AstraZeneca

**Revised Clinical Study Protocol**

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|---|---|
| Drug Substance | TC-5214 (S-mecamylamine) |
| Study Code | D4130C00005 (Fixed Global) |
| Edition Number | [redacted] |
| Date | [redacted] |

# 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

**Sponsor:**

AstraZeneca [redacted]

[redacted] **Global Project Manager** [redacted] Date

[redacted]

Phone: [redacted]



**The following Amendment(s) and Administrative Changes are included in this revised protocol:**

| Amendment No. | Date of Amendment | Local Amendment No. | Date of local Amendment |
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| Administrative change No. | Date of Administrative Change | Local Administrative change No. | Date of local Administrative Change |
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**Sponsor:**

AstraZeneca [redacted]

**The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:**

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AstraZeneca

# PROTOCOL SYNOPSIS

## 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

**International Co-ordinating Investigator**

[redacted]

**Study center(s) and number of subjects planned**

It is estimated that 2236 patients will be screened so that approximately 1520 patients will enter the prospective open-label antidepressant treatment (ADT) period. Of the 1520 patients who enter the ADT period, it is expected that approximately 684 patients will be randomized into the double-blind treatment period to yield data from approximately 664 evaluable patients; 166 patients per randomized treatment group. The study will be conducted at approximately 156 centers in Central Eastern Europe (CEE), European Union (EU), South Africa, and Latin America. Enrollment is expected to continue for approximately 12 months.

| Study period | | Phase of development |
|---|---|---|
| Estimated date of first patient enrolled | [redacted] | III |
| Estimated date of last patient completed | [redacted] | |

**Objectives**

**Primary objective:**

To evaluate the efficacy of TC-5214 compared with placebo as an adjunct to antidepressant (selective serotonin reuptake inhibitor [SSRI]/serotonin/norepinephrine reuptake inhibitor [SNRI]) therapy in patients with major depressive disorder (MDD) who exhibit an inadequate response to antidepressant therapy, as assessed by change in the Montgomery-Åsberg

Depression Rating Scale (MADRS) total score from randomization (Week 8) to end of treatment (Week 16).

**Secondary objectives:**

- 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 depressive symptoms, clinical global outcome regarding severity and improvement, and anxiety.
- 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 patient-reported outcomes (PROs) regarding functional impairment, overall quality of life, and severity of depressive symptoms.
- To investigate pharmacokinetic (PK) properties of TC-5214 in patients with MDD using a population PK analysis methodology. These results will be reported separately from the primary and other secondary objectives.
- Change in overall quality of life and satisfaction from randomization (Week 8) to end of treatment (Week 16) in Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF), items 15 and 16
- Change in health-related quality of life as measured by the European Quality of Life (EuroQol) VAS and 5 dimensions (EQ-5D) from randomization (Week 8) to end of treatment (Week 16)

**Safety objectives:**

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.

**Study design**

This is a multicenter, randomized, double-blind, parallel group, placebo-controlled, Phase III study of the efficacy and safety of 8 weeks of treatment with TC-5214 in fixed doses of 0.1, 1 and 4 mg twice daily (BID) as an adjunct to an antidepressant (SSRI/SNRI) in the treatment of patients with MDD with an inadequate response to an antidepressant (SSRI/SNRI) therapy. Following the screening, washout and open-label antidepressant treatment (ADT) periods, eligible patients will be randomized to 1 of the 4 treatment regimens and assigned in a 1:1:1:1 ratio.

**Target patient population**

The target population for the randomized double-blind treatment period is 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 must be >8 weeks and not exceed 12 months (1 year) in duration. Additionally prior to enrollment in the prospective period, patients may have had an inadequate response to no more than 1 prior ADT in the current episode (any approved drug taken for ≥6 weeks duration at the efficacious dose [per prescribing information]) as assessed by a review of the patients history (Antidepressant Treatment History Form [ATHF]).

Patients who have taken more than 1 prior antidepressant in the current episode may be considered for enrollment if the course of treatment of the second antidepressant was ≤4 weeks and this treatment was discontinued due to tolerability.

Patients will be required to have a clinician-rated 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. These patients will receive treatment with an open-label antidepressant (SSRI/SNRI) therapy (citalopram, escitalopram, fluoxetine, paroxetine CR, sertraline, duloxetine, or venlafaxine XR) selected by the investigator. Patients presenting on a listed background ADT at screening will be switched to a different background ADT during the open-label ADT period of the study.

Only those patients with an inadequate response to prospective ADT will be randomized into the double-blind treatment period. For the purpose of randomization, an inadequate response is strictly defined as a <50% reduction in HAMD-17 total score during the prospective ADT period, a total score of ≥16 as defined by a clinician-rated HAMD-17 and a CGI-S score ≥4.

**Investigational product (IP), dosage and mode of administration**

TC-5214 0.1 mg, 1 mg, or 4 mg tablet administered BID (ie, twice daily), as an adjunct therapy to an ongoing antidepressant (SSRI/SNRI) treatment.

**Comparator, dosage and mode of administration**

Matching placebo tablets will be administered BID.

**Duration of treatment**

The total duration of the study is approximately 21 weeks. The study is 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; 3) an 8-week randomized double-blind treatment period, and; 4) a 2-week post-treatment follow-up period.

**Outcome variables:**

- **Primary efficacy variable:** Change in the MADRS total score from randomization (Week 8) to end of treatment (Week 16)

- **Secondary efficacy variables:**

**Clinician-rated symptoms**

- 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 ≥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 ≥50% reduction from randomization (Week 8) in MADRS total score and 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 Clinical Global Impression-Improvement (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 Hamilton Anxiety Scale (HAM-A) from randomization (Week 8) to end of treatment (Week 16)
- Change in MADRS total score to each assessment following randomization (Week 8)

**Patient-reported outcomes**

- Change in functional impairment from randomization (Week 8) to end of treatment (Week 16) as measured by the Sheehan Disability Scale (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

**Pharmacokinetics**

- TC-5214 plasma concentration levels for population PK analysis
- SSRI/SNRI will be quantified in the open-label ADT period

- **Safety**
  - Adverse events (AEs)/serious adverse events (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 extrapyramidal symptoms (EPS)
  - AEs potentially related to abuse, misuse, non-compliance, and diversion
  - Change from randomization in physical examination results, weight, waist circumference, vital signs, clinical laboratory test results, and electrocardiogram (ECG) results
  - Suicidality as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS) and AEs of suicidality, suicidal ideation, suicide attempts, suicide completion
  - Change from randomization (Week 8) to each assessment timepoint in akathisia and abnormal involuntary movements as measured by BARS and AIMS
  - Change from randomization (Week 8) to end of treatment (Week16) in sexual function as measured by Changes in Sexual Functioning Questionnaire (CSFQ) total score
  - Change from last treatment visit to follow-up visits in the Discontinuation-Emergent Signs and Symptoms Scale (DESS)

**Statistical methods**

Efficacy analyses will be based on the modified intent-to-treat (mITT) analysis set that will include all randomized patients who receive at least one dose of IP (TC-5214 or placebo) and who have a randomization and at least one post-randomization MADRS total score. Analysis of the primary efficacy endpoint will be repeated on the per-protocol (PP) analysis set to test for robustness of results. The PP analysis set will include only those mITT patients who have no significant protocol deviations (which will be detailed in the SAP before database lock) and who received the treatment to which they were randomized.

The safety analysis set will be used to assess safety and tolerability variables. All randomized patients who received at least one dose of IP (TC-5214 or placebo) and for whom any post dose data are available will be included in the safety analysis set.

The primary efficacy variable, the change from randomization in MADRS total score to Week 16 (end of treatment period), will be analyzed using a mixed model repeated measures (MMRM) analysis of all of the post-randomization OC MADRS total scores through Week 16. The MMRM model will include treatment, pooled center, visit and treatment by visit interaction as explanatory variables and randomization MADRS total score as covariate. Treatment, visit and treatment by visit interaction will be fixed effects in the model; pooled center will be a random effect. Robust variance estimates for the fixed effects will be used for testing the treatment the effect for each dose of TC-5214 versus placebo. An unstructured covariance matrix will be used. Model based point estimates, 95% confidence intervals and p-values will be calculated.

An analysis of covariance (ANCOVA) with randomization MADRS total score as covariate, treatment as fixed effect and pooled center as a random effect will be used as a robustness analysis using the last-observation-carried-forward (LOCF) approach.

For change from randomization in continuous secondary efficacy endpoints, MMRM analyses similar to that used for the primary analysis will be used in the mITT analysis set where appropriate. The binary efficacy endpoints will be analyzed using a logistic regression model in the mITT analysis set with treatment and pooled center as factors. For analyzing response and remission in depressive symptoms of MDD, Early and Sustained Response, Sustained Response, and Sustained Remission, the randomization MADRS total score will be used as a covariate; for analyzing CGI-I, the randomization CGI-S will be used as covariate.

For demonstration of superiority for the primary efficacy variable (change from randomization to Week 16 in MADRS total score) and the secondary efficacy variable of special interest (change from randomization to Week 16 in SDS total score, a multiple test procedure will be used to control the overall family-wise error rate for the comparisons of each TC-5214 dose group (0.1, 1, and 4 mg BID) to placebo. Briefly, the procedure only allows a comparison and possible positive result for the 0.1 mg BID group if either the 1 or 4 mg BID dose group demonstrates superiority for the primary efficacy variable—and for the secondary efficacy variable at a particular dose only if the comparison was positive for the primary efficacy variable at the same dose.

Superiority of TC-5214 over placebo will be shown if, following the multiple test procedure, either the 1 or 4 mg BID dose group demonstrates significantly better efficacy than the placebo group for at least the primary efficacy variable. The details of the multiple test procedure are given in Section 12.2.3.

Descriptive statistics will be used to present the safety outcomes including incidence and severity of AEs and SAEs; incidences of AEs leading to treatment or study discontinuation; incidence of AEs of special interest; incidence of abuse potential; changes from randomization in physical examination results, clinical laboratory test results, vital signs, ECG results, weight

and waist circumference, BARS, AIMS, and CSFQ; changes from last treatment visit to follow-up visit in the DESS; and incidence of suicidality as assessed by C-SSRS and AEs.

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Study Protocol.

| Abbreviation or special term | Explanation |
|---|---|
| ADT | Antidepressant treatment |
| AE | Adverse event (see definition in Section 6.4.1) |
| AIMS | Abnormal Involuntary Movement Scale |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| ANOVA | Analysis of variance |
| AST | Aspartate aminotransferase |
| ATHF | Antidepressant Treatment History Form |
| AZDD | AstraZeneca Drug Dictionary |
| BARS | Barnes Akathisia Rating Scale |
| BID | Twice daily |
| BP | Blood pressure |
| BUN | Blood urea nitrogen |
| CEE | Central Eastern Europe |
| CGI-I | Clinical Global Impression-Improvement |
| CGI-S | Clinical Global Impression-Severity |
| CIT | Citalopram |
| CLIA | Clinical Laboratory Improvement Amendments |
| CPK | Creatinine phosphokinase |
| CPMP | Committee for Proprietary Medicinal Products |
| CRF | Case report form (electronic/paper) |
| CRO | Contract Research Organization |
| CSA | Clinical Study Agreement |
| CSFQ | Changes in Sexual Functioning Questionnaire |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| CTCAE | Common Terminology Criteria for Adverse Event |

| Abbreviation or special term | Explanation |
|---|---|
| CV | Coefficient of variation |
| CYP | Cytochrome P450 |
| DAE | Discontinuation of Investigational Product due to Adverse Event |
| DBP | Diastolic blood pressure |
| DES | Patient Safety Data Entry Site |
| DESS | Discontinuation Emergent Signs and Symptoms |
| DNA | Deoxyribonucleic acid |
| DSM-IV-TR | Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision |
| EC | Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee (IEC) |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| ECT | Electroconvulsive therapy |
| eDC | Electronic data capture |
| EDTA | Ethylenediaminetetraacetic acid |
| EPS | Extrapyramidal symptoms |
| EQ-5D | European Quality of Life (EuroQol) VAS and 5 dimensions |
| EU | European Union |
| FDA | Food and Drug Administration |
| FSH | Follicle stimulating hormone |
| GCP | Good clinical practice |
| GMP | Good manufacturing practice |
| GRand | Global Randomization system |
| HAM-A | Hamilton Anxiety Scale |
| HAMD-17 | Hamilton Rating Scale for Depression-17 items |
| $HbA_{1C}$ | Hemoglobin $A_{1C}$ |
| HbsAg | Hepatitis B surface antigen |
| HBV | Hepatitis B virus |
| Hct | Hematocrit |
| HCV | Hepatitis C virus |
| Hgb | Hemoglobin |

| Abbreviation or special term | Explanation |
|---|---|
| HDL | High-density lipoprotein cholesterol |
| HIV | Human immunodeficiency virus |
| IATA | International Airline Transportation Association |
| ICF | Informed consent form |
| ICH | International Conference on Harmonization |
| International Co-ordinating investigator | If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally. |
| IP | Investigational Product |
| IRB | Institutional Review Board |
| ITT | Intent-to-treat |
| IUD | Intrauterine device |
| IVRS | Interactive Voice Response System |
| LC/MS/MS | Liquid Chromatograpy/Tandem Mass Spectrometry |
| LDH | Lactate dehydrogenase |
| LDL | Low-density lipoprotein cholesterol |
| LH | Luteinizing hormone |
| LIMS | Laboratory Information Management System |
| LLOQ | Lower limit of quantification |
| LOCF | Last observation carried forward |
| LPLV | Last Patient Last Visit |
| MADRS | Montgomery-Åsberg Depression Rating Scale |
| MAOI | Monoamine oxidase inhibitor |
| MCH | Mean corpuscular hemoglobin |
| MCHC | MCH concentration |
| MCV | Mean corpuscular volume |
| MDD | Major depressive disorder |
| MedDRA | Medical Dictionary for Drug Regulatory Affairs |
| MINI | Mini-International Neuropsychiatric Interview |
| mITT | Modified intent to treat |
| MMRM | Mixed model repeated measures |
| MRT | Mean residence time |

| Abbreviation or special term | Explanation |
|---|---|
| NIMH | National Institute of Mental Health |
| NNR | Neuronal nicotinic receptor |
| OAE | Other Significant Adverse Event (see definition in Section 11.2.1) |
| OC | Observed case |
| PCP | Phencyclidine |
| PGx | Pharmacogenetics research |
| PI | Principal Investigator |
| PK | Pharmacokinetics |
| PP | Per-protocol |
| PRN | Pro re nata (as needed) |
| PRO | Patient-reported outcome |
| Q-LES-Q-SF | Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form |
| QoL | Quality of Life |
| QTcB | Bazett's-corrected QT interval |
| QTcF | Fridericia-corrected QT interval |
| RBC | Red blood cell |
| RDW | Red cell distribution width |
| SAE | Serious adverse event (see definition in Section 6.4.2). |
| SAP | Statistical analysis plan |
| SBP | Systolic blood pressure |
| SD | Standard deviation |
| SDS | Sheehan Disability Scale |
| SDV | Source data verification |
| SGI-Cog | Subject Global Improvement-Cognition |
| SIS | Sheehan Irritability Scale |
| SNRI | Serotonin/norepinephrine reuptake inhibitor |
| SPC | (EU) Summary of Product Characteristics |
| SPE | Solid phase extraction |
| SSRI | Selective serotonin reuptake inhibitor |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| T3 | Triiodothyronine |
| T4 | Thyroxine |

| Abbreviation or special term | Explanation |
|---|---|
| TCA | Tricyclic antidepressants |
| TEAE | Treatment-emergent adverse event |
| THC | Tetrahydrocannabinol |
| TSH | Thyroid-stimulating hormone |
| UDS | Urine drug screen |
| ULN | Upper limit of normal |
| VAS | Visual analog scale |
| WBC | White blood cells |
| WHO | World Health Organization |
| WOCBP | Women of childbearing potential |

# 1. INTRODUCTION

## 1.1 Background

### 1.1.1 Major depressive disorder (MDD)

Major depressive disorder (MDD) is a psychiatric disorder characterized by the presence of one or more depressive episodes without a history of manic, mixed, or hypomanic episodes. According to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision (DSM-IV-TR), the major depressive episode must not be better accounted for by another Axis I disorder and the symptoms must have been present for at least 2 weeks and represent a change from previous functioning. In addition, one of the symptoms must be depressed mood or loss of interest or pleasure.

