AstraZeneca

Clinical Study Report Synopsis

Drug Substance	TC-5214
Study Code	D4131C00001
Edition Number	1
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A Phase IIb, Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Parallel Group, Multicenter Study to Assess the Safety and Efficacy of 2 Fixed Dose Groups of TC-5214 (S-mecamylamine) as Monotherapy Treatment in Patients with Major Depressive Disorder with an Inadequate Response to Antidepressant Therapy

Study dates: First subject enrolled: 04 February 2011
Last subject last visit: 26 April 2012

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 Objectives and outcome variables

Objectives and outcome variables	Type
Primary	
To evaluate the efficacy of TC-5214 compared with placebo in patients with MDD who exhibit an inadequate response to SSRI/SNRI therapy, as assessed by change in MADRS total score from randomization (Week 8) to end of treatment (Week 16)	Efficacy
Secondary	
To evaluate the efficacy of TC-5214 compared with placebo in patients with MDD who exhibit an inadequate response to SSRI/SNRI therapy as assessed by depressive symptoms, clinical global outcome regarding severity and improvement, and anxiety as assessed by: - Response in depressive symptoms of MDD, defined as a ≥50% reduction from randomization (Week 8) in MADRS total score at end of treatment (Week 16) - Remission in depressive symptoms of MDD, defined as MADRS total score of ≤8 at end of treatment (Week 16) - Early and Sustained Response, defined as a ≥50% reduction from randomization (Week 8) in MADRS total score and a MADRS total score of ≤12 at Week 10, Week 12, Week 14, and end of treatment (Week 16) - Sustained Response, defined as a ≥50% reduction from randomization (Week 8) in MADRS total score and a MADRS total score of ≤12 at Week 12, Week 14, and end of treatment (Week 16) - Sustained Remission, defined as a MADRS total score of ≤8 at Week 12, Week 14, and end of treatment (Week 16) - Change in depressive symptoms from randomization (Week 8) to end of treatment (Week 16) as measured by HAMD-17 total score - Change in the clinician-rated global outcome of severity as measured by the CGI-S score from randomization (Week 8) to end of treatment (Week 16) - Response in the CGI-I defined as CGI-I rating of “very much improved” or “much improved” from randomization (Week 8) to end of treatment (Week 16) - Change in anxiety as measured by HAM-A from randomization (Week 8) to end of treatment (Week 16) - Change in MADRS total score to each assessment following randomization (Week 8)	Efficacy

Objectives and outcome variables	Type
To evaluate the efficacy of TC-5214 compared with placebo in patients with MDD who exhibit an inadequate response to SSRI/SNRI therapy as assessed by PROs regarding functional impairment as assessed by: - Change in functional impairment from randomization (Week 8) to end of treatment (Week 16) as measured by the SDS in total score and each of the 3 domains - Change in health-related quality of life as measured by the EQ-5D from randomization (Week 8) to end of treatment (Week 16)	Efficacy
To investigate PK properties of TC-5214 in patients with MDD using a population PK analysis methodology	PK[a]
Safety	
To evaluate the safety and tolerability of TC-5214 and placebo in patients with MDD by assessing: - AEs/SAEs, including their severity - AEs leading to treatment discontinuation or study withdrawal - AEs of special interest, including but not limited to, orthostatic hypotension, anticholinergic signs and symptoms including urinary retention, EPS, and increased fasting blood glucose - AEs potentially related to abuse, misuse, noncompliance, and diversion - Change from randomization in physical examination results, weight, waist circumference, clinical laboratory test results, vital signs, and ECG results - Suicidality as assessed by the C-SSRS and AEs of suicidality, suicidal ideation, suicide attempts, and suicide completion - Change from randomization (Week 8) to each assessment time point in akathisia and abnormal involuntary movements as measured by BARS and AIMS - Change from randomization (Week 8) to end of treatment (Week 16) in sexual function as measured by CSFQ total score - Change from last treatment visit to follow-up visits in the DESS	Safety
Exploratory	
To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to TC-5214 and/or co-medication. Investigations into the genetic factors influencing disease (depression) may also be undertaken	PGx[a]

[a] Reported separately from the CSR.

