AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2066
Study Code	D0475C00020
Edition Number	1
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A Phase IIa, Multi-centre, Randomized, Double-Blind, Double-Dummy, Active and Placebo Controlled, Parallel Group Study to Assess the Efficacy and Safety of AZD2066 after 6 weeks of treatment in Patients with Major Depressive Disorder

Study dates: First subject enrolled: 27 May 2010
Last subject last visit: 10 November 2010

Phase of development: Therapeutic exploratory (II)

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 Primary and secondary objectives and outcome variables

Objective			Variable
Priority	**Type**	**Description**	**Title and description**
Primary	Efficacy	To prove the principle that AZD2066 reduces depressive symptoms in patients with Major Depressive Disorder (MDD) compared with placebo.	**Primary variable:** Change from baseline to Week 6 in the MADRS total score **Supporting secondary variables**: MADRS response, MADRS remission, CGI-I response, CGI-I total score[a] Change from baseline in HAM-D total, HAM-D item 1, IVRS HAM-D total, CGI-S and QIDS-SR total scores[a]
Secondary	PD	To determine if AZD2066 reduces anxiety symptoms in patients with MDD, compared with placebo[a]	Change from baseline in the HAM-A total score, psychic anxiety subscale and somatic anxiety subscale scores
	PD	To determine if AZD2066 reduces functional impairment in patients with MDD compared with placebo[a]	Change from baseline in the Sheehan Disability Scale (SDS) total score Number of productive days
	Safety	To evaluate the safety and tolerability of AZD2066 in patients with MDD compared with placebo	Vital sign measurements, physical examination, clinical laboratory evaluations, electrocardiograms (ECGs), Columbia Suicide Severity Rating Scale (C-SSRS) and the incidence of AEs
	PK	To investigate pharmacokinetic properties of AZD2066 in patients with MDD	AZD2066 plasma concentration
Exploratory	Efficacy	To explore the efficacy of AZD2066 in treating pain associated with chronic depression[a]	Change from baseline in NRS pain scores

Objective			Variable
Priority	**Type**	**Description**	**Title and description**
	Efficacy	To collect samples for analysis regarding the efficacy of AZD2066 in the treatment of depression using the Human Inflammation Multi-Analyte Panel (MAP)[a]	
	PK/PD	To perform exploratory analysis of AZD2066 exposure-response relationship[a]	
	PG	Furthermore, a blood sample for genotyping will be collected and stored for future, possible exploratory research into genes/genetic variations that may influence response to disposition, efficacy, safety, and tolerability of AZD2066. In addition, susceptibility genes and genes related to underlying disease may be explored[a]	

AE Adverse Event; CGI-I Clinical Global Impression-Improvement; CGI-S Clinical Global Impression; CSP Clinical study protocol; C-SSRS Columbia Suicide Severity Rating Scale; ECG Electrocardiogram; HAM-A Hamilton Rating Scale for Anxiety; HAM-D Hamilton Rating Scale for Depression; Severity; MADRS Montgomery-Åsberg Depression Rating Scale; MDD Major Depressive Disorder; PD Pharmacodyamics; PG Pharmacogenetics; PK Pharmacokinetics; QIDS-SR Quick Inventory of Depressive Symptoms – Self Report; SDS Sheehan Disability Scale

[a] Will not be reported in the CSR

Study design

This study was a randomized, double-blind, double-dummy, active and placebo controlled parallel-group study conducted in male and female patients diagnosed with MDD who were between the ages of 18 and 65 years old inclusive.

Target subject population and sample size

60 evaluable patients were planned to be included in each of the three treatment arms AZD2066, placebo and duloxetine. With 60 patients there is 80% power for AZD2066 to be statistically significant better than placebo at a significance level of 10% (one-sided). The sample size was calculated to test the null hypothesis H0: no difference between AZD2066 and placebo with regards to the primary efficacy variable versus the alternative hypothesis H1: that the difference between AZD2066 and placebo is not equal to zero. The standard deviation was assumed to be 9.

The study was prematurely stopped after an SAE (mood elevation with a severe psychotic episode in a patient administered AZD2066) in the concurrent Phase IIa NP-MH study. Due to premature termination of the study the planned number of evaluable patients was not achieved.

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

AZD2066 capsules (2mg [Formulation# D0800252; Batch# 09-006793AZ] and 8 mg [Formulation# D0800253; Batch# 09-006795AZ]), AZD2066 placebo capsules [Formulation# D0800211; Batch# 09-003867AZ] and duloxetine placebo capsules [Formulation# D0900442; Batch# 10-002755AZ] were manufactured by AstraZeneca and were taken orally once daily. Duloxetine HCL capsules (30 mg [Formulation# D0900441; Batch# 10-002752AZ]) were manufactured by Eli Lilly and were taken orally once daily.