Major depressive episodes may begin at any age, however the average age of onset is in the mid-20s. The lifetime risk for MDD is estimated at 5% to 12% for men and 10% to 25% for women. MDD has a high mortality rate. It has been estimated that up to 15% of patients with severe major depressive episodes commit suicide. In addition, individuals with MDD have high medical morbidity and are often plagued with more pain and physical illness than the general population. Many patients have decreased social, occupational, and educational functioning.

Antidepressant medications have become the first line of treatment of MDD. The selective serotonin reuptake inhibitors (SSRIs) and the dual serotonin/norepinephrine reuptake inhibitors (SNRIs), have replaced the use of older agents such as tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs). They offer safety and tolerability advantages; however, no agent has shown an obvious superiority in efficacy. Despite the availability of several antidepressant choices, physicians are challenged to find effective treatments for patients who fail to respond to current strategies. In a National Institute of Mental Health (NIMH)-sponsored clinical trial of depressed patients that was conducted in a naturalistic setting (Sequenced Treatment Alternatives to Relieve Depression study or STAR*D), it was found that <40% of depressed patients achieved remission after treatment with a first-line antidepressant treatment (Rush et al 2006). For this reason, there is a need for newer therapeutic options with improved efficacy and tolerability.

### 1.1.2 Mecamylamine

Mecamylamine HCl (N,2,3,3-tetramethyl-bicyclo[2.2.1]heptan-2-amine hydrochloride) was developed and characterized by Merck & Co., Inc. as a nicotinic ganglionic blocker with hypotensive actions. Unique characteristics of mecamylamine, including exceptional oral efficacy, rapid onset, long duration of action, and nearly complete absorption from the gastrointestinal tract, made the drug, at that time, a more desirable alternative than the existing ganglionic blockers. Consequently, Merck successfully marketed mecamylamine for many years as an antihypertensive agent (NDA 10-251, Inversine®). Mecamylamine was acquired by Layton Biosciences in March 1998 then by Targacept in August 2002.

The safety/tolerability profile of mecamylamine in man has been established during its decades of clinical use as an antihypertensive agent. Using sales data provided by Merck, estimated cumulative exposure using these antihypertensive doses was approximately 20,000 patient years. The most common adverse reactions to the marketed drug include constipation, orthostatic dizziness, urinary retention, and blurred vision.

Mecamylamine HCl, 3 mg/kg as free base, was studied in mice via the forced swim test and showed activity suggesting an antidepressant effect, and was more potent than the positive control, fluoxetine. In a tail suspension test, suboptimal doses of mecamylamine and either imipramine or citalopram were given together and a synergistic effect was observed. These data suggest that when given together with an SSRI, mecamylamine may enhance antidepressant activity in humans (Popik et al 2003).

A clinical trial (TC-5213-023-CRD-001) to test the efficacy, safety and tolerability of mecamylamine in patients with MDD was completed by Targacept in 2006. Patients with MDD who were inadequate responders to citalopram in a 6-week open-label phase were randomized to receive mecamylamine HCl 5.0 to 10.0 mg or placebo, added onto citalopram for a further 8 weeks. Statistically significant improvement in depressive symptoms were seen when mecamylamine HCl was added to citalopram, compared to placebo; the combination was generally well tolerated, and no new safety concerns were identified compared to the well-established safety profile of mecamylamine.

### 1.1.3 TC-5214 (S-mecamylamine)

In [redacted], Targacept and AstraZeneca entered into a collaboration and license agreements for the global development and commercialization of TC-5214. TC-5214 (S-mecamylamine) is the (S)-(+)-enantiomer of racemic mecamylamine and it is the more active enantiomer. Like racemic mecamylamine, TC-5214 is a non-competitive nicotinic channel blocker. However, TC-5214 differs pharmacologically from mecamylamine in an important way. Like mecamylamine, TC-5214 inhibits functional activation at the low-sensitivity form of the α4β2 neuronal nicotinic receptor (NNR); however, in contrast to mecamylamine, TC-5214 enhances activation at the high-sensitivity form of the α4β2 NNR.

TC-5214 demonstrates a superior efficacy and tolerability profile in preclinical models of depression and anxiety, compared to racemic mecamylamine or to the other enantiomer (TC-5213). Most importantly, these findings suggested that TC-5214 would be more efficacious and better tolerated than racemic mecamylamine as augmentation therapy in patients who respond inadequately to an approved antidepressant therapy.

### 1.1.4 Clinical efficacy of TC-5214

In a Phase IIb study (TC-5214-CRD-001) that completed in [redacted], patients who met DSM-IV-TR criteria for MDD were enrolled into an open label phase during which they received treatment with citalopram (CIT) 20 mg daily for the first four weeks and then 40 mg daily for the second four weeks. Patients with an inadequate response to CIT (as measured at the end of eight weeks of open label CIT treatment) were randomized into double blind treatment with add-on TC-5214 or add-on placebo to continuing CIT. The primary outcome

measure was mean change from Week 8 to Week 16 on the Hamilton Rating Scale for Depression-17 item (HAMD-17). Group differences were assessed via an analysis of covariance (ANCOVA) using baseline score as a covariate. There was a clinically relevant and statistically significant ($p<0.0001$) advantage in favor of TC-5214+CIT over placebo+CIT on an ITT basis on the HAMD-17. A statistically significant advantage for TC-5214+CIT over placebo+CIT ($p<0.0001$) was found for all of the secondary measures (Clinical Global Impression –Severity of Illness [CGI-S], CGI-Global Improvement [CGI-I], MADRS, Sheehan Irritability Scale [SIS], Sheehan Disability Scale [SDS], and Subject Global Improvement - Cognition [SGI-Cog] scales).

### 1.1.5 Safety profile of TC-5214

In the Phase IIb study (TC-5214-CRD-001), described previously, it was also found that TC-5214 + citalopram (CIT) treatment combination was generally well tolerated. Three treatment-emergent adverse events (TEAEs) were present in at least 5% of the safety population (n = 270) and were reported more often in the TC-5214 + CIT cohort (n = 135) than in the placebo + CIT cohort (n = 135): headache (9% vs. 3%, respectively), constipation (8% vs. 1%, respectively), and dizziness (6% vs. 3%, respectively). These TEAEs were all mild or moderate in intensity.

There were 2 TEAEs leading to withdrawal, 1 in the TC-5214-23 + CIT cohort and 1 in the placebo + CIT cohort. In both cases, AEs of QTcB interval measurement >450 msec after 8 weeks of open-label treatment with CIT were reported; neither subject had a QTcF absolute value > 460 msec, nor a change from Baseline >60 msec.

There were 2 serious adverse events (SAE) in the study.

The first one occurred in a 50-year-old male. Initially the event was reported by the Investigator as dystonia; then changed to seizure before database lock; and later changed again to dystonia by the investigator after database lock. This subject had no history of seizures and had normal physical examination and laboratory parameters with the exception of a positive urine drug screen for benzodiazepines. He received 1 mg TC-5214-23+CIT BID for 4 days before the event. The subject was hospitalized for several days at a local hospital, where a head CT scan was normal. He was discharged without being placed on an anticonvulsant. Hospital records have been unobtainable.

The second SAE occurred in a 51-year-old female after the follow-up visit. The SAE reported was menorrhagia. The subject was perimenopausal and had a past history of a unilateral salpingoophorectomy. She took her last dose of 1 mg TC-5214-23+CIT at the end of study, one week before the event occurred. She was admitted to a local hospital and transfused, with a recommendation to undergo a total hysterectomy.

In the study, electrocardiograms (ECGs), vital signs, and laboratory findings were clinically unremarkable and showed no significant patterns of shift over the course of the study. Additionally, there were no meaningful clinical changes in suicidality scales.

## 1.2 Research hypothesis

The primary goal of this study is to test the hypothesis that TC-5214 when used as adjunctive therapy to antidepressants (SSRI/SNRI) will demonstrate superiority over placebo adjunctive to SSRI/SNRI therapy in treating patients with MDD with an inadequate response on SSRI/SNRI.

## 1.3 Rationale for conducting this study

The rationale for this study is to assess the antidepressant effect of TC-5214 as an adjunct to an antidepressant (SSRI/SNRI) in patients who have an inadequate response to an antidepressant (SSRI/SNRI) alone.

In many clinical trials involving patients with MDD, large numbers of patients fail to respond completely. Typically, up to 50% of patients will be inadequate responders, despite the administration of full doses of antidepressant and adequate duration of treatment (6 to 8 weeks).

In an attempt to expand the treatment options currently available for the treatment of MDD and to build upon existing clinical data observed with TC-5214, AstraZeneca will explore the use of TC-5214 in fixed doses of 0.1, 1 and 4 mg BID as adjunctive therapy in the treatment of MDD, in patients who fail to respond adequately to a first-line treatment with an approved SSRI or SNRI.

In a previous study when (S)-(+) mecamylamine (TC-5214) 2 to 8 mg was added to CIT in MDD patients (Study TC-5214-23-CRD-001), significant antidepressant efficacy was seen even at the lowest total dose of 2 mg total (1 mg BID). For this reason, a lower dose will be explored in this study in an attempt to identify a low-effect or no-effect dose; as well as the same dose range found effective in the prior study to replicate those results.

## 1.4 Benefit/risk and ethical assessment

Antidepressant medications have become the first line treatment of MDD, but it is still a challenge to find effective treatments for patients who fail to respond. Typically, 25 to 35% of the patients in clinical studies will be inadequate responders. It has been estimated that up to 15% of patients with severe major depressive episodes commit suicide. In addition, individuals with MDD have high medical morbidity and decreased social, occupational, and educational functioning. In an attempt to expand the currently available treatment options and to build upon existing clinical data observed with TC-5214, AstraZeneca will explore the use of TC-5214, the (S)-(+)-enantiomer of mecamylamine, in the treatment of MDD.

TC-5214 has demonstrated robust efficacy ($p<0.0001$) in a Phase IIb study when TC-5214 was given as an adjunct treatment to MDD patients who did not respond adequately to citalopram alone.

Potential adverse effects of TC-5214 identified during the pre-clinical studies were decreased body weight/food intake and effects related to the anti-cholinergic action of the compound

(eg, slowing of gastric motility, dry mouth, dilated pupils, partially closed eyes/eyelids and tremors). In the 8 week Phase IIb study, headache, constipation and dizziness were more common in patients who received citalopram plus TC-5214 than in patients who received citalopram plus placebo at dose of 1 to 4 mg BID.

The most common adverse events (AEs) reported after intake of racemic mecamylamine (Inversine®) are constipation, orthostatic dizziness, urinary retention, and blurred vision. Although there is a potential risk that AEs observed with Inversine® also will be observed with TC-5214, the doses to be used in the clinical studies will be much lower than the maximum doses of Inversine® used in clinical practice.

Because TC-5214 is primarily eliminated renally as parent drug, and has not been tested in special populations with renal impairment, it is recommended that TC-5214 is not administered to subjects with significant renal insufficiency. Likewise, because the compound has not yet been tested in subjects with hepatic impairment, inclusion of subjects with significant hepatic impairment is not allowed at this time. Finally, since the hypotensive actions of TC-5214 have not yet been fully evaluated, the blood pressure of patients taking antihypertensive drugs should be monitored regularly in the clinical studies. Women of childbearing potential can continue to be included, providing adequate contraceptive protection is used, as described in Section 4.1.

The potential benefit of studying TC-5214 as an adjunct treatment in depressed patients who are inadequate responders to SSRIs/SNRIs is considered to outweigh the potential risks.

# 2. STUDY OBJECTIVES

## 2.1 Primary objective

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).

## 2.2 Secondary objectives

- 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 ≥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 ≥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 Clinical Global Impression-Severity (CGI-S) score from randomization (Week 8) to end of treatment (Week 16)

  - Response in the Clinical Global Impression-Improvement (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 Hamilton Anxiety Scale (HAM-A) from randomization (Week 8) to end of treatment (Week 16)

  - Change in MADRS total score to each assessment following randomization (Week 8)

- 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 patient reported outcomes (PROs):

  - Change in functional impairment from randomization (Week 8) to end of treatment (Week 16) as measured by the Sheehan Disability Scale (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 Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) percent (%) maximum total score

- To investigate pharmacokinetic (PK) properties of TC-5214 in patients with MDD using a population PK analysis methodology. SSRI/SNRI will be quantified in the

open-label ADT period. These results will be reported separately from the primary and other secondary objectives.

- 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 EuroQol VAS and 5 dimensions (EQ-5D) from randomization (Week 8) to end of treatment (Week 16)

## 2.3 Safety objectives

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/serious adverse events (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 extrapyramidal symptoms (EPS)
- AEs potentially related to abuse, misuse, non-compliance, and diversion
- Change from randomization in physical examination results, weight, waist circumference, clinical laboratory test results, vital signs, and electrocardiogram (ECG) results
- Suicidality as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS) and AEs of suicidality, suicidal ideation, suicide attempts, suicide completion
- Change from randomization (Week 8) to each assessment timepoint in akathisia and abnormal involuntary movements as measured by Barnes Akathisia Rating Scale (BARS) and Abnormal Involuntary Movement Scale (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 Discontinuation-Emergent Signs and Symptoms (DESS)

## 2.4 Exploratory objectives

This study includes the collection of data for exploratory analyses. These analyses will be conducted and may be reported separately from those of the primary and secondary objectives

in the clinical study report (CSR). The exploratory objectives, along with their corresponding outcome variables of this study are the following:

- 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

# 3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol (CSP) has been subjected to a peer review according to AstraZeneca standard procedures.

## 3.1 Overall study design and flow chart

This is 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, 1 and 4 mg BID as an adjunct to an antidepressant (SSRI/SNRI) in the treatment of patients with MDD who exhibit an inadequate response to antidepressant treatment.

Patients will be evaluated for eligibility criteria twice: first at the screening visit (Visit 1) and a second time at the randomization visit (Visit 6).

To enter the initial 8-week prospective open-label period of the study, patients will be required to have a clinician-rated HAMD-17 total score of ≥20 and CGI-S of ≥4. Additionally, prior to enrollment in the prospective period, patient may have had an inadequate response to no more than 1 prior antidepressant treatment in the current episode (taken for ≥6 weeks duration at the efficacious dose [per prescribing information]) as assessed by a review of the patients history (Antidepressant Treatment History Form [ATHF]). Patients who have taken more than 1 prior antidepressant in the current episode may be considered for enrollment if the course of treatment of the second antidepressant was ≤4 weeks and this treatment was discontinued due to tolerability.

During the prospective open-label ADT period, these patients will receive treatment with an open-label antidepressant (SSRI/SNRI) therapy (citalopram, escitalopram, fluoxetine, paroxetine CR, sertraline, duloxetine, venlafaxine XR) selected by the investigator. Dose adjustment for efficacy and tolerability will be allowed within the first 4 weeks of the prospective open-label ADT period. Patients presenting on a listed background ADT at screening will be switched to a different background ADT during the open-label prospective ADT period of the study. Patients who present ADT-naïve in the current episode may enroll and be started on one of the 7 background ADTs. Patients receiving an ADT other than the 7 allowed agents can be enrolled provided they meet all study eligibility criteria and have failed no more than one agent in the current episode.

Only those patients with an inadequate response to prospective ADT period will be randomized into the double-blind treatment period. For the purpose of randomization, an inadequate response is strictly defined as a <50% reduction in HAMD-17 total score during the prospective ADT period, a total score of ≥16 as defined by a clinician-rated HAMD-17 and a CGI-S score ≥4.

The study will be conducted at approximately 156 centers in CEE, EU, South Africa, and Latin America. Enrollment is expected to continue for approximately 12 months. It is estimated that 2236 patients will be screened so that approximately 1520 patients will enter the prospective open-label ADT (SSRI/SNRI) period. Of the 1520 patients who enter the ADT period, it is expected that approximately 684 patients will qualify for randomization and 664 patients (166 patients per randomized treatment group) are expected to be evaluable.

An evaluable patient is defined as a randomized patient who received at least 1 dose of investigational product (IP) (TC-5214 or placebo) and who has a randomization and at least 1 post-randomization MADRS total score.

The primary outcome variable is the change from randomization (Week 8) to end of treatment (Week 16) in the MADRS total score.

The study is comprised of 4 periods:

- A screening/washout period lasting up to 21 days
- An 8-week prospective open-label ADT period
- An 8-week randomized, double-blind treatment period
- A 2-week post-treatment follow-up period

This study includes the option for enrolled patients to provide a blood sample from which deoxyribonucleic acid (DNA) will be extracted and archived for genetic research. Patients who choose to participate will be asked to sign a separate informed consent form (ICF) for genetic research which will not affect their participation in the overall study.

