AstraZeneca

Clinical Study Report Synopsis

Drug Substance	TC-5214
Study Code	D4130C00005
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A Multicenter, Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Phase III, Efficacy and Safety Study of 3 Fixed Dose Groups of TC-5214 (S-mecamylamine) as an Adjunct to an Antidepressant in Patients with Major Depressive Disorder Who Exhibit an Inadequate Response to Antidepressant Therapy

Study dates: First subject enrolled: 1 September 2010
Last subject last visit: 30 January 2012

Phase of development: Therapeutic confirmatory (III)

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

Objectives and outcome variables	Type
Primary	
To evaluate the efficacy of TC-5214 compared with placebo as an adjunct to antidepressant (SSRI/SNRI) therapy in patients with MDD who exhibit an inadequate response to antidepressant 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 as an adjunct to an antidepressant (SSRI/SNRI) in patients with MDD who exhibit an inadequate response to antidepressant therapy 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 as an adjunct to an antidepressant (SSRI/SNRI) in patients with MDD who exhibit an inadequate response to antidepressant therapy by assessing changes from randomization (Week 8) to end of treatment (Week 16) of the following PROs: - 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 overall quality of life and satisfaction from randomization (Week 8) to end of treatment (Week 16) by assessing the Q-LES-Q-SF percent (%) maximum total score - Change in overall quality of life and satisfaction from randomization (Week 8) to end of treatment (Week 16) in Q-LES-Q-SF, items 15 and 16 - 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 as an adjunct to an antidepressant (SSRI/SNRI) in patients with MDD who exhibit an inadequate response to antidepressant therapy by assessing: - AEs/SAEs, including their severity - AEs leading to treatment discontinuation or study withdrawal - AEs of special interest, including but not limited to, anticholinergic signs and symptoms, changes in blood pressure, suicidality, withdrawal, glucose impairment, and EPS - 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; Q-LES-Q-SF Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form; SAE serious adverse event; SDS Sheehan Disability Scale; SNRI serotonin/norepinephrine reuptake inhibitor; SSRI selective serotonin reuptake inhibitor.

Study design

This was a multicenter, randomized, double-blind, parallel group, placebo-controlled, Phase III study of the efficacy and safety of 8 weeks of TC-5214 treatment in fixed doses of 0.1 mg, 1 mg, and 4 mg twice daily (BID) as an adjunct to an antidepressant (SSRI/SNRI) in the treatment of patients with major depressive disorder (MDD) who exhibited an inadequate response to antidepressant treatment (ADT). TC-5214 is a selective neuronal nicotinic receptor (NNR) channel modulator developed as an adjunct treatment for MDD in patients with inadequate response to ADT. Following the screening, washout, and prospective open-label ADT periods, eligible patients were randomized to 1 of the 4 following treatment regimens in a 1:1:1:1 ratio: SSRI/SNRI + 0.1 mg BID TC-5214; SSRI/SNRI + 1 mg BID TC-5214; SSRI/SNRI + 4 mg BID TC-5214; SSRI/SNRI + placebo BID.

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 antidepressant therapy (SSRI/SNRI) within the current episode as demonstrated prospectively. The current episode of depression had to be >8 weeks and not exceed 12 months (1 year) in duration**.**

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 ADT period. During this period patients received treatment with an SSRI/SNRI selected by the Investigator.

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

The sample size calculation in this study was based for demonstrating the superiority of TC-5214 compared with placebo as an adjunct to SSRI/SNRI with respect to the primary outcome variable, change from randomization (Week 8) to Week 16 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score. Assuming a standard deviation (SD) of 9 (based on historical data), a true difference of 3.5 between the treatment groups, 664 evaluable patients (166 per treatment) were needed to reject the null hypothesis of no difference with a power of 90% using a significance level of 5% (2.5% for each of the 2 higher doses versus placebo).

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

TC-5214 0.1 mg, 1 mg, or 4 mg tablet administered BID as an adjunct therapy to an ongoing antidepressant (SSRI/SNRI) treatment. Three batches of 0.1 mg TC-5214, 3 batches of 1 mg TC-5214, 2 batches of 4 mg TC-5214, and 1 batch 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 21 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 ADT (SSRI/SNRI) period to identify the target patient population of inadequate responders to ADT; 3) an 8-week double-blind randomized treatment period with adjunctive TC-5214 or placebo and; 4) a 2-week post-treatment follow-up period.

