AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD6765
Study Code	D6702C00015
Edition Number	1
Date	28 November 2012

An Investigation of the Antidepressant Effects of a Low-trapping Mixed NR2A/2B Antagonist in Treatment-Resistant Major Depression

Study dates: First subject enrolled: 7 January 2010
Last subject last visit: 19 December 2011

Phase of development: Phase IIa

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

Study center

The study was conducted at The Mark O. Hatfield Clinical Research Center of the National Institute of Health Intramural Clinical Research Program in Bethesda, MD, by the National Institute of Mental Health (NIMH) under a Cooperative and Development Research Agreement. In accordance with that agreement, the study was conducted in full by NIMH personnel.

Publications

Zarate CA Jr, Mathews D, Ibrahim L, Chaves JF, Marquart C, Ukoh I, et al. A randomized trial of a low trapping non-selective N-methyl-D-aspartate (NMDA) channel blocker in major depression. Biological Psychiatry. Prepublication abstract; http://journals.elsevierhealth.com/periodicals/bps/content/1201260abs. Accessed 5 November 2012.

Objectives and criteria for evaluation

The objectives of this study and criteria for their evaluation are provided in Table S1.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To assess the efficacy of a single dose of iv AZD6765 compared with placebo in improving overall depressive symptomatology in patients with treatment-resistant MDD currently in an episode of major depression	Change from baseline in the MADRS total score
Secondary	Efficacy	To determine whether AZD6765 will demonstrate a superior antidepressant efficacy compared to placebo, as assessed by the proportion of subjects in remission (defined as MADRS total score ≤10)[a]	Proportion of subjects in remission (MADRS total score ≤10)[a]
Secondary	Efficacy	To determine whether AZD6765 will demonstrate a superior response compared to placebo, as assessed by the proportion of subjects with response (defined as a ≥50% reduction from baseline in the MADRS total score)	Proportion of subjects with response (≥50% reduction from baseline in MADRS total score)
Secondary	Efficacy	To evaluate the efficacy of AZD6765 in reducing suicidal ideation, as assessed by a change from baseline in SSI total score	Change from baseline in the SSI total score
Secondary	Efficacy	To investigate the effects of AZD6765 on mood, anxiety, perception, and cognitive function—as determined from scoring on the HDRS, VAS, CADSS, BPRS, BDI, CGI tool,[a] YMRS, and CogState[b]	Change from baseline in HAM-A, HDRS, VAS, CADSS, BPRS, BDI, CGI tool[a], YMRS and CogState[b] scores

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Safety	To assess the safety and tolerability of a single dose of AZD6765 (150 mg per infusion) via iv administration when administered to treat depression as assessed by incidence of AEs using the NIMH-DSEC, vital signs, changes in clinical laboratory evaluations, and ECGs	Incidence and nature of AEs; vital signs; weight and BMI changes; physical examination changes; clinical laboratory evaluations; ECG
Secondary	PK/PD	To explore potential PK/PD relationships between AZD6765 exposure—as determined by C_{max} and AUC at doses of 150 mg—and cognitive function, MADRS score, or both[c]	PK/PD
Exploratory		To determine if change in anterior cingulate activation to an emotional (fearful faces presentation) and a cognitive (n-back) task correlates with antidepressant response to AZD6765 in patients with treatment-resistant major depression	MEG analysis[d]
Exploratory		To determine if change in brain neurochemicals (glutamate/GABA) changes correlates with antidepressant response (decrease in MADRS total scores) to AZD6765 in patients with treatment-resistant major depression[e]	MRS analysis[e]
Exploratory		To collect blood samples to determine if 150 mg iv of AZD6765 will increase plasma/serum BDNF, and/or decrease VEGF mRNA levels in peripheral leukocytes compared to placebo and/or baseline levels	Levels of BDNF and VEGF[f]

[a] Remission was analyzed as MADRS total score <10.
[b] CGI and CogState data were not collected.
[c] This secondary objective was not evaluated.
[d] MEG data will be analyzed separately; evaluation of this objective may be included in an addendum to the clinical study report.
[e] This exploratory objective was not evaluated; MRS data were not collected.
[f] Results of this objective are reported in the CSR.