AE adverse event; AIMS Abnormal Involuntary Movement Scale; BARS Barnes Akathisia Rating Scale; CGI-I Clinical Global Impression-Improvement; CGI-S Clinical Global Impression-Severity; CSFQ Changes in Sexual Functioning Questionnaire; CSR Clinical study report; C-SSRS Columbia-Suicide Severity Rating Scale; DESS Discontinuation-Emergent Signs and Symptoms; ECG Electrocardiogram; EPS Extrapyramidal symptoms; EQ-5D EuroQol - 5 dimensions; HAM-A Hamilton Anxiety Scale; HAMD-17 Hamilton Rating Scale for Depression-17 items; MADRS Montgomery-Åsberg Depression Rating Scale; MDD Major Depressive Disorder; PGx Pharmacogenetic; PK Pharmacokinetic; PROs Patient reported outcomes; SAE Serious adverse event; SDS Sheehan Disability Scale; SNRI Serotonin/norepinephrine reuptake inhibitor; SSRI Selective serotonin reuptake inhibitor.

Study design

This was a Phase IIb, multicenter, randomized, double-blind, placebo-controlled, active controlled, parallel group study of the safety and efficacy of 8 weeks of treatment with TC-5214 in 2 fixed doses as monotherapy in the treatment of patients with major depressive disorder (MDD) with an inadequate response to selective serotonin reuptake inhibitor (SSRI)/ serotonin/norepinephrine reuptake inhibitor (SNRI) therapy as demonstrated prospectively within the study. Following the screening, washout, and prospective open-label SSRI/SNRI periods, eligible patients were randomized to 1 of the 4 following treatment regimens in a 1:1:1:1 ratio: 1 mg twice daily (BID) TC-5214; 4 mg BID TC-5214; 60 mg once daily (QD); placebo.

Four short-term Phase III studies in the Renaissance program investigated efficacy, tolerability, and safety of TC-5214 as an adjunct therapy to an antidepressant in patients with major depressive disorder (MDD) who did not respond adequately to initial antidepressant treatment. The primary efficacy endpoint was not met in any of these studies. In the Phase III adjunct program, TC-5214 was generally safe and well tolerated with a tolerability profile consistent with the known pharmacology of the compound, and findings in earlier studies. As TC-5214 did not show superiority over placebo on the primary and secondary efficacy endpoints in the Renaissance program, continued exposure of patients with similar disease characteristics to TC-5214 in the current study was not justified; therefore, the study was terminated early.

Target subject population and sample size

The target population for the double-blind randomized treatment period was patients diagnosed with MDD (18 to 65 years of age) with an inadequate response to SSRI/SNRI therapy within the current episode as demonstrated prospectively. Additionally, prior to enrollment in the prospective period, patients must have had:

1. an inadequate response to no more than 1 prior antidepressant treatment (ADT) in the current episode (any locally approved drug taken for ≥6 weeks duration at the efficacious dose [per prescribing information]) as assessed by a review of the patient's history (Antidepressant Treatment History Form [ATHF])

   OR

2. no prior ADT during this current episode of MDD,

AND patients must <u>not</u> have had:

3. a previous inadequate response, sensitivity or treatment refractory to duloxetine ever in their history.

The length of current major depressive episode could be no longer than 1 year.

Patients were required to have a Hamilton Rating Scale for Depression-17 items (HAMD-17) total score of ≥20 and Clinical Global Impression-Severity (CGI-S) of ≥4 at screening to be enrolled into the 8-week prospective open-label SSRI/SNRI period. During this period patients received treatment with an SSRI/SNRI selected by the Investigator.

Patients with an inadequate response to prospective SSRI/SNRI therapy were randomized into the 8-week double-blind treatment period. Inadequate response was defined as a <50% reduction in HAMD-17 total score during the prospective open-label SSRI/SNRI period, a total score of ≥16 as defined by HAMD-17 and a CGI-S score ≥4.

The sample size calculation in this study was based for demonstrating the superiority of TC-5214 versus placebo with respect to the primary outcome variable change from randomization (Week 8) to Week 16 in MADRS total score. Assuming a standard deviation of 10 (based on historical data), a true difference of 4.5 between the treatment groups, 344 evaluable patients (86 per treatment) were needed to reject the null hypothesis of no difference with a power of 90% using a 1-sided significance level of 10% (5% for each of the 2 doses versus placebo).

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

TC-5214 1 mg or 4 mg tablet administered BID. Duloxetine 20 and 30 mg capsules (The total daily dose of duloxetine used during the study was 60 mg QD titrated up from 20 mg QD or 30 mg QD.) Three batches of 1 mg TC-5214, 3 batches of 4 mg TC-5214, 1 batch of 60 mg duloxetine, and 2 batches of placebo were used in this study. Individual batch numbers and further information are included in the CSR appendix.