### 3.1.1 Screening/washout period (Weeks -3 to Day 0)

The screening/washout period will be up to 21 days for current treatment for MDD (including fluoxetine). For patients not on current treatment for MDD at the time of screening, the screening period will be up to 21 days, to include time needed for all screening assessments to be completed (eg, laboratory results received).

Patients currently on an antidepressant will be washed out at least 7 days prior to prospective open-label ADT (14 days prior to Day 1 for fluoxetine). Lifetime use of drugs for depression (collected on the ATHF) and pre-study medications for all other concomitant medication use from up to 30 days prior to open-label baseline (Visit 2) will be recorded in the appropriate sections of the source documentation and electronic case report form (eCRF).

Patients who are screen failures due to laboratory abnormalities may be re-tested for the laboratory abnormality on one additional occasion.

Re-testing of missed laboratory safety assessments or deleted laboratory results is allowed within the screening period. All cases of re-testing require approval by the Study Physician. Re-testing should be performed with the same E-code and preferably within the screening period.

At screening, patients must meet the DSM-IV-TR clinical diagnosis of MDD, single episode (296.2) or recurrent (296.3), confirmed by the Mini International Neuropsychiatric Interview (MINI) version 6.0. Previous ADT treatment in the current episode will be assessed by the ATHF.

Patients must have a HAMD-17 total score of ≥20 and CGI-S of ≥4 at screening to be enrolled. Patients who are taking 1 of 7 allowed SSRI/SNRI at a dose lower than that allowed in the protocol (Table 1; column 4) can enter the study provided they met all other criteria. These patients would enter the study at open label treatment described below in Section 3.1.2 and these patients would have to be washed out of the previous ADT to another allowed ADT among the 7 described below. If patients have taken more than 1 prior ADT medication to treat depression during the current episode of depression, they are allowed to be enrolled provided that they took the second antidepressant for ≤4 weeks and this treatment was discontinued due to tolerability.

Screen failures who fail because of taking a prohibited medicine too close to their first screening visit may be screened on one additional occasion, provided that the time criteria pertaining to the washout of that prohibited medication are satisfied. All other reasons for screen failures would require approval by the Study Physician. Depending on the time duration between screening and re-screening visit, psychiatric evaluations may need to be performed to confirm the patient's eligibility. Re-screening must occur within the same episode of depression. All cases of re-screening require approval by the Study Physician.

For the procedures and assessments performed during screening, refer to the Study Plan, Table 2.

During the screening period, the investigator will determine the appropriateness of the patient for study inclusion by methods including assessing the capacity of the patient to provide consent, determining if the patient is likely to maintain outpatient status during the study, and describing the measures taken to minimize patient risk (eg, exclusion of suicidal ideation, identification of caregiver, weekly telephone contact when no clinic visits are scheduled).

During the washout period, if any subject requires hospitalization, at the investigator's discretion this can be performed as per local practices of the hospital; this will be reported as a SAE and the subject will not be eligible for participation in this study.

Prior to enrolling the subject into the trial, the site will be required to submit information to the Sponsor/designee on a pre-enrollment form to ensure that patients meet enrollment

criteria. The investigator is responsible for ensuring the accuracy of the information provided on the form. The pre-enrollment form will be reviewed by the contract research organization (CRO)/Sponsor, and clarification will be sought with the Principal Investigator (PI) and Sponsor in instances where patients appear to be inappropriate for the study. After a discussion between the Sponsor/designee and the PI occurs, a determination about eligibility will be made jointly with the investigator.

### 3.1.2 8-week prospective open-label ADT period (Weeks 1 through 8)

The PI will select the background SSRI/SNRI treatment for the patient during the 8-week prospective open-label ADT period from Table 1.

Patients presenting on a listed background ADT at screening will be switched to another listed ADT for the duration of the prospective open-label ADT portion of the study. Patients not currently on an ADT will be started on 1 of the 7 listed ADTs (SSRI/SNRI) for the duration of the study. Patients who are on an ADT that is not 1 of the 7 background ADTs listed in Table 1 will be washed out of their current medication and started on 1 of the 7 allowed ADTs. Investigators will be encouraged not to limit their use of background ADT to predominantly 1 or 2 SSRI/SNRI.

A pharmacokinetic sample will be taken to quantify SSRI/SNRI concentration levels during the prospective open-label ADT period (Visit 4; Week 2). The date and time of background therapy administration will be recorded in the electronic case report form (eCRF).

**Table 1 Administration of background SSRI/SNRI during 8-week prospective open-label ADT period**

| | ADT Period | | | |
|---|---|---|---|---|
| **SSRI/SNRI[a]** | **Day 1 (mg/day)** | **Week 1 (mg/day)** | **Week 2 (mg/day)** | **Week 4 and after (mg/day)** |
| **SSRI** | | | | |
| Citalopram | 20 | 20 | 20 | 20-40 |
| Sertraline | 50 | 50 | 100 | 100-150 |
| Escitalopram | 10 | 10 | 10 | 10-20 |
| Fluoxetine | 20 | 20 | 20 | 20-40 |
| Paroxetine CR | 25 | 25 | 37.5 | 37.5-50 |
| **SNRI** | | | | |
| Duloxetine | 30 | 60 | 60 | 60 |
| Venlafaxine XR | 37.5 | 75 mg/day by end of Week 1 | 150 | 150-225 |

[a] SSRI/SNRI doses listed above are in accordance with prescribing information or package insert.

The investigator should increase the dose of the ADT based on tolerability and per package insert instructions. Dose up-titration after Week 4 is not allowed. Investigators are allowed one dose reduction of SSRI/SNRI depending on tolerability. Patients should at least be at the minimum dose listed at Week 4 and stay at this dose for the remainder of the study. Patients who do not tolerate a reduced SSRI/SNRI dose are withdrawn from the study.

The purpose of the prospective open-label ADT period is to allow monitoring of patient safety and to establish a response to SSRI/SNRI treatment.

Patients may participate in the optional exploratory genetic research part of the study, where permitted. A separate blood draw (10 mL) will occur at Visit 2 (Day 1) or after. The blood sample will be collected after the Genetics Informed Consent has been obtained from the patient.

### 3.1.3 8-week randomized double-blind treatment period (Weeks 8 through 16)

At the randomization visit (Week 8), eligibility for participation is re-confirmed. For the purpose of randomization, an inadequate response is strictly defined as <50% reduction in HAMD-17 from Day 1 (the prospective open-label ADT period baseline, Visit 2), HAMD-17 total score ≥16, a CGI-S score ≥4. Patients will continue the background SSRI/SNRI treatment at the final dose of the prospective open-label ADT period, and be randomized to 1 of the 4 following treatment regimens in a 1:1:1:1 ratio:

- SSRI/SNRI+TC-5214 0.1 mg BID
- SSRI/SNRI+TC-5214 1 mg BID
- SSRI/SNRI+TC-5214 4 mg BID
- SSRI/SNRI+placebo BID

PK samples will be collected to quantify TC-5214 concentration levels during the double-blind treatment period (Table 2).

For the procedures and assessments performed during the double-blind treatment period, refer to the Study Plan, Table 2.

Patients who discontinue before Week 16 should be asked to return to the center for end-of-treatment assessments.

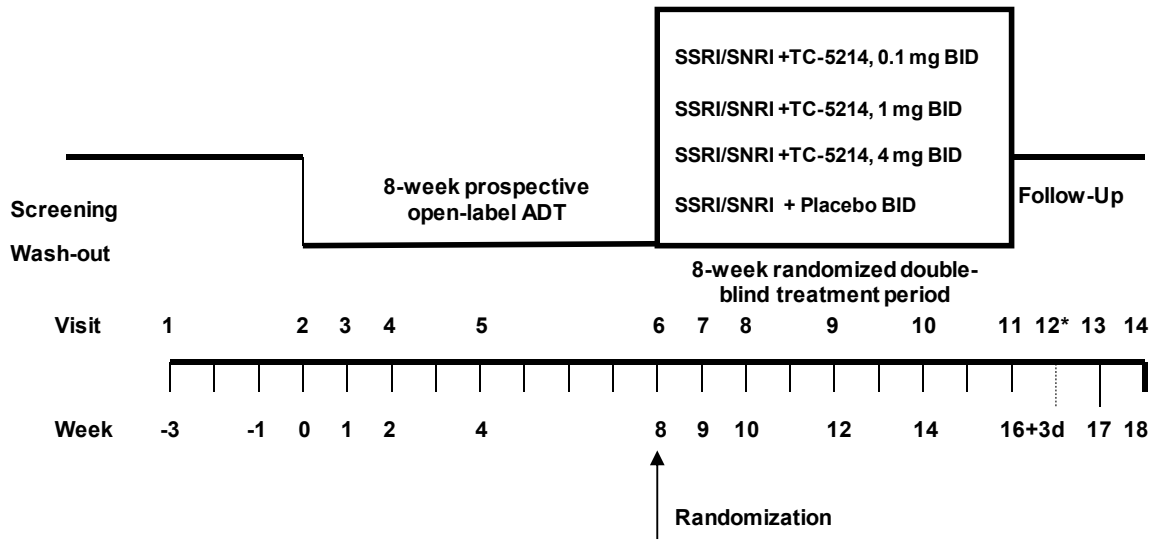
### 3.1.4 2-week post-treatment period (Weeks 17 through 18)

The 2-week post-treatment follow-up period will assess AEs following discontinuation of TC-5214. Patients will continue on their background ADT throughout this period. A telephone call will take place on Day 3 of the post-treatment period (Week 16 + 3 days) to assess concomitant medications, AEs, DESS, and C-SSRS. Other follow-up visits will be scheduled at Week 17 and Week 18. At each of these visits, patients will return to the site to

capture the DESS rating, AEs, concomitant medications, and other scheduled assessments (Study Plan, Table 2).

The study design is illustrated in Figure 1. The schedule of the procedures and assessments of the study plan is presented in Table 2.

**Figure 1 Study flow chart**




Visit 12 is a telephone call.

**Table 2 Study plan**

| | Enrollment[a] | 8-week prospective open-label ADT period | | | | 8-week randomized double-blind treatment period | | | | | | Post-treatment period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening/ Washout | Lead-in | | | | R[b] | | | | | | 2-week follow-up | | |
| **Visit** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 (Tel)[c] | 13 | 14 |
| **Week** | -3 to Day0 | 0 | 1 | 2 | 4 | 8 | 9 | 10 | 12 | 14 | 16 | 16+3d | 17 | 18 |
| **Day (±x days)** | -21 to 0 | 1 (±2) | 8 (±2) | 15 (±2) | 29 (±2) | 57 (±2) | 64 (±2) | 71 (±2) | 85 (±5) | 99 (±5) | 113 (±2) | 116 (±2) | 120 (±2) | 127 (±2) |
| Informed consent | X | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | | | | | X | | | | | | | | |
| MINI version 6.0 | X | | | | | | | | | | | | | |
| Psychiatric history including number of depressive episodes | X | | | | | | | | | | | | | |
| Medical & Surgical History | X | | | | | | | | | | | | | |
| ATHF | X | | | | | | | | | | | | | |
| Nicotine use | X | | | | | X | | | | | X | | | |
| Employment status | X | | | | | X | | | | | X | | | |
| Vital signs (sitting, supine, & standing BP & pulse)[d] | X | X | X | X | X | X | X | X | X | X | X | | X | X |
| Physical examination[e] | X | | | | | X[e] | | | | | X | | | X |
| Height & weight[f] | X | X | | | | X | | | | | X | | | X |
| Waist circumference | | X | | | | X | | | | | X | | | X |
| 12-lead ECG | X | X | | | | | X | | X | | | | | |

**Table 2 Study plan**

| | Enrollment[a] | 8-week prospective open-label ADT period | | | | 8-week randomized double-blind treatment period | | | | | | Post-treatment period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening/ Washout | Lead-in | | | | R[b] | | | | | | 2-week follow-up | | |
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12 (Tel)[c]** | **13** | **14** |
| **Week** | **-3 to Day0** | **0** | **1** | **2** | **4** | **8** | **9** | **10** | **12** | **14** | **16** | **16+3d** | **17** | **18** |
| **Day (±x days)** | **-21 to 0** | **1 (±2)** | **8 (±2)** | **15 (±2)** | **29 (±2)** | **57 (±2)** | **64 (±2)** | **71 (±2)** | **85 (±5)** | **99 (±5)** | **113 (±2)** | **116 (±2)** | **120 (±2)** | **127 (±2)** |
| 12-lead ECG (triplicate)[g] | | | | | | X | | | | | X | | | |
| Hematology & clinical chemistry[h] | X | X[k] | | | | X[k] | X | | X | | X[k] | | | X[k] |
| PK sampling[i] | | | | X | | X[k] | | | X | | X[k] | | | |
| PGx sampling (optional)[j] | | X | | | | | | | | | | | | |
| HIV, HBV, HbsAg, and HCV serology | X | | | | | | | | | | | | | |
| Glucose and lipids[k] | | X[k] | | | | X[k] | | | | | X[k] | | | X[k] |
| $HbA_{1C}$ | X | | | | | X | | | | | | | | X |
| FSH, LH (to determine menopausal status) | X | | | | | | | | | | | | | |
| Urinalysis | X | X | | | | X | | | X | | X | | | X |
| Urine drug screen[l] | X | | | | | | | | | | | | | |
| Urine pregnancy for WOCBP | X | X | | | | X | | | | | X | | | X |
| AEs | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Prohibited medication washout period (see Table 4 & Table 5) | X | X | | | | | | | | | | | | |

**Table 2 Study plan**

| | Enrollment[a] | 8-week prospective open-label ADT period | | | | 8-week randomized double-blind treatment period | | | | | | Post-treatment period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening/ Washout | Lead-in | | | | R[b] | | | | | | 2-week follow-up | | |
| **Visit** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 (Tel)[c] | 13 | 14 |
| **Week** | -3 to Day0 | 0 | 1 | 2 | 4 | 8 | 9 | 10 | 12 | 14 | 16 | 16+3d | 17 | 18 |
| **Day (±x days)** | -21 to 0 | 1 (±2) | 8 (±2) | 15 (±2) | 29 (±2) | 57 (±2) | 64 (±2) | 71 (±2) | 85 (±5) | 99 (±5) | 113 (±2) | 116 (±2) | 120 (±2) | 127 (±2) |
| **PROs** | | | | | | | | | | | | | | |
| SDS | | X | | | | X | | | X | | X | | | |
| Q-LES-Q-SF | | X | | | | X | | | | | X | | | |
| CSFQ | | X | | | | X | | X | X | | X | | | |
| EQ-5D | | X | | | | X | | | X | | X | | | |
| **Rating scales** | | | | | | | | | | | | | | |
| HAM-A | | X | | | | X | | | | | X | | | |
| HAMD-17 | X | X | | | | X | | | | | X | | | |
| MADRS | | X | | | | X | X | X | X | X | X | | | |
| CGI-S | X | X | X | X | X | X | X | X | X | X | X | | | |
| CGI-I | | | | | | | X | X | X | X | X | | | |
| C-SSRS | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| BARS | | X | | | | X | | | X | | X | | | X |
| AIMS | | X | | | | X | | | X | | X | | | X[m] |
| DESS | | | | | | | | | | | X | X | X | X |
| Prior & Concomitant medication[n] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

## Table 2 Study plan

| | Enrollment[a] | 8-week prospective open-label ADT period | | | | 8-week randomized double-blind treatment period | | | | | | Post-treatment period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening/ Washout | Lead-in | | | | R[b] | | | | | | 2-week follow-up | | |
| **Visit** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 (Tel)[c] | 13 | 14 |
| **Week** | -3 to Day0 | 0 | 1 | 2 | 4 | 8 | 9 | 10 | 12 | 14 | 16 | 16+3d | 17 | 18 |
| **Day (±x days)** | -21 to 0 | 1 (±2) | 8 (±2) | 15 (±2) | 29 (±2) | 57 (±2) | 64 (±2) | 71 (±2) | 85 (±5) | 99 (±5) | 113 (±2) | 116 (±2) | 120 (±2) | 127 (±2) |
| **IP (including placebo)** | | | | | | | | | | | | | | |
| Dispense IP[o] | | | | | | X | | | X | | | | | |
| Collect IP | | | | | | | | | X | | X | | | |

R Randomization

Note: PROs will be done first followed by the clinician assessments (rating scales).

Note: For patients who withdraw early from the study, Week 16 assessments should be performed.

[a] Enrollment assessments must be conducted within 21 days prior to Day 1 (Visit 2), lead-in (see Section 3.1.1).

[b] Following dosing at randomization (Week 8), patients will remain at the center for up to 4 hours of observation.