Duration of treatment

AZD2066 and duloxetine were administered for a total of 42 days. During Day 1 to Day 7 patients received either 12 mg AZD2066 and duloxetine placebo, 30 mg duloxetine and AZD2066 placebo or both duloxetine and AZD2066 placebo. From Day 8 to Day 42 patients received either 18 mg AZD2066 and duloxetine placebo, 60 mg duloxetine and AZD2066 placebo or both duloxetine and AZD2066 placebo.

Statistical methods

The primary efficacy variable was analyzed using a mixed effects repeated measures (MMRM) model, including center, treatment, respective baseline score, day and day-by-treatment as explanatory variables. Least square (LS) means and differences in LS means estimates between active treatment and placebo, together with 2-sided 80% confidence intervals and p-values were also calculated.

Continuous variables were presented using descriptive statistics (n, mean, standard deviation, median, minimum and maximum). Categorical variables were presented using descriptive statistics (frequency and percentage) within treatment group.

Safety data were summarized descriptively and consisted of patient listings, graphs (where appropriate) and summary statistics.

Subject population

A total of 249 patients were enrolled in the study at 13 medical clinics in the United States. Of these patients, 131 were randomized, and 129 received treatment: 40 received AZD2066, 43 received placebo and 46 received duloxetine. The imbalance in the number of randomized patients across treatment groups results a combination of using centre-specific randomization schemes and the early termination of the study. Of the 131 randomized patients in the study, 44.3% (58/131 patients) completed treatment. At the time the study was prematurely stopped there were 45 (34.4%) patients still receiving treatment (14 AZD2066, 14 duloxetine and 17 placebo patients). Excluding patients who were discontinued due to study closure, treatment completion rates were 76.9%, 59.4%, and 73.1% for AZD2066, duloxetine, and placebo groups respectively. A total of 26 patients discontinued prematurely for reasons other than study closure, with the most common reasons being adverse events (7 patients), loss to follow up (6 patients), and withdrawal by patient (6 patients).

Overall, the mean age was 40.1 years (range 20 to 61 years), and 58.8% of patients were female and 41.2% were male. There was a higher percentage of female patients in the placebo group (68.2%) than in the AZD2066 (57.5%) and duloxetine (51.1%) groups. The majority of patients in the study were white (66.4%), but there was a lower percentage of white patients in the AZD2066 group (55.0%) than in the duloxetine (70.2%) and placebo (66.4%) groups.

Summary of efficacy results

Reductions in MADRS total scores from baseline to week 6 were observed in all treatment groups (LS mean change from baseline: AZD2066 –13.2; duloxetine – 14.0; placebo –14.2). However, there were no numerical trends indicating superior efficacy for either AZD2066 or duloxetine versus placebo in this prematurely terminated study. A smaller reduction in mean MADRS score was observed in the AZD2066 group than in the duloxetine or placebo groups at each timepoint.

The number of patients who were considered MADRS responders (≥50% reduction from baseline in MADRS total score) was similar across treatments. In each of the AZD2066, placebo and duloxetine groups 9 patients (42.9%, 47.4%, and 45.0% respectively) were classified as being responders to treatment at Day 42. In total, 5 patients (23.8%) who received AZD2066 were classified as in remission (MADRS ≤10) whereas 7 patients (36.8%) in the placebo group were classified as in remission. Remission rates for the AZD2066 group were lower than those of the placebo group across all remission criteria. In the duloxetine group 8 patients (40.0%) were classified as in remission at Day 42.

Summary of pharmacokinetic results

No formal PK analysis was undertaken. Plasma concentration data demonstrated that the intended exposure was achieved in the majority of patients receiving AZD2066. However, drug concentrations of AZD2066 below or close to LLOQ were recorded in 5 patients (15%) and drug concentrations of duloxetine below or close to LLOQ were recorded in 2 patients (4.3%), indicating poor compliance for these patients. The plasma concentrations were approximately as expected based on the previous study in PDN patients. Plasma exposure in female patients appear to be higher as compared to male patients

Summary of safety results

The most common AEs observed in the AZD2066 group were headache, nausea, upper respiratory tract infection and insomnia. One SAE of bilateral ovarian mass was recorded during treatment with AZD2066. This was judged unrelated to study treatment. Discontinuations due to adverse events were infrequent, and spread across all 3 treatment groups, and most AEs were mild or moderate in severity. AEs observed in the duloxetine treatment group were consistent with the drug profile (i.e. nausea, diarrhoea, dry mouth, headache). There were no notable differences between AZD2066 and placebo in any of the laboratory parameters, vital signs, ECG variables and physical examination findings.

In this study AZD2066 was considered to be well tolerated.