), within treatment group.

The statistical test for the primary efficacy endpoint was set at a 2-sided significance level of 5%, based on the adjusted p-values from Dunnett's procedure. Secondary efficacy analyses were reported using the same primary efficacy model but no multiplicity adjustments were made to the p-values. Where appropriate, model-based point estimates were presented together with their 95% confidence intervals (CIs).

Subject population

Overall, a total of 152 patients were randomized to the study. Of these, 94.7% (144/152 patients) completed the treatment period, 80.9% (123/152 patients) completed the study (including treatment and follow-up periods), and 19.1% (29/152 patients) discontinued from the study. Of the 29 patients who discontinued from the study, 1 had co-morbid GAD. Two patients experienced AEs leading to permanent discontinuation of IP during the treatment period: 1 patient (2.0%) in the 100 mg group due to the AE of paraesthesia and 1 patient (2.0%) in the 150 mg group due to the AE of rash pruritic vs. none in the placebo group.

In general, baseline demographic data were similar across treatment groups, with the exception of a higher percentage of men (39.2%) in the AZD6765 150 mg group. Overall, most patients enrolled in this study were White (69.1%), and the mean age of patients was 45.6 years (range 24 to 65 years). The percentage of participating females was higher than males (67.1% females vs. 32.9% males). The mean weight and body mass index (BMI) at baseline was 85.8 kg and 30.38 kg/m^2, respectively. Mean anxiety scores (HAM-A) at baseline were 21.0 for placebo and 20.6 each for AZD6765 100 and 150 mg.

Summary of efficacy results

Primary efficacy

The primary efficacy variable was the change from baseline to Week 3 in the MADRS total score. Higher MADRS scores indicate higher levels of depressive symptoms, thus, a negative change from baseline indicates a reduction (or improvement) in depressive symptoms.

Patients treated with AZD6765 (100 mg or 150 mg per infusion) exhibited a significantly greater antidepressant effect than the placebo-treated patients, as assessed by the primary efficacy variable, change from baseline to Week 3 in the MADRS total score. The mean change from baseline was -13.4 for the 100 mg group and -12.7 for the 150 mg group vs. -7.9 for the placebo group. The difference between AZD6765 100 mg and placebo and 150 mg and placebo was –5.5 (95% CI= -9.1 to -1.9, p=0.003) and -4.8 (95% CI= -8.5 to -1.2, p=0.010), respectively. The adjusted p-values (adjusted for multiplicity) were 0.006 and 0.019, respectively; thus, the difference between the antidepressant effect of each AZD6765

group and that of the placebo group at Week 3 was statistically significant at the 2-sided 5% level of significance.

Secondary efficacy

- Patients treated with AZD6765 (100 mg or 150 mg per infusion) did not show a significantly superior antidepressant effect at 3 days vs. placebo-treated patients, as assessed by change from baseline to Day 4 (Infusion 2, T_0) in the MADRS total score. The mean change from baseline was -6.1 for the 100 mg group and -5.0 for the 150 mg group vs. -5.1 for the placebo group. The difference between AZD6765 100 mg and placebo and 150 mg and placebo was –0.9 (95% CI=–3.2 to +1.4, p=0.439) and 0.1 (95% CI=–2.3 to +2.5, p=0.933), respectively. Thus, the difference between the antidepressant effect of each AZD6765 group and that of the placebo group at 3 days was not statistically significant at the 2-sided 5% level of significance.

- Patients treated with AZD6765 (100 mg or 150 mg per infusion) did not show a more rapid antidepressant effect at 1 day after infusion vs. placebo-treated patients, as assessed by change from baseline to Day 2 in the QIDS-SR-16 total score. The mean change from baseline was -3.9 for the 100 mg group and -2.7 for the 150 mg group vs. -4.3 for the placebo group. The difference between AZD6765 100 mg and placebo and 150 mg and placebo was +0.4 (95% CI=-1.1 to +1.8, p=0.619) and +1.6 (95% CI=+0.2 to +3.0, p=0.029), respectively. Thus, the difference between the antidepressant effect of the AZD6765 100 mg group and that of the placebo group at 1 day was not statistically significant at the 2-sided 5% level of significance; but the AZD6765 150 mg group at 1 day had significantly higher depression severity compared to the placebo group at the 2-sided 5% level of significance.

- Patients treated with AZD6765 (100 mg or 150 mg per infusion) generally showed higher remission rates than the placebo-treated patients from Weeks 1 to 8. In particular, at Week 3, the remission rates for AZD6765 were 20% for 100 mg and 22% for 150 mg vs. 10% for placebo. The adjusted odds-ratios at Week 3 for 100 mg and 150 mg vs. placebo were 2.2 (95% CI=0.7 to 7.0, p=0.186) and 2.4 (95% CI=0.8 to 7.4, p=0.144), respectively. Despite a noticeable numerical advantage over placebo for both AZD6765 groups, they failed to show statistical significance at the 2-sided 5% level.