[c] A telephone call will take place at Visit 12 (Day 3 post-treatment) to assess concomitant medications, AEs, DESS, and C-SSRS.

[d] Vital signs performed at Week 8 (randomization) will be performed at predose and 2-3 hours postdose (for the order of blood pressure and pulse measurements, refer to Sections 6.4.9.1 and 6.4.9.2).

[e] Physical examination should be conducted **after** psychiatric assessments have been completed.

[f] Height should be measured only at screening.

[g] ECG at randomization (Week 8) and Week 16 are to be performed in triplicate (3 readings in rapid succession and not more than 2 minutes apart). ECG should be performed at predose and 2-3 hours postdose at randomization (Week 8).

[h] Clinical chemistry and hematology samples are not required to be fasting. At Visit 1, the following will be collected: clinical chemistry, bicarbonate, follicle stimulating hormone (FSH)/luteinizing hormone (LH), thyroid panel, serology for HIV+HBV+HCV, $HbA_{1c}$, hematology, urinalysis, urine drug screen, and urine pregnancy test for women of childbearing potential (WOCBP). FSH/LH should be done on all women.

[i] Blood samples for SSRI/SNRI concentration assessment will be drawn at Week 2 (Visit 4) during the 8-week prospective open-label ADT period. Blood samples drawn during the randomized double-blind treatment period are to quantify TC-5214 concentration levels only. The exact blood sampling time and date and exact time and date of the last TC-5214 dose must be recorded. At Week 8 (Visit 6), a sample will be taken 2-3 hours after TC-5214 administration. At Week 12 (Visit 9), a predose sample will be taken. At Week 16 (Visit 11), a predose and 2-3 hour postdose sample will be taken. Patients should be instructed not to take IP on PK visit days and that IP will be taken at the study center for the PK visit.

[j] It is preferred that blood samples for PGx sampling be collected at Visit 2, but may be collected at any visit through the end of the study provided the Genetic Testing Informed Consent has been obtained.

k Fasting samples for glucose and lipids are to be collected at the scheduled visits. Additional samples required at these visits (eg, PK [Visits 2, 6 and 11] and PGx (Visit 2) should also be collected in a fasting state. Patients must have fasted for 12 hours prior to collection of blood samples.

l The investigator may also order a urine drug screen at any time during the study in order to confirm suspected drug abuse.

m If any abnormalities are identified, a follow-up evaluation is requested.

n Prior medications will be collected for 1 month (30 days) before enrollment.

o Patients should take IP in the morning and evening, except at the start of Visit 6 (randomization), and Visits 9 and 11 (in the morning prior to PK assessments).

## 3.2 Rationale for study design, doses and control groups

For the overall rationale for the study, see Section 1.3.

The dose of TC-5214 was chosen on the basis of a Phase IIb study (Study TC-5214-23-CRD-001). When 1 to 4 mg BID doses of TC-5214 in a flexible titration study was added to CIT in MDD patients, significant antidepressant efficacy was seen even at 1 mg BID. To further characterize the exposure/dose versus effect relationship of TC-5214 as an adjunctive antidepressant, a lower dose of TC-5214 will be included in the current study. Therefore, the free base dose range selected in the current study of TC-5214, as adjunct therapy to SSRIs/SNRIs given at an efficacious dose per prescribing information, will be 0.2 mg to 8 mg total daily dose (0.1 mg BID to 4 mg BID) of TC-5214 free base equivalent.

SSRI/SNRI antidepressants were chosen as the background therapy for TC-5214, as these drugs are currently standard initial therapy. No one agent has been shown to be superior and the choice of agent is usually tailored to the individual patient. The SNRIs (duloxetine and venlafaxine XR) and SSRIs (citalopram, escitalopram, fluoxetine, paroxetine CR and sertraline) used in this study include some of the most commonly prescribed antidepressants in clinical practice.

The value of a washout period in clinical trials is to allow subjects to discontinue certain medications they were using before entering the trial so the results of the trial are not confounded by the medications.

This study will allow a patient to have no more than one historical antidepressant treatment for the current episode of depression as documented by the ATHF prior to enrolling into the 8-week prospective open-label ADT period. However, if patients have taken more than 1 ADT during the current episode of depression, they are allowed to be enrolled provided that they took the second ADT for ≤4 weeks and this treatment was discontinued due to tolerability.

The target population for TC-5214 is patients with an inadequate response to SSRI/SNRI. There is no gold-standard definition of an inadequate responder to antidepressant treatments in clinical trials. Conventional definitions of inadequate responders include subjects with less than a 50% response to treatment, or subjects who still have a moderate or greater severity of illness despite treatment. For the purpose of entry into the randomized double-blind treatment period of this study, inadequate response is strictly defined as <50% reduction in HAMD-17 from the prospective open-label ADT period baseline (Day 1, Visit 2), and a HAMD-17 total score ≥16, a CGI-S score ≥4.

Clinical experience has shown that an 8-week duration for both the prospective open-label ADT period and for the randomized double-blind treatment period is sufficient to identify responders vs. inadequate responders.

The choice of a prospective, open-label, investigator-chosen ADT period was felt to be a reasonable reflection of clinical practice prior to the initiation of adjunct therapy in inadequate

responders to initial ADT. Investigators will be encouraged not to limit their use of background ADT to predominantly 1 or 2 SSRI/SNRI, depending on local ADT availability.

MADRS is the most widely used observer-rated depression scale in the world. It is considered superior to the HAM-D in the conduct of clinical trials in part because it is extremely sensitive to the changes brought on by antidepressants. The use of MADRS in the current study will allow comparison to previous results as well as to results from other marketed products.

To avoid confounding the primary outcome measure (MADRS) for this study, the HAMD-17 total score will be used to define the open label and double blind randomization criteria. The HAMD-17 total score was the primary efficacy outcome variable for the Phase IIb study (Study TC-5214-23-CRD-001).

The double-blind study design was adopted to minimize bias, an important consideration in depression studies where many of the clinical endpoints are self- or clinician-reported graded scales.

# 4. SUBJECT SELECTION CRITERIA

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

Each patient must meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule, and no waivers will be issued.

## 4.1 Inclusion criteria

For inclusion in the study, patients should fulfill the following criteria:

1. Provision of signed and dated informed consent before initiation of any study-related procedures.

2. Patients must provide acceptable proof of identity documentation to confirm initials and date of birth.

3. Male or female patients aged 18-65 years, inclusive:

    - **Male patients**: Male patients who are sexually active must use a double barrier method of contraception (condom with spermicide) from the first dose of IP until 12 weeks after their last dose.

    - **Women of childbearing potential:** Women of child-bearing potential (WOCBP) must have a negative urine pregnancy test and confirmed (by the investigator) use of a highly effective form of birth control for 1 month before

enrollment and until 3 months after their last dose of IP. The following methods of highly effective birth control include the birth control option plus the use of a condom by the male sexual partner: vasectomized sexual partner, tubal occlusion, intrauterine device (IUD [copper banded coils only]), intrauterine system (eg, Mirena), Depo-Provera, implants (Implanon, Norplant), normal and low dose combined oral pills, ethinylestradiol transdermal system (Evra Patch), and intravaginal device (NuvaRing). Highly effective birth control can also include true sexual abstinence (starting at the screening visit and through completion of the study). The investigator will assess the method of birth control and compliance at each study visit.

- **Women of non-child-bearing potential**. Women of non child-bearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy but excluding bilateral tubal occlusion) or who are postmenopausal. Women will be considered postmenopausal if they are amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

    - Women under 50 years old would be considered post menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in the post-menopausal range.

    - Women ≥50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment and LH and FSH levels in the post-menopausal range.

4. Primary clinical diagnosis meeting criteria in the current episode from the DSM-IV-TR:

    - 296.2x Major Depressive Disorder (MDD), Single Episode, Unspecified **or**

    - 296.3x Major Depressive Disorder (MDD), Recurrent, Unspecified

    as confirmed via the Mini-International Neuropsychiatric Interview (MINI) version 6.0 diagnostic scale.

5. History during current depressive episode of an inadequate response to no more than one antidepressant (eg, SSRI/SNRI or any other antidepressant given as monotherapy) as assessed by a review of the patient's history (ATHF). For an inadequate response, the duration of treatment with an antidepressant treatment (both approved and non-approved medications) must be at least 6 weeks. Antidepressant treatments/medications discontinued within 4 weeks of initiation due to intolerance would not count towards the 1 antidepressant. Patients who are

not currently receiving treatment with antidepressant drugs during this current depressive episode are allowed.

6. Documented HAMD-17 as follows:

   - Screening (Visit 1) and open-label baseline (Visit 2): Clinician-rated total score ≥20.
   - Randomization (Week 8/Visit 6): Clinician rated ≥16 total score and a <50% reduction in total score compared to open-label baseline (Visit 2).

7. Have a HAMD-17 score ≥2 on item 1 (depressed mood) at screening (Visit 1) and open-label baseline (Visit 2).

8. Documented CGI-S as follows:

   - Screening (Visit 1): CGI -S score ≥4
   - Randomization (Week 8/Visit 6): CGI-S score ≥4

9. Be able to understand and comply with the requirements of the study, as judged by the investigator.

10. Outpatient status at enrollment and randomization (Week 8) other than social hospitalization as locally allowed.

For inclusion into the optional exploratory genetic sample collection, patients must fulfill the following additional criterion:

11. Have provided written informed consent for genetic sampling before initiation of any genetic sampling.

If a patient declines to participate in the optional genetic portion of the study, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study described in this CSP, so long as they consent.

## 4.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Patients with: a) lifetime history of bipolar disorder or psychotic disorder; MDD with psychotic features is excluded; b) current (within 12 months before open-label baseline [Visit 2]) manic episode, post-traumatic stress disorder, as assessed by the MINI 6.0 or current attention deficit hyperactivity disorder that has been diagnosed or treated in the past year prior to visit, or c) current (within 12 months before open-label baseline [Visit 2]) dysthymic disorder (as assessed by the investigator) or generalized anxiety disorder, panic disorder, obsessive compulsive disorder or social

anxiety disorder as assessed by the MINI 6.0 and considered by the investigator to be primary (causing a current clinically significant degree of distress or impairment due to these disorders)

2. Patients with a diagnosis of DSM-IV-TR Axis II disorder which has a major impact on the patient's current psychiatric status.

3. Patients whose current episode of depression started less than 8 weeks before screening and is greater than 1 year in duration.

4. History of hypersensitivity or intolerance to drugs with a similar chemical structure or class to TC-5214.

5. Patients with a positive urine toxicology screen will be excluded, with the exception of patients testing positive for cannabinoids (THC) or for drugs legally available by valid prescription. Patients with a positive UDS for a drug(s) legally available by prescription must provide evidence of the prescription for the drug(s), and may be allowed to participate in the study if, in the clinical judgment of the investigator, they are not abusing the medication. One repeat urine drug test may be allowed in cases where subjects tested positive for prescribed medications that the PI feels could be discontinued per protocol. The repeat urine drug test must be negative for that prescribed substance prior to the end of the screening period meeting the protocol required washout time for the substance in question.

6. Patients with a history of suicide attempts in the past year and/or seen by the investigator as having a significant history of risk of suicide or homicide, or in the investigator's judgment, considered at risk for suicide or homicide during the study. Also patients who have a HAMD-17 item 3 score of ≥3 and is judged by the Investigator to be at imminent risk of self-injury.

7. Presence of renal insufficiency as evidenced by creatinine clearance of ≤50 mL/min (measured using Cockroft-Gault equation).

8. Any significant renal, pulmonary, cardiovascular (including uncontrolled hypertension defined as higher than 160/100 mm Hg), ophthalmologic, neurologic, or any other medical conditions that might confound the study or put the patient at greater risk during study participation. Any significant unstable hepatic infection and/or condition (including Hepatitis B [HBV] and Hepatitis C [HCV]) or a newly diagnosed Hepatitis B or C (ie, identified at screening). Patients with chronic, stable HBV or HCV are allowed

9. Positive test results for human immunodeficiency virus (HIV) antibody.

10. History of renal insufficiency or impairment or conditions that could affect absorption or metabolism of investigational product (eg, malabsorption syndrome, severe liver disease, history of gastric bypass, gastrointestinal motility disorder

including chronic constipation, pyloric stenosis, or history or ileus), as judged by the investigator.

11. Patients on thyroid medication unless at a stable dose for ≥3 months; thyroid level must be within normal range by either investigator judgment or review of past laboratory results.

12. A diagnosis of cancer (except basal or squamous cell skin carcinoma), unless in remission for at least 5 years.

13. Any other severe progressive or uncontrolled medical condition, or chronic medical illness even if well controlled (eg. fibromyalgia, chronic pain conditions, obstructive sleep apnea).

14. Known presence of raised intraocular pressure or history of narrow-angle glaucoma.

15. Evidence of uncontrolled diabetes mellitus as judged by the investigator or exhibited by hemoglobin $A_{1c}$ ($HbA_{1c}$) >8%.

16. Alanine aminotransferase (ALT) or asparate aminotransferase (AST) ≥ 3.0 times the upper limit of normal (ULN) or total bilirubin ≥1.2 times the ULN (unless documented Gilbert's syndrome).

17. History of severe medication allergy/hypersensitivity or ongoing medication allergy/hypersensitivity other than seasonal allergies, as judged by the investigator.

18. History of stroke or transient ischemic attack.

19. Myocardial infarction within 180 days before screening (Visit 1).

20. History of seizures or seizure disorder (single infant febrile seizure with full recovery is acceptable).

21. History of head trauma, including closed head injury, in which loss of consciousness occurred.

22. Receipt of electroconvulsive therapy (ECT) within the last 2 years.

23. Use of prohibited treatments (refer to Table 4 and Table 5 for additional information on prohibited medications).

24. Patients who, in the investigator's opinion, will require any form of psychotherapy during the study period, unless psychotherapy has been ongoing for a minimum of 3 months prior to study start.

25. Pregnancy or lactation.

26. Clinically significant deviation from the reference range in clinical laboratory test results at enrollment, as judged by the investigator.

27. Donation of plasma or blood products within 14 days of Day 1. Blood or plasma donation will not be allowed from the screening visit through completion of the study (patients who completed double-blind treatment and 1-2 week follow-up are considered as completing the study).

28. History of orthostatic hypotension.

29. Clinically significant electrocardiogram (ECG) abnormalities as determined by the investigator and/or central ECG reader.

30. QTcF (Fridericia-corrected) ≥450 msec as measured by central reader (on repeated tests) at screening (Visit 1) or randomization (Visit 6), or a medical history or family history of long QT syndrome.

31. Involvement in the planning and/or conduct of this study (applies to both Sponsor staff and/or staff at the study site).

32. Previous randomization in this study.

33. Patients who previously received TC-5214 (S-mecamylamine) or Inversine®.

34. Randomization in another clinical trial currently or within 3 months of screening for this study or participation (ie, having been screened) in more than 2 trials in the 12 months prior to screening for this study.

35. Judgment by the investigator that the patient should not participate in the study if he/she considers patient unlikely to comply with study procedures, restrictions, and requirements.

In addition, the following are considered criteria for exclusion from the genetic research:

36. Have had previous allogeneic bone marrow transplant.

37. Received non-leukocyte depleted whole blood transfusion in the 120-day period preceding the date of genetic sample collection.

Procedures for withdrawal of incorrectly enrolled patients, see Section 5.3.

# 5. STUDY CONDUCT

## 5.1 Restrictions during the study

Refer to Section 5.6 for a detailed discussion of permitted and prohibited concomitant medications during the study.

## 5.2 Subject enrollment and randomization

The PI will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Assign potential patient a unique enrollment number, beginning with 'E#'.

3. Determine patient eligibility. See Sections 4.1 and 4.2.

4. Register the patient in the IVRS which will assign a unique randomization code.

As patients are screened for the study, they must be allocated an enrollment code (E-code). The E-code is a 7-digit number made up of the center number and the patient number within that particular center.

One PK sample will be taken in the ADT period to quantify SSRI/SNRI. Compliance with ADT therapy is a requirement for randomization. PK analysis can be a measure of compliance.

At Week 8 (Visit 6), the investigator will reconfirm if the patient meets the randomization criteria and document this in the appropriate CRF. That is, only those eligible patients with an inadequate response to prospective open-label ADT period at Week 8 (a <50% reduction in HAMD-17 total score, a HAMD-17 total score >16, and a CGI S score ≥4) will be randomized into the 8-week randomized double blind treatment period.

An IVRS will be used to centrally randomize patients. If a patient withdraws from participation in the study, then his/her enrollment/randomization code (if assigned) cannot be reused.