Statistical methods

For the primary efficacy variable and the key secondary efficacy variable (change in the Sheehan Disability Scale [SDS] total score from randomization to end of treatment), a multiple test procedure was used to control the overall family-wise error rate at $\alpha = 0.025$ (one-sided) for the comparison of each TC-5214 dose group (0.1 mg, 1 mg, and 4 mg) to the placebo group across the 2 variables. The statistical test for the primary efficacy variable 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 treatment, pooled center, visit, and treatment by visit interaction as explanatory variables, and the randomization MADRS total score as a covariate. Continuous secondary efficacy analyses were reported using the same primary efficacy model, but no multiplicity adjustments were made to the p-values. Binary secondary variables were analyzed using a logistic regression model using treatment and pooled center as factors.

Subject population

A total of 1566 patients were enrolled in the study and of these, 1289 patients received SSRI/SNRI treatment during the prospective open-label ADT period (876 patients received SSRI and 413 patients received SNRI). A total of 696 patients completed the prospective open-label ADT period and were randomized to study treatment (174 patients each to 0.1 mg BID TC-5214, 1 mg BID TC-5214, 4 mg BID TC-5214, and to placebo). Of these, 99.6% received treatment, 83.8% completed treatment, 83.0% completed the study, and 17.0% withdrew from the study.

The most common reason for study withdrawal was AE (7.0%). The percentage of patients who withdrew due to AEs was 5.7% in the 0.1 mg BID TC-5214 group, 7.5% in the 1 mg BID TC-5214 group, 13.2% in the 4 mg BID TC-5214 group, and 1.7% 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. Compliance was

generally high and similar between treatment groups. The use of concomitant medications was similar between treatment groups.

Summary of efficacy results

Primary efficacy

The primary 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.

TC-5214 (at fixed doses of 0.1 mg, 1 mg, and 4 mg BID) was not superior at any dose to placebo as an adjunct to SSRI/SNRI in reducing depressive symptoms as assessed by change in MADRS total score after 8 weeks of treatment for MDD in patients with an inadequate response to SSRIs/SNRIs.

Mean MADRS total scores decreased from randomization to end of treatment for all TC-5214 and placebo groups, indicating a reduction in depressive symptoms in all groups. The LS mean change in MADRS total score was -11.6 for 0.1 mg BID TC-5214, -12.2 for 1 mg BID TC-5214, -12.2 for 4 mg BID TC-5214, and -12.7 for placebo. None of the TC-5214 treatment groups had a statistically significant difference relative to placebo.

Secondary efficacy

TC-5214 was not superior to placebo for any of the secondary efficacy variables (see Table S1).

Summary of safety results

TC-5214 (at fixed doses of 0.1 mg BID, 1 mg BID, and 4 mg BID) was generally well tolerated as an adjunct to an SSRI/SNRI over 8 weeks of treatment for MDD in patients with an inadequate response to SSRIs/SNRIs:

- The frequency of patients experiencing at least 1 AE during the randomized treatment or follow-up periods was 56% in patients who received TC-5214 and 53% in the placebo group. Constipation (12% vs 6%), dizziness (6% vs 3%), and dry mouth (5% vs 2%) 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, and dose-dependent effects on AE frequency were noted for these events. Most AEs were mild or moderate in intensity. The frequency of patients experiencing AEs that resulted in discontinuation of IP was 8% in patients who received TC-5214 and 2% in the placebo group, and in patients who received TC-5214 a dose-dependent effect was noted.

- During the study, 8 patients who received TC-5214 (1.5%) and 2 patients in the placebo group (1.1%) experienced SAEs. One event of suicide attempt in a patient

who received TC-5214 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 AEs of constipation and dry mouth was noted in patients treated with TC-5214.

- Within the AEs prespecified as potentially related to blood pressure, a dose-dependent increase in frequency of the AEs of orthostatic hypotension and hypotension 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: 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 numerically higher 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 was no clinically meaningful difference between TC-5214 and placebo with respect to sexual functioning as assessed by CSFQ.

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