AstraZeneca

Clinical Study Report Synopsis

Drug Substance	TC-5214
Study Code	D4130C00007
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A Multicenter, Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Phase III, Long-Term Safety and Tolerability Study 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: 22 June 2010
Last subject last visit: 07 February 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 long-term safety and tolerability of TC-5214 compared with placebo as an adjunct to an antidepressant (SSRI/SNRI) therapy in patients with MDD who exhibit an inadequate response to ADT	Safety
Secondary	
To evaluate the safety and tolerability of TC-5214 and placebo in combination with an antidepressant (SSRI/SNRI) 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, reduction of BP, 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 examinations, weight, waist circumference, vital signs, clinical laboratory test results, and ECG parameters - Suicidality as assessed by the C-SSRS and AEs of suicidality, suicidal ideation, suicide attempts, and suicide completion - Change from randomization in EPS (akathisia and abnormal involuntary movements) as measured by: BARS and AIMS - Change from last treatment visit to follow-up visit in the DESS scale	Safety
To evaluate the efficacy of TC-5214 and placebo in combination with an antidepressant (SSRI/SNRI) in patients with MDD by assessing: - Change from randomization in MADRS total score, CGI-S score, SDS score, Q-LES-Q-SF % maximum total score, EQ-5D total score, and HRUWA	Efficacy
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.

ADT Antidepressant therapy; AE Adverse event; AIMS Abnormal involuntary movement scale; BARS Barnes akathisia rating scale; BP Blood pressure; CGI-S Clinical global impression-severity; CSR Clinical study report; C-SSRS Columbia-suicide severity rating scale; DESS Discontinuation-emergent signs and symptoms; DNA Deoxyribonucleic acid; ECG Electrocardiogram; EPS Extrapyramidal symptoms; EQ-5D EuroQol VAS and 5 dimensions; HRUWA Healthcare resource utilization and work absence;

MADRS Montgomery-Åsberg depression rating scale; MDD Major depressive disorder; PGx Pharmacogenetic; 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; VAS Visual analog scale.

Study design

This was a 52-week, multicenter, double-blind, randomized, parallel group, placebo-controlled, Phase III, long-term safety and tolerability study of TC-5214, flexibly dosed (1 mg to 4 mg twice daily [BID]), in combination with an antidepressant (selective serotonin reuptake inhibitors [SSRIs] or the dual serotonin/norepinephrine reuptake inhibitors [SNRIs]) in the treatment of patients with major depressive disorder (MDD) with an inadequate response to SSRI/SNRI therapy. TC-5214 is a selective neuronal nicotinic receptor channel modulator developed an adjunct treatment for MDD in patients with inadequate response to antidepressant treatment (ADT).

To enter the 52-week, long-term, double-blind randomized treatment and follow-up periods, patients had to exhibit an inadequate response to ADT. With the exception of Group 3 from the 3 groups highlighted below, patients had to have a HAMD-17 total score of ≥10 and a CGI-S score ≥3.

Group 1: Patients not on a SSRI/SNRI (new patients or efficacy study screen failures)
Group 1 patients were required to exhibit an inadequate response to SSRIs/SNRIs and complete the screening period and 6-week prospective open-label ADT period.

Group 2: Patients on a SSRI/SNRI (new patients or efficacy study non-completers)
Group 2 patients were receiving treatment with a permitted SSRI/SNRI for a minimum of 6 weeks at study start and continued to be inadequate responders.

Group 3: Efficacy study completers on a SSRI/SNRI
Group 3 patients were receiving treatment with a permitted SSRI/SNRI and consisted of patients who had completed a TC-5214 Phase III efficacy study. These patients entered the current study at the randomization visit.

The study was comprised of 4 periods: 1) a screening period lasting up to 3 weeks; 2) a 6-week prospective open-label ADT period to identify the target patient population of inadequate responders; 3) a 52-week double-blind randomized treatment period with adjunctive TC-5214 or placebo, and; 4) a 2-week post-treatment follow-up period. The screening period was applicable for Group 1 and Group 2 patients and the prospective open-label ADT period was only applicable for Group 1 patients, while the randomized treatment and follow-up periods were the same for all patients.

Eligible patients were randomized to 1 of the 2 treatment regimens (adjunctive TC-5214 or matching placebo) and assigned in a 3:1 ratio.

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 ADT (SSRIs/SNRIs) within the current episode as demonstrated prospectively. The current episode of depression had to be >6 weeks and not exceed 24 months (2 years) in duration. Additionally, patients may have had an inadequate response to no more than 1 prior ADT in the current episode (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). Patients who had taken more than 1 prior antidepressant in the current episode could be considered for enrollment if the course of treatment of the prior antidepressant was ≤4 weeks and this treatment was discontinued due to tolerability.

New or screen failure (Group 1) patients who had not been treated with a permitted SSRI/SNRI treatment were required to have a Hamilton Rating Scale for Depression-17 items (HAMD-17) total score of ≥15 and Clinical Global Impression-Severity (CGI-S) of ≥4 to be enrolled into the 6-week prospective open-label ADT period. During this period, patients received treatment with an SSRI/SNRI selected by the Investigator.

Patients who had completed a prospective SSRI/SNRI treatment and who had an inadequate response to the SSRI/SNRI therapy (Group 3) were randomized into the 52-week, double-blind randomized treatment period. Inadequate response was defined as a HAMD-17 total score of ≥10 as defined by a HAMD-17 and a CGI-S score ≥3.