### 5.2.1 Procedures for randomization

A blocked randomization schedule will be generated and provided by AstraZeneca using AstraZeneca's Global Randomization system (GRand). Randomization will not be stratified by center; randomization codes will be assigned strictly sequentially as patients become eligible for randomization. Eligible patients will be randomized to 1 of the 4 treatment groups in a 1:1:1:1 ratio.

## 5.3 Procedures for handling subjects incorrectly enrolled or randomized

**Patients who fail to meet the inclusion/exclusion criteria** should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

No member of the study team in AstraZeneca, Targacept, or its representative, at investigational centers or any CRO handling data will have access to the randomization scheme during the conduct of the study with the exception of AstraZeneca's Investigational Products and Patient Safety.

Where patients that do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post-initiation, the investigator should inform the AstraZeneca Global Study Delivery Team Physician or representative immediately. The AstraZeneca Global Study Delivery Team Physician or representative is to ensure all such contacts are appropriately documented.

## 5.4 Blinding and procedures for unblinding the study

### 5.4.1 Methods for ensuring blinding

Study medication and placebo tablets will be identical in physical appearance and will be labeled to ensure the blind. The treatment each patient will receive will not be disclosed to the investigator, study center personnel, patient, Sponsor, or the Sponsor's designee.

### 5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the investigator(s) or pharmacists, and the personnel who are independent to the study evaluation at the Patient Safety Department from the IVRS.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

## 5.5 Treatments

### 5.5.1 Identity of investigational product(s)

The IP will consist of 0.1, 1 and 4 mg TC-5214 tablets and matching placebo tablets, as adjunct therapy to one ongoing antidepressant (SSRI/SNRI) treatment.

AstraZeneca or a company acting on its behalf will supply the IP to the investigator. The IP will be supplied as tablets for oral use according to the description in Table 3. Sufficient medication will be dispensed during the randomized treatment period to cover dosing for the visit duration.

The SSRI/SNRI used in this study will be prescribed and filled through normal prescribing methods, and will not be directly supplied by AstraZeneca.

Placebo will be supplied as tablets matching TC-5214 to ensure the blinding of the study treatment.

**Table 3 Investigational product**

| Investigational product | Dosage form and strength | Manufacturer |
|---|---|---|
| TC-5214 | 0.1 mg tablets | [redacted] |
| TC-5214 | 1 mg tablets | [redacted] |
| TC-5214 | 4 mg tablets | [redacted] |
| Placebo to match TC-5214 | 0 mg tablets | [redacted] |

TC-5214 tablets and matching placebos may contain lactose, which may cause discomfort in lactose-intolerant individuals.

### 5.5.2 Doses and treatment regimens

During the randomized double-blind treatment period (Visits 6 through 11), patients will continue the background SSRI/SNRI at the final dose of the prospective ADT period along with 1 of the 4 following treatment regimens. Patients will take their last dose of TC-5214 or placebo on the day of Visit 11.

- SSRI/SNRI+TC-5214 0.1 mg BID
- SSRI/SNRI+TC-5214 1 mg BID
- SSRI/SNRI+TC-5214 4 mg BID
- SSRI/SNRI+placebo BID

### 5.5.3 Background therapy

During the randomized double-blind treatment period, all patients will receive one of the SSRI/SNRI antidepressant drugs at doses provided in Week 4 (see Table 1) in addition to either TC-5214 or placebo. During the randomized treatment period, the patient will remain on the same SSRI/SNRI therapy and the dose cannot be changed. If a dose reduction is required, the patient must be withdrawn from the study.

### 5.5.4 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into the local language where appropriate.

Study medication will be provided in labeled bottles. Information on the bottle labels will include study number, Kit ID number, blinded contents, and storage conditions.

### 5.5.5 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The IP label on the bottle specifies the appropriate storage. All study medications shall be stored in their original containers. Only staff members who are authorized to dispense the drug supplies shall have access to them.

## 5.6 Concomitant and post-study treatment(s)

Patients will continue to take the background SSRI/SNRI at the final dose of the prospective SSRI/SNRI period. Patients will continue on background therapy throughout the randomized double-blind treatment period and will receive a 30-day SSRI/SNRI prescription.

Refer to Section 5.6.1 for prohibited medications during the study.

**Permitted medications**

Non psychopharmacologic drugs with psychotropic effects (eg, hormone replacement therapy, beta blockers) are permitted if the patient has been taking a stable dose of the drug for at least 90 days before Study Day 1 and is expected to continue taking the drug without dose changes throughout the study. The PRN (or as needed) use of medicines either prescribed or over the counter used to treat symptoms of the common cold is permitted (sympathomimetic cold medicines and preparations containing dextromethorphan are prohibited); however, patients will be instructed not to take these medicines within 24 hours before a study visit. Supportive nonbehavioral psychotherapy is permitted provided that there has been no change in intensity or frequency within 90 days prior to patient start into the long term study and no change is anticipated for the duration of the study. Other treatments are permitted if not specifically indicated.

Patients are permitted to take one of the following treatments for insomnia (at bedtime) up to the specified dosage per night and no more than 4 times a week:

- Lorazepam max 2 mg/day or equivalent, which includes the following:
  - Alprazolam 1 mg
  - Estazolam 4 mg
  - Oxazepam 30 mg

- Tempazepam 60 mg

– Zolpidem tartrate 10 mg

– Zaleplon 20 mg

– Zopiclone 7.5 mg

– Eszopiclone 2.0 mg

Patients are not to take these medications 24 hours prior to a study visit.

Patients are allowed to take trazodone ≤150 mg for sleep prior to enrollment in addition to ADT; however, patients must be willing to wash-out trazodone and be willing to take benzodiazepine/non-benzodiazepine sleep aids as noted above at the dose allowed in the protocol.

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the electronic case report form (eCRF). Refer to Table 4 for information regarding approved sleep aids during the study.

### 5.6.1 Prohibited/restricted medications

A list of medications prohibited before and during the study and their washout periods are shown in Table 4. All ADTs (including SSRI/SNRI) used before the study must have at least 7-day washout prior to Study Day 1 (start of prospective open-label ADT period). Agents listed in Table 4 and Table 5 are prohibited during the washout and the entire study.

**Table 4 Prohibited/restricted medications and treatments**

| | Number of days to first day of open-label antidepressant treatment | | | | | |
|---|---|---|---|---|---|---|
| **Excluded treatments** | **2 years** | **90** | **60** | **30** | **14** | **7** |
| Sedative hypnotics other than zaleplon, zopiclone, eszopiclone, or zolpidem[a] | | | | | | X |
| Other psychotropic drugs or substances, including opiates/narcotic analgesics[b], sedating antihistamines | | | | | | X |
| Nonpsychopharmacologic drugs with psychotropic effects[c,d] | | | | | | X |

**Table 4 Prohibited/restricted medications and treatments**

| | Number of days to first day of open-label antidepressant treatment | | | | | |
|---|---|---|---|---|---|---|
| **Excluded treatments** | **2 years** | **90** | **60** | **30** | **14** | **7** |
| Anxiolytics (benzodiazepines (except for alprazolam and lorezapam[e])and nonbenzodiazepines) | | | | | | X |
| Antidepressants[f] | | | | | | X |
| Herbal products intended to treat anxiety, insomnia, and depression or symptoms related to these illnesses | | | | | X | |
| Monoamine oxidase inhibitors, including Linezolid | | | | | X | |
| Sumatriptan, naratriptan, zolmitriptan[g] | | | | | X | |
| Antipsychotics | | | | | X | |
| Cimetidine | | | | | | X |
| Smoking cessation agents | | | | X | | |
| Formal psychotherapy[g] | | X | | | | |
| Stimulants[i] | | | | | | X |
| ECT therapy | X | | | | | |
| Isotretinoin | | | X | | | |

[a] Permitted but not greater than 4 times per week. Patients will be instructed not to take zaleplon, zopiclone, eszopicline or zolpidem 24 hours before any visit.
[b] Permitted for short course treatment, for no more than 7 days in duration.
[c] Prohibited unless the patient has maintained a stable dose for at least 90 days.
[d] Common cold preparations are permitted on a PRN (as needed) basis (sympathomimetic cold medicines and those containing dextromethorphan are prohibited). Patients will be instructed not to take these medications 24 hours before any visit.
[e] Benzodiazepines and non-benzodiazepines administered for the diagnosis of insomnia are permitted but not greater than 4 times per week. Patients will be instructed not to take any of these agents 24 hours before any visit.
[f] 14 days of washout for fluoxetine.
[g] Including drugs that have a similar mechanism of action.
[h] Supportive non-behavioral psychotherapy is permitted provided that there has been no change in intensity or frequency within 90 days prior to study day 1 and no change is anticipated for the duration of the study.
[i] Stimulants used for a short duration and stopped due to tolerability issues would be permitted with an adequate washout. If stimulants required for longer than four weeks in combination with an antidepressant, the patient should be excluded. If stimulants were used as monotherapy for depression, the investigator needs to verify that the involved patient does not have any other medical comorbidities.

The list of medications and cytochrome P450 (CYP)-influencing medications prohibited during screening and treatment periods is shown in Table 5.

**Table 5 Prohibited medications and treatments during the study**

| Drug Classification or Treatment | Drug Names |
|---|---|
| Analgesics, opioid type | For example, morphine, fentanyl, methadone |
| Sympathomimetic cold medicines or cough medicines | For example, contains ephedrine or dextromethorphan |
| Acne medications | isotretinoin |
| Anticoagulants and antiplatelet drugs[a] | warfarin |
| Asthma drugs (oral)[a] | theophylline |
| Antismoking drugs | bupropion, varenicline, nicotine replacement therapy |
| Digitalis glycosides[a] | digitoxin, digoxin |
| Drugs of abuse | According to DSM-IV-TR criteria: alcohol, amphetamine, barbiturates, cannabis, cocaine, hallucinogens, opiates |
| ECT | Receipt of ECT within the last 2 years |
| Psychotherapy | Unless stable appointments that began at least 90 days before screening |
| CYP3A4 inducers[a] | For example, rifampin, rifabutin, St. John's Wort |
| Strong and moderate P450 CYP3A4 inhibitors[a] | For example, clarithromycin, itraconazole, ketoconazole, telithromycin, erythromycin, nefazodone, cimetidine, mibefradil, norfloxacin, fluconazole, verapamil, diltiazem |

[a] Drugs with narrow therapeutic indices should be monitored for blood levels.

## 5.7 Treatment compliance

The administration of all study drugs (including IP) should be recorded in the appropriate sections of the eCRF.

Compliance for TC-5214 will be monitored at each visit after randomization. Any patient found to be taking less than 80% or more than 120% of the assigned study drug will be considered non-compliant as assessed by tablet counts. Patients who are repeatedly or severely non-compliant should be discontinued. However, patients judged to be occasionally non-compliant may continue in the study at the discretion of the investigator and should be counseled on the importance of taking their medication regularly.

### 5.7.1 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the patient.

It is the investigator's responsibility to establish a system for handling study treatments, including investigational medicinal products, to ensure that:

- The investigator/designee correctly receives deliveries of IP.
- The study center personnel will account for all received study drugs.
- IP is to be handled and stored safely, properly, and in agreement with the given storage instructions.
- IP is to be dispensed only by the investigator or designee.
- The study center personnel will account for all study drugs dispensed to and returned from the patient. Any discrepancies must be documented, investigated and appropriately resolved. Certificates of delivery should be signed by the investigator or designee.
- Under no circumstances will the investigator or other study personnel allow the IP to be used for purposes other than those directed by the protocol.
- Patients must return all unused study drug and empty containers to the Investigator or designee, who will retain these items until they are collected by authorized personnel.

The study monitor or designee will return all unused drugs to a vendor designated by the sponsor. The study center personnel will account for all drugs dispensed and returned. Certificates of study drug return must be signed by the investigator or designee.

The administration of all medication (including IP) must be recorded in the appropriate sections of the eCRF.

The investigator is responsible for discussing methods to ensure high treatment compliance with the patient before randomization. Compliance will then be discussed at each study visit, assessed based on returned tablet counts, and documented in the eCRF and the dispensing record. Patients judged to be non-compliant may continue in the study, but should be counseled on the importance of taking their study medication as prescribed. Patients who are repeatedly or severely non-compliant may, at the investigator's discretion, be discontinued.

## 5.8 Discontinuation of investigational product

Patients may be discontinued from IP in the following situations:

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment

- Objective measures of compliance will be assessed by Sponsor or delegate. Patients who are non-compliant may be discontinued from the study.
- Incorrectly enrolled patient (unless the investigator and AstraZeneca study physician agree to allow the patient to continue)
- Patient lost to follow-up
- Pregnancy
- Safety reasons as judged by the investigator and/or AstraZeneca, particularly a clinically significant or serious AE that would not be consistent with continuation in the study, as determined by the investigator, AstraZeneca, or the patient
  - An imminent risk of suicide, based on the investigator's judgment
- ALT or AST >8x ULN or
- ALT or AST >5x ULN for more than 2 weeks or
- ALT or AST >3x ULN **and** (total bilirubin >2x ULN) or
- ALT or AST >3x ULN and symptoms of possible hepatic injury
- Significant renal insufficiency as evidenced by creatinine clearance of ≤42.5 mL/min **(**confirmed by two separate samples)
- Cardiac/prolonged QT
  - Significant cardiovascular AEs with clinical signs and symptoms
  - ECG findings : persistent (more than 10 mins) QTcF >500 msec
- Orthostatic hypotension
  - Decrease in systolic blood pressure (SBP) of ≥20 mm Hg and/or a decrease in diastolic blood pressure (DBP) of ≥10 mm Hg from supine to a standing position and clinically significant symptoms as judged by the investigator
- Meeting an exclusion criteria, if possible, it is recommended that AstraZeneca be contacted before discontinuation
- The study is terminated by AstraZeneca, regulatory authorities, or Institutional Review Board (IRB)

## 5.9 Withdrawal from study

Patients are at any time free to withdraw from study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator. AEs will be followed up (see Sections 6.4.3 and 6.4.4); and all study drugs should be returned by the patient.

Withdrawn patients will not be replaced.

Specific reasons for discontinuing a patient from optional exploratory genetic research are:

- A patient may withdraw from this optional exploratory genetic research at any time, independent of any decision concerning participation in other aspects of the main study described within this protocol. Voluntary discontinuation by the patient will not prejudice further treatment.

Withdrawal of consent for PGx and biological sampling is included in Section 7.5.

### 5.9.1 Procedures for discontinuation of a patient from the study

A patient that decides to discontinue will always be asked about the reason(s) for discontinuation and the presence of any AEs and SAEs. If possible, they should be seen and assessed by a physician. AEs and SAEs will be followed up until resolved or until, in the investigator's opinion, the condition has become stable and is unlikely to change further (See Sections 6.4.3 and 6.4.4) and all study drugs should be returned by the patient.

Any patient who withdraws and has clinically significant abnormal results for any safety assessments should be followed-up at appropriate intervals, as determined by the investigator, until the abnormality resolves or until, in the investigator's opinion, the condition has become stable and is unlikely to change further or the investigator has lost contact with the patient. Patients who withdraw outside the double-blind treatment period with AEs, SAEs, or clinically significant abnormal results, should be followed through completion/resolution of the event (see Sections 6.4.3 and 6.4.4).

If a patient discontinues during the prospective open-label ADT period, the following assessments will be conducted: review of any AEs/SAEs, review of concomitant medications and C-SSRS. If the patient is unable or unwilling to return for these assessments at the next scheduled visit, then the visit date should be recorded on the eCRF as an unscheduled visit.

If a patient discontinues during the randomized treatment period all assessments required at the final treatment visit (Visit 11/Week 16) will be conducted, including return of investigational product and should be recorded on the electronic Case Report Form (eCRF). If a patient discontinues during the follow-up period, all assessments required at the final follow-up visit (Visit 14/Week 18) will be conducted and should be recorded on the eCRF. The category in the eCRF specifying the reason for discontinuation as "Other" should only be used when no other category is satisfactory.

The investigator must notify AstraZeneca or representative of any hospitalization. Hospitalization is a SAE and should be reported as described in Sections 6.4.3 and 6.4.4. If a patient is hospitalized, the patient will be discontinued from the study and all assessments and procedures required at Visit 11/Week 16 will be conducted. Refer to Study Plan, Table 2.

In cases of discontinuation, please inform your site's monitor.