- Patients treated with AZD6765 (100 mg or 150 mg per infusion) showed consistently higher response rates than placebo-treated patients from Weeks 1 to 8. In particular, at Week 3, the response rates for AZD6765 were 37% for 100 mg and 29% for 150 mg vs. 16% for placebo. The adjusted odds-ratios at Week 3 for 100 mg and 150 mg vs. placebo were 3.3 (95% CI=1.3 to 8.8, p=0.014) and 2.1 (95% CI=0.8 to 5.7, p=0.137), respectively—statistically significant for 100 mg vs.

placebo, not statistically significant for 150 mg vs. placebo, at the 2-sided 5% level of significance.

- Patients treated with AZD6765 (100 mg or 150 mg per infusion) generally showed better results than placebo-treated patients on mood, anxiety, and quality of life as measured by a battery of scales: QIDS-SR-16, MADRS, CGI-S, CGI-I, HAM-A, HAM-D, and VAS. In particular, at Week 3, AZD6765 100 mg was statistically superior to placebo on QIDS-SR-16, MADRS, CGI-S, CGI-I, HAM-A, and HAM-D at the 2-sided 5% level; AZD6765 150 mg was statistically superior to placebo on MADRS, CGI-S, CGI-I, and HAM-A at the 2-sided 5% level.

Summary of pharmacokinetic (PK) results

PK data were collected for population PK analysis. The results are not included in the CSR but will be reported as a separate population PK report.

Summary of safety results

Both doses (100 mg and 150 mg) of AZD6765 were generally safe and well tolerated. No deaths were reported in this study. No patients reported SAEs during the treatment period. Six patients reported SAEs during the follow-up period (of these, 2/6 had previously been randomized to placebo and 4/6 had been randomized to AZD6765). One discontinuation of IP due to AE (DAE) each in the 100 mg (dizziness, confusion) and 150 mg (rash) group were reported for AZD6765 during the treatment period compared to none for placebo. No DAEs were reported in the follow-up period.

The incidence of AEs during the treatment period was higher in the AZD6765 150 mg group (78.4%) than in the AZD6765 100 mg group (64.7%) or placebo group (62.0%). The use of AZD6765 was associated with more CNS-related AEs than placebo, such as dizziness and somnolence. Of note, most of these 2 events occurred within 4 hours of infusion. Most overall AEs during the treatment period were mild or moderate in intensity.

The incidence of AEs during the follow-up period was higher in the placebo group (62.0%) than in the 100 mg (41.2%) or 150 mg (27.5%) group. Most AEs during the follow-up period were mild or moderate in intensity. Of note, 2 suicide attempts were reported as SAEs during the follow-up period (one previously randomized to the AZD6765 100 mg group and one to the 150 mg group). Neither event was considered related to IP by the investigator.

Eight patients experienced at least one AE potentially related to psychosis (as defined, a priori, in the statistical analysis plan) during the treatment period (3 patients in the 100 mg group and 5 patients in the 150 mg group). No placebo patient reported a psychosis-related AE. Further review suggested that these AEs were actually more related to dissociation-type events than psychosis, proper.

AEs potentially related to abuse potential were generally infrequent; however, the frequency noted with AZD6765 was somewhat higher than placebo.

AEs related to renal and urinary type disorders were similar in type and frequency between AZD6765 and placebo.

No clinically meaningful treatment group differences were seen in body weight, BMI, physical examination, or hematology, clinical chemistry and urinalysis findings.

Elevations in supine BP were noted after infusion of AZD6765 and were somewhat more prominent at the 150 mg dose. These elevations were transient in nature (ie, typically resolving with a period of no longer than 24 hours) and limited in degree (ie, mean elevations of 4-8 mmHg). Potentially clinically important increases in supine BP were also more frequently noted with AZD6765 patients than placebo. Additionally, AZD6765 patients were more likely than placebo to have potentially clinically significant orthostatic decreases in BP. However, only few AEs related to increased or decreased BP were reported and none led to discontinuation or required treatment or were SAEs.

ECG findings were in general similar between AZD6765 patients and placebo for most parameters. However, note is made of small ($\leq$8.2 ms) increases in mean QTcF intervals for patients randomized to AZD6765 150 mg which were not clearly noted for the placebo or 100 mg group. In addition, more patients on AZD6765 (ie, 100 mg and 150 mg) had potentially clinically important QTcF findings (ie, $\geq$450 ms threshold value and/or $\geq$60 ms increase from baseline) than did placebo patients. However, no patient had a QTcF value that exceeded 500 ms during this trial and none of these potentially clinically important elevations were associated with a clear cardiac AE; hence, the QTcF findings described here remain of uncertain clinical significance.

The incidences of suicidal ideation and suicidal behavior, as assessed by the C-SSRS, were similar between the AZD6765 and placebo groups; additionally, patients treated with AZD6765 (100 or 150 mg per infusion) showed reduced suicidal ideation and dissociation symptoms at Week 3, as assessed by the BSS and CADSS. Of note, AZD6765 patients were more likely than placebo to have minor increases in the CADSS rating scale immediately after their initial infusion with drug; however, subsequent measurements did not demonstrate a continued elevation in this score compared to placebo.