AE Adverse event; AUC Area under the curve; BDI Beck Depression Inventory; BDNF Brain-derived neurotrophic factor; BMI Body mass index; BPRS Brief Psychiatric Rating Scale; CADSS Clinician-Administered Dissociative States Scale; CGI Clinical Global Impression; C_{max} Maximum plasma concentration; CSP Clinical study protocol; CSR Clinical study report; ECG Electrocardiogram; GABA Gamma-aminobutyric acid; HAM-A Hamilton Anxiety Rating Scale; HDRS Hamilton Depression Rating Scale; iv Intravenous; MADRS Montgomery-Asberg Depression Rating Scale; MDD Major depressive disorder; MEG Magnetic encephalography; MRS Magnetic resonance spectroscopy; NIMH-DSEC National Institute of Mental Health Data Safety Event Codes; PD Pharmacodynamics; PK Pharmacokinetics; SSI Scale for Suicide Ideation; VAS Visual Analogue Scale; VEGF Vascular endothelial growth factor; YMRS Young Mania Rating Scale.

Study design

This was a randomized, double-blind, placebo-controlled, single-dose, crossover, single-site, inpatient study to assess the efficacy and safety of an intravenous (iv) infusion of 150 mg of AZD6765, a mixed NR2A/2B subunit antagonist, in patients meeting diagnostic criteria for

major depressive disorder (MDD) according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, and confirmed by the Structured Clinical Interview for the Diagnostic Manual of Mental Disorders, Fourth Edition, Patient Version.

Patients were washed out of their current medication and randomly assigned via a random numbers chart to receive either a single iv infusion of AZD6765 150 mg or saline solution over 60 minutes as the first study treatment. To avoid carry-over effects between the different test phases, there was an interval of 7 to 14 days before patients received the opposite study treatment.

Patients and staff remained blinded to the drug assignment throughout the study. Data analysis was performed with the blinding intact, and unblinding was allowed following the analysis phase.

Target subject population and sample size

Approximately 24 patients with major depression without psychotic features were to be recruited for this study to allow 20 patients to cross over. A previous pilot study of AZD6765 demonstrated improvement in depression at 72 hours with an effect size of d=0.67. Using α=0.05 (2-tailed), 20 patients with major (unipolar) depression would provide 81% power to detect an effect of the same size as previously reported with a double-blind crossover study.

A total of 22 patients were analyzed for efficacy and safety.

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

AstraZeneca supplied the investigational product, AZD6765, as 150 mg/45 mL fluid in syringes. The study center procured placebo (0.9% saline) to match the AZD6765 fluid in syringes. AZD6765 was administered via a single iv infusion, with a final volume of 30 mL given at an infusion rate of 2.50 mg/min for over 60 minutes. AZD6765 was manufactured by AstraZeneca Pharmaceuticals SE (batch number 11-000216AZ) and Recipharm, SE (batch numbers H2101-01-01-01 and C09032).

Duration of treatment

The study consisted of 3 phases. In Phase 1, patients were tapered off their current medications over a 7- to 14-day period and then entered a 14-day drug-free period. In Phase 2, patients were randomized to receive either a single iv infusion of AZD6765 (150 mg) or saline solution over 60 minutes. Patients had study procedures performed for 7 days and then started Phase 3, a single iv infusion of the other treatment. An additional 7 days between treatments were permitted to accommodate for scheduling of procedures or if response was maintained. Patients maintaining response to Phase 2 treatment after 1 week received an additional 1-week washout before being crossed over to Phase 3.

Statistical methods

The primary analysis of the difference between AZD6765 and placebo from baseline to endpoint used a linear mixed model with restricted maximum likelihood estimation where drug and all observed time points are included in a within-subjects factor. The maximum likelihood procedure permitted inclusion of patients who completed only 1 phase of the study or had missing values during the study, and the variance-covariance structure provided estimates of means to calculate test statistics. Schwarz's Bayesian Criterion was used to determine the best-fitting covariance structure, which was compound symmetry. Drug and time main effects and their interaction were included in the model. The phase-specific baseline was used as a covariate in the intent-to-treat analysis. Bonferroni post-hoc tests were used to follow up on significant drug-by-time interactions. Cohen's d was calculated for overall drug effects and drug differences at specific time points; for comparisons at specific time points, positive values indicated lower scores on AZD6765, and negative values indicated lower scores on placebo. Significance was evaluated at $p<0.05$, 2-tailed. Significance levels were reported prior to correction with the exception of post-hoc tests.