### 5.9.2 Procedures for discontinuation from optional genetic aspects of the study

Patients who discontinue from the study should always be asked specifically whether they are withdrawing or continuing their consent for this genetic research. It must be established whether the patient:

- Agrees to the genetic sample and any DNA extracted from the sample being kept for genetic research in the future.
- Withdraws consent for the sample to be kept for genetic research in the future and wishes the sample to be destroyed. Destruction of the sample (or the DNA extracted from the sample) will only be possible so long as the particular sample is traceable. In the event that genetic research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

The PI is responsible for providing written notification to AstraZeneca of any patient who has withdrawn consent for the use of the sample taken for genetic research. AstraZeneca will provide written confirmation to the investigator of the actions taken with the sample, which must be filed in the investigator study file.

# 6. COLLECTION OF STUDY VARIABLES

## 6.1 Recording of data

The electronic Data Capture (eDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

## 6.2 Data collection and enrollment

### 6.2.1 Screening and demographic measurements

Any patient considered for enrollment into the study must provide written informed consent (signed and dated) prior to conducting any study specific procedure.

The following data will be collected at the screening visit:

- Demographic data - date of birth, sex, race, ethnicity
- Inclusion/exclusion criteria
- Diagnosis of MDD as assessed by the MINI version 6.0
- Psychiatric history including number of depressive episodes
- Medical and surgical history
- Nicotine use
- Inadequate response to antidepressant therapy as assessed by the ATHF
- Employment status
- Blood pressure (sitting, supine and standing) and pulse (see Section 6.4.9)
- A complete physical examination including general appearance, skin, head, neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular system, respiratory system, abdomen, and neurological examination
- Height & weight
- Resting 12-lead ECG
- Blood samples (non-fasting) will be collected for the following:
  - Clinical chemistry and hematology assessments, including hemoglobin $A_{1C}$ ($HbA_{1C}$) and thyroid function tests
  - LH and FSH to determine menopausal status (on all women)
  - HBV, HCV, and HIV serology evaluations
- Fasting (12 hours) blood sample for glucose and lipids taken at Visit 2
- A urine sample will be collected for urinalysis and urine drug screen
- A urine sample will be collected for pregnancy testing on all WOCBP
- Assessment of depression and suicidality by the following scales: clinician-rated HAMD-17, CGI-S, C-SSRS, and AEs
- Assess AEs

- Record prior and concomitant medications
- Washout of prohibited medications

### 6.2.2 Follow-up procedures

A telephone call will take place on Day 3 of the 2-week post-treatment follow-up period (Week 16+3 days) to assess concomitant medications, DESS, AEs, and C-SSRS.

The following follow-up procedures will be performed post treatment at Week 18 (Visit 14):

- A complete physical examination including general appearance, skin, head, neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular system, respiratory system, abdomen, and neurological examination
- Weight and waist circumference
- Blood samples (non-fasting) will be collected for clinical chemistry and hematology assessments, including $HbA_{1C}$ and thyroid function tests
- Fasting (12 hours) blood sample for glucose and lipids
- A urine sample will be collected for urinalysis
- A urine sample will be collected for pregnancy testing on all WOCBP
- Assess AEs
- Assessment of akathisia and abnormal involuntary movements by BARS and AIMS

The following follow-up procedures will be performed at both Weeks 17 (Visit 13) and 18 (Visit 14):

- Blood pressure (seated, supine, and standing BP & pulse) and pulse (see Section 6.4.9)
- Assessment of suicidality by C-SSRS and AEs
- Assessment of discontinuation signs and symptoms by DESS
- Assess AEs
- Record prior and concomitant medications

## 6.3 Efficacy

For the timing of individual assessments refer to Study Plan, Table 2.

The primary efficacy of TC-5214 on MDD will be assessed using the MADRS. The secondary measures on depression, anxiety, and disability will be measured by HAMD-17, CGI-S, CGI-I, and HAM-A. The PROs are described in Section 6.5. To ensure consistency throughout the study, every effort should be made that the same rater conduct all assessments of a specific scale for a given patient.

For each rating scale, individual item scores will be reported on a specifically designed eCRF. Signs and symptoms revealed and recorded during the ratings should only be reported as AEs if they fulfill the criteria for a SAE or are the reason for discontinuation from treatment with the IP.

### 6.3.1 Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS is a 10-item scale for the evaluation of depressive symptoms (Montgomery and Åsberg 1979). Each MADRS item is rated on a 0 to 6 scale. Higher MADRS scores indicate higher levels of depressive symptoms.

The MADRS will be administered by a rater of suitable skill and experience as defined by AZ or its representative. Each rater administering the MADRS must receive training and certification on the use of the MADRS.

### 6.3.2 Hamilton Rating Scale for Depression-17 items (HAMD-17)

The HAMD-17 is a 17-item clinician-rated scale that assesses depressive symptoms (Hamilton 1960). The HAMD-17 consists of 17 symptoms, each of which is rated from 0 to 2 or 0 to 4, where 0 is none/absent.

The HAMD-17 will be administered by a rater of suitable skill and experience as defined by AZ or its representative. Each rater administering the HAMD-17 must receive training and certification on the use of the HAMD-17.

### 6.3.3 Hamilton Anxiety Scale (HAM-A)

The HAM-A is a 14-item clinician-administered scale for the evaluation of anxiety symptoms (Guy 1976a; Hamilton 1959). Each HAM-A item is rated on a 0 to 4 scale. Higher HAM-A scores indicate higher levels of anxiety.

All HAM-A assessments should evaluate the patient's symptoms during the past week.

### 6.3.4 Clinical Global Impression (CGI)

The CGI is a 3-part, clinician-administered scale that assesses global illness severity (Guy 1976b). For the purposes of this study, only the first 2 parts of the scale will be used.

The first part, the Severity of Illness item (CGI-S), is scored to rate the patient's current clinical state. The second part, Global Improvement item (CGI-I), is scored to rate the patient's change post treatment.

Each CGI item is scored on a scale from 1 to 7. A CGI-S score of 1 indicates that a patient is "Normal, not ill" and a score of 7 indicates that a patient is "Among the most extremely ill patients". A CGI-I score of 1 indicates that a patient is "very much improved" and a score of 7 indicates that a patient is "very much worse". The CGI is administered at various times during the course of the study to assess patient progress. Higher CGI-S scores indicate greater illness severity. CGI-I scores greater than 4 indicate worsening, while scores less than 4 indicate improvement.

The CGI is only to be administered by the primary physician rater. In the event that the primary physician rater is not available, a designated back-up rater may perform the rating. The back-up rater must meet the same qualifications as the primary physician rater and be authorized by the PI to conduct the ratings; exceptions must be authorized by AZ or its representative.

## 6.4 Safety

The PI is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

Safety will be evaluated in terms of AEs (including SAEs), discontinuations due to AE clinical laboratory analyses, vital signs, weight, waist circumference, ECG changes, physical examination, AEs related to abuse, and other AEs special interest including but not limited to anticholinergic signs and symptoms, changes in blood pressure, suicidality, withdrawal, glucose impairment and EPS.

The methods for collecting safety data are described below.

### 6.4.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

### 6.4.2 Definition of serious adverse event

A SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening

- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B to the CSP.

Psychiatric hospitalization is at times required and is expected for MDD. If hospitalization is needed due to the exacerbation of, or for the stabilization of for MDD, it will be reported as an SAE. The psychiatric assessments will reflect the worsening of the patient's condition and the need for hospitalization. These hospitalizations will be reported in the eCRF. Further guidance on the reporting of deterioration of the patient's condition with respect to MDD is contained in the following Section 6.4.3.

### 6.4.3 Recording of adverse events

**Time period for collection of AEs**

AEs and SAEs will be collected from the time of signature of informed consent throughout the prospective and treatment periods and including the follow-up period. Unsolicited SAEs will be collected for 30 days post last study treatment.

**Follow-up of unresolved AEs**

Any AEs that are unresolved at the patient's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca or its representative retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

**Variables**

The following variables will be collect for each AE:

- AE (verbatim)
- the date when the AE started and stopped
- maximum intensity
- whether the AE is serious or not
- investigator causality rating against the IP (yes or no)
- action taken with regard to IP

- AE caused patient's withdrawal from study (yes or no)
- outcome

In addition, the following variables will be collected for SAEs:

- date AE met criteria for serious AE
- date Investigator became aware of serious AE
- AE is serious due to
- date of hospitalization
- date of discharge
- probable cause of death
- date of death
- autopsy performed
- causality assessment in relation to Study procedure(s)
- causality assessment in relation to Other medication
- description of AE

**Intensity**

If the intensity of an AE changes, only the maximum intensity of the event will be recorded. Intensity is defined as one of the following:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

**AEs associated with abuse or misuse of study drug or ADT**

Study drug abuse, misuse of study drug, and/or prescription medications taken in a way other than as prescribed (either intentionally or unintentionally) or if symptoms are invented or exaggerated in order to acquire a prescription, is an AE but is not considered an SAE unless accompanied by serious sequelae.

Should an overdose of IP or ADT occur, it must be reported in accordance with the procedures described in Section 13.2, Overdose. An overdose with symptoms is to be reported as AE, overdose without symptom is not an AE, however is captured in Overdose collection form.

**Causality collection**

The Investigator will assess causal relationship between IP and each AE, and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the IP?"

Causal relationship in cases where the disease under study has deteriorated due to lack of effect will be classified as no reasonable possibility.

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as "yes".

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

**AEs based on signs and symptoms**

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit?", or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

**AEs based on examinations and tests**

The results from protocol mandated laboratory tests and vital signs will be summarized in the clinical study report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the IP, or if the investigator insists.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

**Rating scales**

Signs and symptoms revealed and recorded during the rating of any of the MADRS, HAMD-17, CGI scales or DESS should not be reported as AEs, unless they fulfill a criterion for a SAE or lead to discontinuation of treatment with IP.

PRO questionnaires should not be used as instruments for collecting safety data. However, if information about an AE is elicited, this will be recorded on the AE eCRF page.

**Disease under study**

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. Worsening of depression should be considered as disease progression and not an AE.

However, if it is felt that the study medicine may have contributed to the deterioration, this should be treated as an AE; hospitalization due to worsening of depression will be considered an SAE.

Symptoms of disease progression that result in discontinuation of treatment with the IP must be identifiable, whether or not they are captured as AEs, and appropriately recorded on the termination form or equivalent of the eCRF.

### 6.4.4 Reporting of SAEs

All SAEs have to be reported, whether or not considered causally related to the IP, ADT, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives within one day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

A social hospitalization (hospitalization unrelated to an AE) is allowed and is not defined as an SAE, if the reason for the visit is to accommodate travel requirements of the patient, and is not for medical management of any condition or illness.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the eDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the eDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

Refer to the study-specific Safety Handling Plan for details on SAE reporting using the eDC system.

**European Union (EU) only:** The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug and the EU Summary of Product Characteristics (SPC) for the active comparator product (including any AstraZeneca comparator.).

#### 6.4.4.1 Reporting of Suicidality

Suicide and attempted suicide, irrespective of the method, should be reported as AEs or SAEs. This event should be identified as suicide or attempted suicide, and the method of the suicide or attempt should be provided. If an attempted suicide meets the criteria for an SAE, the event must be reported according to the guidelines in Section 6.4.4. Suicidal thoughts should also be regarded as AEs.

All events of suicidality will be carefully monitored. These include events of suicide attempts, suicidal ideation, completed suicides, and suicidal behavior. The last category includes behavioral AEs or SAEs in which the investigator cannot rule out underlying suicidal thinking, eg, motor vehicle accident or behaving in a dangerous or unsafe way, and other self-injurious behaviors.

Any patient who, based on the investigator's judgment, poses an imminent risk of suicide should be discontinued from the study (see Sections 5.8 and 5.9). All efforts should be taken to minimize the risk of suicide and the investigator should carefully monitor the patient (see Section 6.4.10).

### 6.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be collected at the times indicated in Study Plan, Table 2. The date and time of collection will be recorded in the appropriate eCRF.

In the screening period, re-testing of missed laboratory safety assessments (eg, due to hemolyzed samples), deleted laboratory results or ECG abnormalities is allowed within the protocol-specified screening period; the same subject E-code should be used for the repeated assessments. Any subjects requiring a laboratory retest beyond the screening period will need to be rescreened and will require the approval of the Study Physician.

Re-testing of missed laboratory safety assessments (eg, due to hemolyzed samples), deleted laboratory results or technically inadequate ECGs is allowed within the protocol-specified visit interval window for visits in the open-label ADT or randomized treatment period; the same subject E-code should be used for the repeated assessments.

The following laboratory variables will be measured (Table 6):

**Table 6 Laboratory assessments**

| Clinical chemistry (serum) | Hematology (blood) | Urinalysis (urine) |
|---|---|---|
| ALT | Hematocrit (Hct) , Hemoglobin (Hgb) | Color |
| AST | Mean corpuscular hemoglobin (MCH), MCH concentration (MCHC), mean corpuscular volume (MCV), red cell distribution width (RDW) | Specific gravity |
| Alkaline phosphatase | White blood cells (WBC) | pH |
| Bilirubin, total (direct and indirect) | WBC differential including: lymphocytes, basophils, monocytes, neutrophils and eosinophils (absolute and percentages) | Glucose |
| Blood urea nitrogen (BUN) | Platelet count | Blood |
| Calcium | HIV, HBV, HbsAg, HCV | Protein |
| Chloride | Red blood cell (RBC) | Nitrites |
| $CO_2$ (Bicarbonate) | | Leukocyte esterase |
| Creatinine | | |
| Creatinine phosphokinase (CPK) | | Urine pregnancy test[c] |
| Glucose (fasting) | | |
| FSH, LH[a] | | Urine drug screen |
| $HbA_{1c}$ | | |
| LDH | | |
| Potassium | | |
| Sodium | | |
| Total protein | | |
| **Lipid panel (fasting)** | | |
| Total cholesterol | | |

**Table 6 Laboratory assessments**

| Clinical chemistry (serum) | Hematology (blood) | Urinalysis (urine) |
|---|---|---|
| High-density lipoprotein (HDL) cholesterol | | |
| Low-density lipoprotein (LDL) cholesterol | | |
| Triglycerides | | |
| **Thyroid panel**[b] | | |
| Triiodothyronine (Free $T_3$) | | |
| Thyroxine (Free $T_4$) | | |
| Thyroid-stimulating hormone (TSH) | | |

[a] LH and FSH will be used to determine menopausal status at the screening visit only (should be done on all women).
[b] A blood sample for a thyroid panel will be collected along with the clinical laboratory evaluations at the screening visit only.
[c] Positive urine pregnancy test will be confirmed with a reflex serum pregnancy test.

For blood volume to be collected during the study, see Section 7.1.

**For those visits that require fasting**

Fasting requires the patient not to eat and drink fluids other than water for more than 12 hours and the blood sample collection to be performed preferably between 08:00 and 10.00 in the morning. The date and time of the last meal (food and fluid intake, other than water) prior to blood sample collection will also be recorded to verify that the sample was taken under fasting conditions.

It is advised that the investigator contact the patient prior to a required fasting blood sample collection as a reminder. If the patient has not been fasting at the time of the study visit, the blood sample should be drawn and processed and shipped to the central laboratory for analysis, noting "non-fasting".

Fasting blood samples will be collected only for glucose and lipid analyses.

#### 6.4.5.1 Serology testing

Serology testing for HIV antibody, Hepatitis B (HBV) or HBsAg, and Hepatitis C (HCV) will be performed on all patients at screening only. If the test result for HIV antibody is positive, or if the hepatitis testing confirms new diagnosis of HBV or HCV, the patient will not be allowed to proceed in the study.

Note: Although the results of the HIV and hepatitis screens must be documented in the patient's file, these results will not be collected on the eCRF and will therefore not be recorded in the study database.

#### 6.4.5.2 Urine pregnancy test

A urine pregnancy test will be performed on all WOCBP at the scheduled visits in Table 2. If the urine pregnancy test is positive, it must be confirmed with a reflex serum pregnancy test. A patient with a confirmed pregnancy will be terminated (please see Section 13.3).

#### 6.4.5.3 Urine drug screen (UDS)

A urine sample for drugs of abuse will be evaluated at the screening visit. Additional evaluations may be performed at the discretion of the investigator. These additional assessments can be performed using a dipstick method such as a CLIA Waved dipstick but if positive the test should be confirmed by a full urine drug screen.

The sample will be tested for the following drugs of abuse: methamphetamines (including ecstasy), benzodiazepines, cocaine and/or metabolites, amphetamines, opiates, phencyclidine (PCP), tetrahydrocannabinol (THC) and barbiturates.