The sample size of this study was based on the regulatory exposure requirement that at least 300 patients were required to complete a 6-month TC-5214 treatment, and, of those, at least 100 patients were required to complete a 12-month TC-5214 treatment within the dose range 1 mg to 4 mg BID. It was expected that approximately 50% of patients who received active treatment would complete 26 weeks and approximately 25% of patients who received active treatment would complete 52 weeks. Based on these assumptions and a randomization ratio of 3:1, the study needed to randomize 800 patients with 600 to receive TC-5214 and 200 to receive placebo. Assuming the above drop-out rate, 400 patients were expected to complete 6 months of treatment (300 patients on TC-5214) and 200 patients were expected to complete 12 months of treatment (150 on TC-5214).

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

TC-5214 1 mg, 2 mg, or 4 mg tablet administered BID as an adjunct to antidepressant (SSRI/SNRI) treatment. After 2, 4, and 8 weeks of randomized treatment, TC-5214 dose was titrated based on a pre-specified change in the MADRS total score from baseline (Week 0) along with the Investigator's assessment of tolerability. Patients randomized to the TC-5214 group could remain at the same dose, be increased to a maximum of 4 mg BID, or have their dose decreased. Down-titration could occur only once. Seven batches of 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 ranged from 55 weeks to 61 weeks, depending upon the source of patients for the study.

Statistical methods

For the primary safety variables, descriptive statistics were used to summarize the safety outcomes for the double-blind, randomized treatment period and the follow-up period, overall and by treatment. The continuous safety variables were summarized at each visit including end of treatment (the last visit during the double-blind randomized treatment period) and end of follow-up visit (the last visit during the post-treatment period) if applicable. No inferential analyses of safety data were planned.

For the secondary efficacy variables, data were summarized using descriptive statistics by treatment group and visit where applicable. Sustained efficacy was analyzed using a logistic regression model.

Subject population

A total of 1934 patients were enrolled in the study and of these, 1329 patients received SSRI/SNRI treatment during the prospective open-label ADT period. A total of 795 patients completed the prospective open-label ADT period and of these, 96.7% (769/795 patients) were classified as inadequate responders to treatment and were randomized to study treatment. The 769 patients eligible for randomization included new patients not on a SSRI/SNRI and patients not receiving treatment with a permitted SSRI/SNRI from prior TC-5214 Phase III efficacy studies. A further 44 patients were randomized to the double-blind treatment period: 8 were TC-5214 Phase III efficacy study (D4130C00002 or D4130C00004) completers, 10 were screen failures not receiving treatment with a permitted SSRI/SNRI from the D4130C00002 or D4130C00004 studies and 26 were Phase III efficacy study non-completers.

Of the 813 randomized patients (610 patients to TC-5214 and 203 patients to placebo), 99.4% received treatment, 47.0% completed treatment, 45.3% completed the study, and 54.7% withdrew from the study.

The most common reasons for study withdrawal were patient lost to follow-up (14.6%) and patient decision (12.4%).

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

Secondary efficacy

- There was no notable difference observed between TC-5214 (flexible doses of 1 mg to 4 mg BID) and placebo, as assessed by the following secondary and exploratory variables: change from randomization in the MADRS total score at each assessment; sustained efficacy (for at least 3 or 9 months), as assessed by MADRS total scores; change from randomization to end of treatment in the CGI-S score; change from randomization to end of treatment in the SDS total score and 3 individual domain scores; change from randomization to end of treatment in the Q-LES-Q-SF % maximum total score; change from randomization to end of treatment in the EQ-5D index score and the EQ VAS score; and in the evaluation of healthcare resource utilization.

Summary of safety results

TC-5214 (flexible doses of 1 mg to 4 mg BID) was generally well tolerated as an adjunct to an SSRI/SNRI over 52 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 82% in the TC-5214 group and 85% in the placebo group. Constipation (20% vs 6%), upper respiratory tract infection (16% vs 15%), dizziness (12% vs 7%), and dry mouth (10% vs 5%) were the most common AEs occurring at a higher frequency in the TC-5214 group 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 10% in the TC-5214 group and 7% in the placebo group.

- During the study, 3.6% of patients (22 patients) in the TC-5214 group and 2.5% of patients (5 patients) in the placebo group experienced SAEs. Of these patients, only 3 had SAEs assessed by the Investigator as related to IP: suicide attempt (TC-5214 group) and spontaneous abortion and diabetic ketoacidosis (placebo group).

- Two AEs with outcome of death occurred during the study: 1 patient in the TC-5214 group died as a result of toxicity to various agents (verbatim term: accidental death: tramadol intoxication) and 1 patient in the placebo group died as a result of a subarachnoid hemorrhage. Neither event was assessed by the Investigator as related to IP.

- 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, discontinuation symptoms, glucose impairment, EPS, and abuse potential.

- Within the AEs prespecified as potentially related to anticholinergic signs and symptoms, an increase in frequency of the AEs of constipation and dry mouth was noted in patients treated with TC-5214 compared with placebo.

- An increase in frequency of the AEs prespecified as potentially related to changes in blood pressure was noted in patients treated with TC-5214 compared with placebo.

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

- As assessed by the C-SSRS, both suicidal behavior and suicidal ideation after randomization occurred at a similar frequency in both treatment groups.

- 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 the individual discontinuation symptoms, based on mean change in DESS total score, with the exception of irritability and nervousness or anxiety, both of which were observed at a higher frequency in the TC-5214 group compared with the placebo group during follow-up.