Duration of treatment

The total duration of the study was approximately 20 weeks. The study was comprised of 4 periods: 1) a screening/washout period lasting up to 3 weeks; 2) an 8-week prospective open-label SSRI/SNRI period to identify the target patient population of inadequate responders to SSRI/SNRI therapy; 3) an 8-week double-blind randomized treatment period with TC-5214, duloxetine, or placebo and; 4) a 2-week post-treatment follow-up period which included a 1-week treatment taper period.

Statistical methods

The statistical test for the primary efficacy endpoint was a mixed model repeated measures (MMRM) analysis of all of the post-randomization observed case (OC) MADRS total scores through Week 16. The MMRM model included region (Japan, not Japan), responsiveness, treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization MADRS total score as a covariate.

Subject population

A total of 815 patients were enrolled in the study and of these, 472 patients received SSRI/SNRI treatment during the prospective open-label SSRI/SNRI period. A total of

145 patients completed the prospective open-label SSRI/SNRI period and were randomized to study treatment. Of these, 100.0% received treatment, 48.3% completed treatment, 42.8% completed the study, and 57.2% withdrew from the study.

The most common reason for study withdrawal was other (33.1%), which included patients who were withdrawn due to premature termination of the study. The percentage of patients who withdrew due to AEs was 5.4% in the 1 mg BID TC-5214 group, 2.8% in the 4 mg BID TC-5214 group, 5.4% in the 60 mg QD duloxetine group, and 8.6% in the placebo group.

Treatment groups were similar with regard to disposition, demographics, and baseline characteristics. The patient population recruited to the study was considered representative of the target population for TC-5214 and was appropriate for this study.

Summary of efficacy results

The efficacy outcome variable was the change in the MADRS total score from randomization (Week 8) to end of treatment (Week 16). Higher MADRS scores indicate higher levels of depressive symptoms; thus, a negative change from baseline indicates a reduction (or improvement) in depressive symptoms.

Due to the early termination of the study, the potential efficacy of TC-5214 (fixed doses of 1 mg and 4 mg) compared to placebo in reducing depressive symptoms after 8 weeks of treatment in MDD patients with an inadequate response to SSRI/SNRI could not adequately be determined. The LS mean change in MADRS total score was -9.1 for 1 mg BID TC-5214, -11.2 for 4 mg BID TC-5214, -11.4 for 60 mg QD duloxetine, and -7.6 for placebo.

Summary of safety results

TC-5214 (at fixed doses of 1 mg BID and 4 mg BID) was generally well tolerated as a treatment for MDD in patients with an inadequate response to SSRIs/SNRIs. Few patients were exposed to 8 weeks of TC-5214 due to early termination of the study; therefore, interpretation of this data over 8 weeks of treatment was not feasible.

- The frequency of patients experiencing at least 1 AE during the randomized treatment or follow-up periods was 68% in patients who received TC-5214, 57% in the duloxetine group, and 69% in the placebo group. Constipation (TC-5214: 12%; duloxetine: 5%; placebo: 6%) and nausea (TC-5214: 10%; duloxetine: 14%; placebo: 6%) were the most common AEs occurring at a higher frequency in patients who received TC-5214 compared with the placebo group during the randomized treatment period. Most AEs were mild or moderate in intensity. The frequency of patients experiencing AEs that resulted in discontinuation of IP was 4% in patients who received TC-5214, 5% in the duloxetine group, and 9% in the placebo group.

- During the study, 1 patient in the TC-5214 1 mg BID group, no patient in the duloxetine group, and 1 patient in the placebo group experienced SAEs. The event

of abdominal pain in the placebo group was assessed by the Investigator as related to IP. No deaths occurred in the study.

- Within the AEs prespecified as potentially related to anticholinergic signs and symptoms, a dose-dependent increase in frequency of the AE of constipation was noted in patients treated with TC-5214.

- There were no clinically meaningful differences between TC-5214 and placebo with respect to the incidence of AEs prespecified as potentially related to the following safety areas of special interest: changes in blood pressure, suicidality, withdrawal, glucose impairment, EPS, and abuse potential.

- There were no clinically meaningful differences between TC-5214 and placebo with respect to change from randomization in physical examination results, weight, waist circumference, clinical laboratory test results, vital signs, or ECG results.

- As assessed by the C-SSRS, the frequencies of suicidal behavior and suicidal ideation after randomization were similar in patients who received TC-5214 compared with the placebo group.

- There were no clinically meaningful differences between TC-5214 and placebo with respect to EPS as assessed by BARS and AIMS.

- There were no clinically meaningful differences between TC-5214 and placebo with respect to sexual functioning as assessed by CSFQ.

- There were no clinically meaningful differences between TC-5214 and placebo with respect to discontinuation symptoms, based on mean change in DESS total score.