Patients with a positive urine toxicology will be excluded, with the exception of patients testing positive only for cannabinoids (THC) or for drugs legally available by valid prescription.

Patients with a positive UDS for a drug(s) legally available by prescription must provide evidence of the prescription for the drug(s), and may be allowed to participate in the study if, in the clinical judgment of the investigator, they are not abusing the medication. One repeat urine drug test may be allowed in cases where subjects tested positive for prescribed medications that the PI feels could be discontinued per protocol. The repeat urine drug test must be negative for that prescribed substance prior to the end of the screening period meeting the protocol required washout time for the substance in question.

Note: Although the results of the UDS must be documented in the patient's file, the results will not be collected on the eCRF and will therefore not be recorded in the study database.

### 6.4.6 Physical examination

A physical examination will be performed at times indicated in Study Plan, Table 2 and will include an assessment of the following: general appearance, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities), cardiovascular, respiratory, and neurological systems.

Complete physical examination data to be recorded on the eCRF will include:
1) normal/abnormal/not done, and 2) a description of any abnormalities. Except for the enrollment examination, if there has been no change from the physical examination performed at Visit 1, only new or aggravated information will be recorded.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the randomization assessment will be reported as an AE.

In addition, during physical examination, an assessment regarding constipation is to be performed. The following questions should be asked and documented in the source notes:

1. How many spontaneous bowel movements/week do you have?

2. Do you use laxatives? If yes, which laxative and at what frequency?

3. On a scale 0-3, please rate your difficulty with evacuation

   - 0= no difficulty
   - 1= mild difficulty
   - 2= moderate difficulty
   - 3= severe difficulty

Also, during the trial, for any patient who reports the concept of "severe constipation" or for whom the PI deems has "severe constipation", the same above 3 questions should to be asked and it should be recorded in the AELOG eCRF and a targeted physical exam should be performed (e.g. palpate abdomen). It is suggested that the patient be sent for an abdominal x-ray or other appropriate medical follow up if they meet 2 out of 3 criteria below or by PI judgment:

- Patient rates difficulty with evacuation as "severe difficulty" on the scale, and/or
- ≤1 spontaneous bowel movement/week for the preceding 2 weeks, and/or
- Patient has signs/symptoms of constipation on physical exam

All these assessments will be documented in the source documents at the investigative sites.

### 6.4.7 Medical, surgical and medication history

A detailed medical history including surgical and medication history will be recorded for each patient. Significant medical conditions that have occurred or conditions that are ongoing (ie, headache, backache, indigestion) are to be recorded in the eCRF.

Any medications taken within 30 days are to be recorded. The medication history must identify any known drug allergies, presence or history of drug abuse and use of chronic medications.

### 6.4.8 ECG

#### 6.4.8.1 Resting 12-lead ECG

A resting digital 12-lead ECG will be obtained using the ECG equipment provided by the central reader after the patient has been resting in the supine position for at least10 minutes at times indicated in the Study Plan, Table 2. If indicated, additional ECG assessments can be made at the discretion of the investigator. These assessments should be entered as an unscheduled assessment on the appropriate eCRF. Re-testing of ECG abnormalities is allowed within the protocol-specified screening period; the same subject E-code should be used for the repeated assessments. Re-testing for technically-inadequate ECGs may be obtained for visits outside of the screening period as long as the re-test is performed within the specified visit interval; the same subject E-code should be used for the repeated assessments.

The safety ECG will be documented in the eCRF by recording the date and time the measurement was performed and whether the evaluation was normal or abnormal. If the evaluation is considered to be abnormal the abnormality will be noted as to clinical significance. The paper copy of the ECG report should be signed and dated, and retained at the study site.

#### 6.4.8.2 Digital 12-lead ECG

A resting digital 12-lead ECG will be obtained after the patient has been resting in the supine position for at least10 minutes at times indicated in the Study Plan, Table 2. Re-testing of ECG abnormalities is allowed within the protocol-specified screening period; the same subject E-code should be used for the repeated assessments. Re-testing for technically-inadequate ECGs may be obtained for visits in the open label or randomized periods as long as the re-test is performed within the specified visit interval; the same subject E-code should be used for the repeated assessments. If the retesting falls outside of the visit interval window, it should be considered an unscheduled visit.

ECGs for all patients at all study centers will be performed using an ECG machine provided by the central ECG vendor and will be transmitted to the central ECG library. Quality assurance of the ECG waveform and patient demographics will be conducted by a central laboratory operator at the central ECG vendor. ECGs will be processed through a computer interpretation program and then reviewed by an ECG analyst and then by a board-certified cardiologist. The results from the ECG should be reported to the investigator within 48 hours. For ECG analyses, the electronic file transferred from the central ECG vendor to AstraZeneca or its representative will be considered source data.

Individual protocol mandated ECG results should only be reported as AEs if they fulfill the criteria for an SAE (see Section 6.4.2) or are the reason for discontinuation of treatment with the IP.

### 6.4.9 Vital signs

For the timing of vital signs assessments, refer to the Study Plan, Table 2.

#### 6.4.9.1 Seated blood pressure and pulse

Blood pressure measurement with a properly calibrated and validated instrument should be used. Patients should be seated quietly for at least 5 minutes in a chair rather than on an examination table, with feet on the floor and arm supported at heart level. An appropriate-sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure accuracy. At least 2 measurements should be made. The average of 2 readings is to be entered in the eCRF. This will be documented in the source documents at the investigative site.

Blood pressure and pulse measurement must be performed first in the seated position, then in the supine position, and then in the standing position.

#### 6.4.9.2 Orthostatic blood pressure and pulse

To assess for orthostatic hypotension, the following will be performed. This sequence of measurements should be taken once.

Supine systolic and diastolic blood pressure and pulse will be recorded using a semi-automatic blood pressure recording device with an appropriate cuff size. The patient will be required to rest in a supine position for at least 10 minutes prior to the assessment. This will be documented in the source documents at the investigative site.

Standing blood pressure and pulse will follow the supine blood pressure and pulse evaluations and will be recorded using a semi-automatic blood pressure recording device with an appropriate cuff size. Have patient stand and immediately measure blood pressure and heart rate. Record and observe any symptoms (e.g., dizziness). After the patient remains standing for 3 minutes, measure blood pressure and heart rate. This will be documented in the source documents at the investigative site.

#### 6.4.9.3 Height, weight, and waist circumference

Height will be measured in centimeters (cm) and weight will be measured in kilograms (kg).

The patient should remove outer coats and/or jackets and be wearing light clothes and no shoes. The same scale should be used for all assessment, and the scale should be calibrated once per year.

Waist circumference, measured in centimeters (cm) will be measured in the morning. The waist circumference should be measured in the following manner; patient is to relax with arms at the side; expose the waist w/undergarment pulled below waist level; locate the upper hipbone and the right iliac crest; place a measuring tape in a horizontal plane, around the abdomen, at the level of the iliac crest. Before reading the tape measure, be sure the tape is snug but not pressing the skin. Have the patient inhale and exhale and then take the measurement after normal expiration.

### 6.4.10 Suicidality assessment using the C-SSRS

**Description**

The Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner et al 2007) assesses the suicidal behavior and suicidal ideation in patients. Occurrence of suicidal behavior is defined as having answered "yes" to a least one of the 4 suicidal behavior sub categories (actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behavior) at any post randomization evaluation.

Occurrence of suicidal ideation after randomization is defined as having answered "yes" to at least one of the suicidal ideation sub-categories (wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any methods [not plan] without intent to act, active suicidal ideation with some intent to act [without specific plan], and active suicidal ideation with specific plan and intent) at any post randomization evaluation.

**Rationale**

The C-SSRS is a low burden, clinician administered tool designed to track suicidal AEs throughout any treatment trial and is considered to be the "gold standard" for assessment (Posner et al 2007). The measure succinctly covers the full spectrum of suicidality addressing both behavior and ideation and is now required by the US Food and Drug Administration (FDA) in clinical trials. It is both the prospective version of the Columbia suicide classification system commissioned by the FDA, which provided the data for their safety analyses, and is used across numerous industry and NIMH-sponsored studies.

**Assessments**

The C-SSRS is a unique, simple and short method of assessing both behavior and ideation that tracks all suicidal events, and provides a summary of suicidality. It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation and deterrents), all of which are significantly predictive of completed suicide.

The timing of the C-SSRS assessments are outlined in Study Plan, Table 2. The trained rater will record the clinical observation on the scale which will be used as the source document. If at all possible, the same individual should perform the assessment at each visit to reduce scoring availability. In the event the primary rater is not available, a designated back-up rater who meets the same qualifications may perform the C-SSRS.

### 6.4.11 Neurological assessments

Extrapyramidal symptoms (EPS) will be assessed as follows: dyskinesia will be assessed using AIMS and akathisia will be measured by BARS. Assessments will be recorded on the appropriate sections of the eCRF.

#### 6.4.11.1 Abnormal Involuntary Movement Scale (AIMS)

The AIMS is a 12-item instrument assessing abnormal involuntary movements associated with antipsychotic drugs, such as tardive dystonia and chronic akathisia, as well as "spontaneous"

motor disturbance related to the illness itself (Guy 1976a). Scoring the AIMS consists of rating the severity of movement in three main anatomic area (facial/oral, extremities, and trunk), based on a 5-point scale (0=none, 4=severe).

The AIMS instrument will be administered by study staff (eg, physician) at the specified visits in the Study Plan, Table 2.

#### 6.4.11.2 Barnes Akathisia Rating Scale (BARS)

The BARS is the most widely used comprehensive rating scale for akathisia (Barnes 1989). Only the global assessment will be captured and is made on a scale of 0 to 5 with comprehensive definitions provided for each anchor point on scale: 0=absent; 1=questionable; 2=mild akathisia; 3=moderate akathisia; 4=marked akathisia; 5=severe akathisia.

The BARS instrument will be administered by the study staff (eg, physician) at the specified visits in the Study Plan, Table 2.

### 6.4.12 DESS (for withdrawal/discontinuation events)

The Discontinuation-Emergent Signs and Symptoms (DESS) scale will be used to monitor patients for discontinuation symptoms. The complete DESS scale will be used to monitor patients for discontinuation symptoms in this study at Visit 11/Week 16+Day 3 post dose (by telephone interview), at Visit 13/Week 17 follow-up on-site visit and at the Visit 14/Week 18 follow-up on-site visit. At each visit interviews, the PI should ask the standard AE question first (and document the information as per standard AE procedure) and then ask the questions in the DESS scale.

### 6.4.13 Other safety assessments

Additional safety assessments in addition to those discussed above can be made at the discretion of the investigator in order to follow the patient's clinical condition. The assessments should be entered as unscheduled assessments in the appropriate sections of the eCRF.

## 6.5 Patient reported outcomes (PROs)

The methods for collecting PRO data are presented below. For the timing of individual assessments, refer to the Study Plan, Table 2. All PRO evaluations are to be assessed before the clinician-reported efficacy scales discussed in Section 6.3. The order of administration of questionnaires is: SDS, Q-LES-Q-SF, CSFQ, and EQ-5D.

For each PRO, individual item scores will be reported on a specifically designed eCRF. Signs and symptoms revealed and recorded during the ratings should only be reported as AEs if they fulfill the criteria for a SAE or are the reason for discontinuation from treatment with the IP. The PROs should be regarded as truly source data and no one except for the patient is allowed to amend or do revisions to the forms. Excluded are some "heading information" such as E-code and patient number.

### 6.5.1 Sheehan Disability Scale (SDS)

The SDS total score will be calculated as the sum of the score for the 3 inter-correlated domains (school/work, social life, and family life/home responsibilities) and can range from 0 to 30 (Leon et al 1997, Sheehan 1983, Sheehan and Sheehan 2008). It is designed for patients to self-rate their level of functional impairment over the last week. The SDS also includes an assessment of lost productivity due to symptoms of illness through two items evaluating lost days and under productive days. Each of these three items is scored on an 11-point scale, where a score of 0 is 'not at all impaired', 5 is moderately impaired' and 10 is 'very severely impaired'. A total SDS score will measure total impairment (range (0 to 30). To calculate the total score the three items within the SDS are summed into a single dimensional measure of functional impairment that ranges from 0 (unimpaired) to 30 (highly impaired). Subscale scores for work, social, and family domains are calculated separately. The subscale numerical ratings range is 0 to 10. Total scores, ranging from 0 to 30, are calculated only for patients who rate all three items.

### 6.5.2 Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)

The Q-LES-Q-SF (Endicott et al 1993) is a widely recommended and often used standard short form assessment of quality of life satisfaction. The Q-LES-Q-SF contains 16 items; only the first 14 items of the short form are summed and used to create the Q-LES-Q-SF total score. The 15th item queries respondents' satisfaction with the medication they are taking and the 16th item is a global rating of overall life satisfaction and contentment. The Q-LES-Q-SF total score is derived by summing scores from items 1-14 and the fourteen Q-LES-Q-SF items are each scored on a 5-point Likert scale ranging from 14 to 70, is then expressed as a percentage of the maximum (or % maximum) total score possible (ranging from 0 to 100) for ease of interpretation.

### 6.5.3 Changes in Sexual Functioning Questionnaire (CSFQ)

The self-administered CSFQ measures sexual dysfunction (Clayton et al 1997a) and consists of separate assessments for males and females. It has been validated in healthy and depressed clinic populations, and used in both longitudinal and cross sectional studies of sexual well-being (Clayton et al 1995, Clayton et al 1997b, Clayton et al 2002; Keller et al 2006). Questions on the CSFQ assess a variety of different causes of change in sexual functioning or desire (eg, relationship changes, stress level, illness, medications, etc). Sexual dysfunction is determined by falling below thresholds of total scores (47 for males and 41 females on a scale of 14 to 70), where lower scores are indicative of decreased sexual desire or functioning. The CSFQ also consists of subscales to assess specific aspects of sexual well-being. Pleasure (scored 1 to 5), desire/interest (scored 3 to 15), desire/frequency (scored 2 to 10), arousal (scored 3 to 15), and orgasm (scored 3 to 15) subscales are all assessed by questions on the CSFQ.

### 6.5.4 European Quality of Life (EuroQol) VAS and 5 dimensions (EQ-5D)

The EQ-5D self-assessment questionnaire provides 2 analysis variables: EQ-5D index score and EQ VAS (EuroQol 1990). The EQ-5D index score is a weighted linear combination over

5 dimensions of health status. The EQ VAS is a visual analog scale with range 0 to 100. For both variables, a higher score indicates a better health state. The scores range from possible negative values to a maximum of 1.0. The score is standardized to the 0.0 (dead) to 1.0 (perfect health) value scale.

### 6.5.5 Administration of PRO questionnaires

Appropriate procedures for minimizing bias and enhancing compliance will be followed throughout the study. To ensure this, a study coordinator at each study site will be responsible for the PRO evaluation and a standardized procedure for the administration of the PRO questionnaires will be applied. The patient will complete the questionnaires independently, so that the responses reflect the patient's perception and views rather that those of family, friends, staff or others.

Each study center will have a designated quiet space in the clinic for patients to complete the questionnaires at each visit. The questionnaires should be completed prior to other examinations, before there are substantial professional encounters with transmission of information, such as disease status. Such information may influence the answers that patients provide on questionnaires.

Training will be provided to study personnel to ensure the data quality through the standardized administration of the PRO questionnaires.

## 6.6 Pharmacokinetics

### 6.6.1 Collection of samples

During the ADT period, blood samples (approximately 4 mL collected in spray-dried K2-ethylenediamine tetraacetic acid [EDTA] tubes) will be collected for the determination of concentrations of citalopram/escitalopram (Celexa/Lexapro), sertraline (Zoloft), fluoxetine (Prozac), paroxetine (Paxil), venlafaxine XR (Effexor) or duloxetine (Cymbalta) in plasma. In the randomized double-blind treatment period, blood samples (approximately 4 mL collected in spray-dried K2-EDTA tubes) will be collected for the determination of concentrations of TC-5214 in plasma. The timing of sample collection is presented in the Study Plan, Table 2. The exact blood sampling time and date and exact time and date of the last TC-5214 dose should be recorded.

Blood samples will be mixed and immediately placed on ice until centrifugation. Plasma will be prepared by centrifugation at 4°C for 10 minutes at 1500 g within 30 minutes of blood sampling. The resulting plasma will be evenly divided into 2 polypropylene tubes with screw caps (2 mL Fisher micro-centrifuge tubes Cat. No. 02-681-343), with Fisher Screw Caps (Cat No. 02-681-354) or a tube and cap approved by AstraZeneca and immediately frozen upright at or below -20°C within 15 minutes of plasma preparation and kept frozen at this temperature or colder before, during, and after transport to the designated laboratory. One of these samples will be retained at the site until the analysis is completed on the original sample and it has been determined that the retention sample can be destroyed.