Subject population

A total of 27 patients were enrolled in the study, and 22 patients (12 males and 10 females) were randomly assigned to either AZD6765 150 mg or placebo as follows: 12 to AZD6765 150 mg→placebo and 10 to placebo→AZD6765 150 mg. One patient discontinued for administrative reasons after the first day on AZD6765, and another patient completed AZD6765 treatment but did not cross over to Phase 3 due to continued improved mood. Thus, 20 of 22 (91%) patients completed the study: 10 of 12 (83%) patients receiving AZD6765 and 10 of 10 (100%) patients receiving placebo in Phase 2 completed the other treatment in Phase 3.

The average patient age was 51.5 years, and about half (55%) of the patients were male. The average age at onset of illness was 23.3 years; the length of the current depression episode was approximately 9 years. About half (55%) of the patients had suffered from anxiety disorder at some time in their lives, and 23% had previously attempted suicide.

Summary of efficacy results

- A single iv infusion of AZD6765 150 mg rapidly improved depressive symptoms in patients with MDD without inducing psychotomimetic effects. A linear mixed model using baseline as a covariate and the Montgomery-Asberg Depression Rating Scale total score as the outcome showed a significant difference at 80 and 110 minutes by drug ($F=12.10$, $df=1,299$, $p<0.001$), where AZD6765 had lower scores than placebo ($d=0.40$). The drug-by-time interaction was not significant ($F=1.16$, $df=7,291$, $p=0.32$).

- A single iv infusion of AZD6765 demonstrated a numerically higher remission (proportion of subjects reaching remission, defined as MADRS total score <10) compared with placebo (18% [4/22] vs 10% [2/20], respectively), but the difference was not statistically significant when tested at each time point ($p=1.00$).

- A single iv infusion of AZD6765 demonstrated a numerically higher response (proportion of subjects with response, defined as a ≥50% reduction from baseline in the MADRS total score) compared with placebo (32% [7/22] vs 15% [3/20], respectively), but the difference was not statistically significant when tested at each time point ($p>0.22$).

- No statistically significant reduction in suicidal ideation was observed with single iv infusion of AZD6765 compared with placebo.

- A single iv infusion of AZD6765 demonstrated statistically significant reductions in the Hamilton Depression Rating Scale, patient-rated Beck Depression Inventory, and Hamilton Anxiety Rating Scale scores compared with placebo. However, no statistically significant differences in the Visual Analogue Scale, Clinician-Administered Dissociative States Scale, Brief Psychiatric Rating Scale, and Young Mania Rating Scale scores were observed with AZD6765 treatment compared with placebo.

Summary of pharmacokinetic results

AZD6765 plasma levels were obtained at 60, 80, 110, and 230 minutes after infusion. Plasma levels were highest at the end of infusion and declined in a biphasic manner after infusion. Exposure to AZD6765 in responders and non-responders appeared to be similar. A responder was defined as a patient who had at least a 50% improvement in the MADRS total score at any time within the first 230 minutes.

Summary of safety results

In this study, each of the 22 patients received 1 dose of AZD6765 150 mg. No deaths, other SAEs, or discontinuations due to AEs were reported in the study. The AEs reported more frequently (at least 10% more) in patients receiving AZD6765 versus placebo were dizziness/faintness (55% vs 15%); concentration difficulty (45% vs 30%); appetite decrease (41% vs 25%); woozy/loopy (45% vs 20%); spacey (41% vs 25%); feeling strange, weird, or bizarre (36% vs 15%); hypertension (36% vs 25%); confusion (27% vs 5%); flushed (27% vs 5%); numbness (27% vs 10%); tingling (27% vs 10%); delayed verbal response (23% vs 10%); increased energy (23% vs 5%); depression (17% vs 5%); euphoria (14% vs 0%); and red blotching (14% vs 0%). AZD6765 treatment was associated with a lower frequency of the following AEs compared with placebo: headache (9% vs 20%), vivid dreams (14% vs 25%), interrupted sleep (45% vs 55%), and feeling like you are dying or are dead (0% vs 10%). No differences between treatments were noted in electrocardiograms, laboratory data, vital signs, or weight.