For blood volume, see Section 7.1.

### 6.6.2 Labeling of TC-5214, SSRI/SNRI plasma samples for shipment

Freezer compatible labels will be applied to the plasma sample tubes. The labels should contain the following information:

Study Number: D4130C00005
Enrollment number:
Study Week:
Sampling Time:
Analyte: TC-5214 or name of specific SSRI/SNRI
Matrix: Plasma

### 6.6.3 Shipment of TC-5214, SSRI/SNRI plasma samples

All TC-5214 and SSRI/SNRI samples accompanied by the sample shipment logs will be shipped to a central laboratory via an agreed upon carrier. Samples will be shipped by the central laboratory to [redacted] The frozen samples must be packed securely to avoid breakage during transit, should be double-bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure that the samples remain frozen for at least 72 hours to allow for potential delays in the shipment. All regulations must be followed. Documentation sufficient to identify each sample must be included with the shipment.

**Schedule of sample shipment**

Open-label ADT: As SSRI/SNRI will be quantified in the open-label ADT period as part of compliance assessment, a rapid turnover is required and samples will be sent on a bi-weekly basis.

Double-blind period: Samples will be shipped on a monthly basis.

**The primary contact, [redacted], AstraZeneca and [redacted] must be notified by email and fax at the time samples are shipped. The fax notification should include a copy of the specimen shipment log.**

Samples should only be shipped on Monday through Wednesday. Do not ship on or within 2 days prior to a legal holiday.

Plasma samples should be shipped to:

[redacted]

The following persons will be notified before dispatch:

[redacted]
Fax: [redacted]
Phone: [redacted]

[redacted]
Fax: [redacted]
Phone: [redacted]

All samples will be analyzed within the timeframe for which the stability of TC-5214 or the SSRI/SNRIs in the samples have been validated and shown to be acceptable.

### 6.6.4 Determination of drug concentration

Samples for the determination of the concentration of TC-5214 and the SSRI/SNRIs in plasma will be analyzed by [redacted] on behalf of AstraZeneca Clinical Pharmacology and DMPK (CPD), using liquid chromatography/tandem mass spectrometry LC/MS/MS. Full details of the analytical method used will be detailed in a separate bioanalytical report.

None of the samples from the placebo treated patients will be analyzed unless unusual results are obtained for patients administered TC-5214.

Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites or determine the reproducibility of the analytical results. Any results from such analyses may be reported separately from the clinical study report.

## 6.7 Pharmacogenetics

Refer to Appendix D for collection of PGx samples for the optional genetic research.

For blood volume, see Section 7.1.

# 7. BIOLOGICAL SAMPLING PROCEDURES

Samples will be frozen (-20°C or below) and transported to the relevant DNA extraction laboratory and must remain frozen at all times.

Where possible, samples should be shipped in batches and shipment should be coordinated with the receiving site to ensure that samples arrive within working hours. A requisition sheet, detailing the study number, enrollment number and/or randomization code, and date of sample collection should accompany this shipment.

Instructions regarding shipment of genetic samples will be provided separately from the protocol.

## 7.1 Volume of blood

Blood samples will be collected for clinical chemistry, hematology, PK and PGx assessments. The amount of blood collected for each assessment and the total volume of blood that will be drawn from each patient in this study is presented in Table 7.

**Table 7 Volume of blood to be drawn from each patient**

| Assessment | | Sample volume (mL) | No. of samples | Total volume (mL) |
|---|---|---|---|---|
| **Safety** | | | | |
| Visit 1 | Clinical chemistry, thyroid panel, FSH+LH | **8.5** | **1** | **8.5** |
| | Bicarbonate, serum pregnancy (tube must not be opened) | **3.5** | **1** | **3.5** |
| | Serology: HIV, HBV, HCV | **8.5** | **1** | **8.5** |
| | Hematology, $HbA_{1c}$ | **4** | **1** | **4** |
| Visit 2 | Clinical chemistry (including glucose & lipids) | **8.5** | **1** | **8.5** |
| | Bicarbonate (reflex serum pregnancy test, if urine is positive) | **3.5** | **1** | **3.5** |
| | Hematology | **4** | **1** | **4** |
| Visit 6 | Clinical chemistry (including glucose & lipids) | **8.5** | **1** | **8.5** |
| | Bicarbonate (reflex serum pregnancy test, if urine is positive) | **3.5** | **1** | **3.5** |
| | Hematology, $HbA_{1c}$ | **4** | **1** | **4** |
| Visit 7 | Clinical chemistry (non-fasting) | **8.5** | **1** | **8.5** |
| | Bicarbonate (reflex serum pregnancy test, if urine is positive) | **3.5** | **1** | **3.5** |
| | Hematology, $HbA_{1c}$ | **4** | **1** | **4** |
| Visit 9 | Clinical chemistry (non-fasting) | **8.5** | **1** | **8.5** |

**Table 7 Volume of blood to be drawn from each patient**

| Assessment | | Sample volume (mL) | No. of samples | Total volume (mL) |
|---|---|---|---|---|
| | Bicarbonate (reflex serum pregnancy test, if urine is positive) | **3.5** | **1** | **3.5** |
| | Hematology, $HbA_{1c}$ | **4** | **1** | **4** |
| Visit 11/early termination | Clinical chemistry (including glucose & lipids) | **8.5** | **1** | **8.5** |
| | Bicarbonate (reflex serum pregnancy test, if urine is positive) | **3.5** | **1** | **3.5** |
| | Hematology, $HbA_{1c}$ | **4** | **1** | **4** |
| Visit 14 | Clinical chemistry (including glucose &lipids) | **8.5** | **1** | **8.5** |
| | Bicarbonate (reflex serum pregnancy test, if urine is positive) | **3.5** | **1** | **3.5** |
| | Hematology, $HbA_{1c}$ | **4** | **1** | **4** |
| **PGx (optional)** | | | | |
| | Visit 2 | **10** | **1** | **10** |
| **PK** | | | | |
| | Visits 4, 6, 9 and 11 | **4** | **10**[a] | **40** |
| Total | | | | **170.5** |

[a] Duplicate PK samples will be taken at each visit, except at Visit 9 (Week 12), where 2 draws of 2 PK samples will be collected.

## 7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here.

The laboratory will provide detailed instructions including processing, handling, storage and shipment of laboratory samples before the study start. The samples should be properly obtained, processed, labeled, stored and shipped in accordance with the instructions provided by the laboratory. Samples should be shipped to the laboratory by courier unless otherwise agreed.

### 7.2.1 Pharmacokinetic samples

Samples will be disposed of after the CSR has been finalized, unless retained for future analyses, see below.

Key samples for validation in incurred samples will be retained at AstraZeneca for a maximum of 1 year following the finalization of the CSR. The results from the validation will not be reported in the CSR, but separately in the PK validation report.

### 7.2.2 Pharmacogenetic samples

Refer to Appendix D for collection and storage of PGx samples.

## 7.3 Labeling and shipment of biohazard samples

The PI ensures that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C "International Airline Transportation Association (IATA) 6.2 Guidance Document".

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca or its representative and appropriate labeling, shipment and containment provisions are approved.

It is the responsibility of the PI to ensure that staff packing the samples for shipment are IATA certified.

## 7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The PI at each center keeps full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca or its representative keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

The contract research organization (CRO) is responsible for keeping oversight of the samples during the study.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

## 7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, AstraZeneca or its representative is not obliged to destroy the results of this research.

As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca or its representative.
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented.
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site.
- Ensures that the patient and AstraZeneca or its representative are informed about the sample disposal.

AstraZeneca or its representative ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

# 8. ETHICAL AND REGULATORY REQUIREMENTS

## 8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

## 8.2 Subject data protection

The Informed Consent Form (ICF) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

Refer to Appendix D for data protection of PGx samples.

## 8.3 Ethics and regulatory review

An Institutional Review Board (IRB)/Ethics Committee (EC) should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable IRB/EC, and to the study site staff.

The opinion of the IRB/EC should be given in writing. The investigator should submit the written approval to AstraZeneca or its representative before enrollment of any patient into the study.

The IRB/EC should approve all advertising used to recruit patients for the study.

AstraZeneca or its representative should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB/EC annually.

Before enrollment of any patient into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca or its representative will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca or its representative will provide Regulatory Authorities, IRB/ECs and PIs with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

If required by local regulations, each PI is responsible for providing the IRB/ECs with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca or its representative will provide this information to the PI so that he/she can meet these reporting requirements.

## 8.4 Informed consent

The PI at each center will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided

- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an IRB/EC.

## 8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised CSP).

The amendment is to be approved by the relevant IRB/EC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PI. For distribution to the IRB/EC, see Section 8.3.

If a protocol amendment requires a change to a center's ICF, AstraZeneca and the center's IRB/EC are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each IRB/EC.

## 8.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an IRB/EC may perform audits or inspections at the center, including source data verification (SDV). The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact AstraZeneca or its representative immediately if contacted by a regulatory agency about an inspection at the center.

# 9. STUDY MANAGEMENT

Study Management will be performed by the contract research organization (CRO).

## 9.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of the CRO to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of the CRO. This will be documented in a Clinical Study Agreement (CSA) between AstraZeneca and the investigator.

## 9.2 Training of study site personnel

Before the first patient is entered into the study, a representative of the CRO will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study-specific procedures and systems utilized.

The PI will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff).

## 9.3 Monitoring of the study

During the study, a representative of the CRO will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to

the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts).

- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The CRO representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

### 9.3.1 Source data

Source data are any data generated as a result of the patients' inclusion in the study (including run-in and/or follow up related to the study) and includes all related medical examinations and other records. Original data recorded on the eCRFs are regarded as source data.

Refer to the Clinical Study Agreement (CSA) for location of source data.

## 9.4 Study agreements

The PI at each/the center should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the PI should be in place before any study-related procedures can take place, or patients are enrolled.

Prior to a patient's enrollment in the study and any study-related procedures are undertaken, the following should be fulfilled:

- signed CSA between AstraZeneca and the PI/study center
- signed CSP and other agreements between AstraZeneca and the PI/study center
- written approval of the study by the IRB/EC
- signed and dated Financial Disclosure forms

### 9.4.1 Archiving of study documents

The Investigator will follow the principles outlined in the CSA.

## 9.5 Study timetable and end of study

The end of the study is defined as "the last visit of the last patient undergoing the study". The end of study definition is for the entire study.

The study is expected to start in [redacted] and to end by [redacted].

The study may be terminated at individual centers if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with TC-5214.

# 10. DATA MANAGEMENT

Data Management (DM) will be performed by the CRO. The data collected through third party sources will be obtained and reconciled against study data.

Data entered in the eDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When the PI has signed the eCRF electronically as per eCRF instructions, then the patient's data will be locked.

**Electronic case report form**

The eCRF and the protocol are both confidential. The eCRF will be created by the CRO and programmed into the eDC system. All sites will need internet access to access the eCRFs and will only have access to data for patients at their own sites. DM and other co-ordinator teams will have access to data at all sites.

AstraZeneca or its representative will supply the eCRFs. All eCRFs are to be completed by an authorized member of the investigational staff and reviewed and signed by the investigator. All entries, corrections, and alterations are to be made by the responsible investigator or an authorized member of the investigational staff. All eCRFs are to be completed in a manner that ensures accurate interpretation of data.

It is each investigator's responsibility to ensure that all discontinued orders or changes in the study or other medications entered on the patient's eCRF correspond to the entries on the patient's medical records.

The eCRFs for any patient leaving the study should be completed at the time study medication is terminated for whatever reason.

The eCRFs must accurately reflect data contained in patient's records (eg, source documents).

**Dataflow**

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

After data is entered into the eCRF by site, autoqueries that are generated by the eDC system should be addressed by site. Data queries will be raised for inconsistent, impossible or missing data. At the monitoring visit, the Study Monitor must perform the SDV of the

required fields on completed forms and if there are no open queries, freeze the form. DM will run manual consistency checks outside of the eDC system and will raise manual queries for sites to address; if the form is frozen, DM will unfreeze to allow sites to amend data. The same process is to be followed by any other groups creating manual queries in the eDC system (eg, for SAE reconciliation). Once all data is entered, SDV complete on required fields, manual queries and electronic data reconciliation complete, and all queries closed, then the casebook can be signed. Once the casebook is signed, DM will then lock the casebook so that no amendments can be made. Any treatment revealing data may thereafter be added and the final database will be locked. All entries to the study database will be available in an audit trail.

**Database lock**

Once all patient casebooks are locked, the final data transfer can be sent to statistics. A database lock checklist will also be completed by DM and the programmer to confirm all applicable quality control checks were performed.

**Coding**

All AEs and Medical Histories recorded in the eCRF will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medications, including those on the ATHF, will be classified according to the AstraZeneca Drug Dictionary (AZDD). The coding will occur outside of the eDC system and will be merged with the clinical datasets sent to statistics.

**Investigator site file**

At the beginning of the study, an investigator's study file will be established at the study center. The investigator/institution is responsible for maintaining the study documents as specified in the guideline for ICH GCP (Committee for Proprietary Medicinal Products [CPMP]/ICH/145/95) and as required by the applicable regulatory requirement(s). The Investigator/institution must take measures to prevent accidental or premature destruction of these documents.

**SAE reconciliation**

The CRO will perform SAE reconciliation between the CRO Clinical Study database and the AstraZeneca Clinical Patient Safety database.

# 11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

## 11.1 Calculation or derivation of efficacy variable(s)

Change from randomization (Week 8) will be calculated as the visit score minus the randomization score.

### 11.1.1 Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS total score will be calculated as the sum of the 10 individual item scores; the total score can range from 0 to 60. Change from randomization will be calculated.

Remission in depressive symptoms of MDD is defined as a MADRS total score ≤8. In addition to achieving a total MADRS score of 8 or less, remission rates will also be evaluated using total MADRS score cutoffs of 10 and 12. Sustained Remission, defined as MADRS total score ≤8 at Week 12, Week 14, and end of treatment (Week 16), will also be evaluated.

Response in depressive symptoms is defined as a ≥50% reduction from randomization in the MADRS total score. Also, Early and Sustained Response and Sustained Response will be evaluated. Early and Sustained Response is defined as ≥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 is defined as ≥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).

### 11.1.2 Hamilton Rating Scale for Depression-17 items (HAMD-17)

The HAMD-17 total score will be calculated as the sum of the 17 individual item scores; the total score can range from 0 to 52. Change from randomization will be calculated.

### 11.1.3 Hamilton Anxiety Scale (HAM-A)

The HAM-A total score will be calculated as the sum of the 14 individual item scores; the total score can range from 0 to 56. Change from randomization will be calculated.

### 11.1.4 Clinical Global Impression (CGI)

CGI-S is a single item score. Change from randomization will be calculated. CGI-I is a single item score. Response in CGI-I will be based on whether or not the CGI-I score is 2 or less (very much improved or much improved).

## 11.2 Calculation or derivation of safety variable(s)

Change from randomization will be calculated as the visit value minus the randomization value.

### 11.2.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered OAEs and reported as such in the Clinical Study Report.

Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

AEs identified prospectively as AEs of special interest will not be considered other significant adverse events (OAEs).

### 11.2.2 Laboratory safety assessments

Change from randomization will be calculated for each continuous clinical chemistry, hematology, and urinalysis measurement.

### 11.2.3 ECG

Change from randomization will be calculated for each ECG parameter: heart rate, QRS duration, PR interval, RR interval, QT and QTcF interval.

### 11.2.4 Vital signs

Change from randomization will be calculated for each vital sign: SBP, DBP and heart rate (seated, supine and standing).

### 11.2.5 Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidal behavior is defined as having answered "yes" to a least one of the 4 suicidal behavior sub categories (actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behavior) at any post randomization evaluation.

Suicidal ideation after randomization is defined as having answered "yes" to at least one of the suicidal ideation sub-categories (wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any methods [not plan] without intent to act, active suicidal ideation with some intent to act [without specific plan], and active suicidal ideation with specific plan and intent) at any post randomization evaluation.

### 11.2.6 Abnormal Involuntary Movement Scale (AIMS)

The AIMS total score will be calculated as the sum of the first 7 individual item scores, and can range from 0 to 28. Change from randomization will be calculated.

### 11.2.7 Barnes Akathisia Rating Scale (BARS)

The BARS is a rating scale for drug-induced akathisia including 4 items. The last item (global clinical assessment of akathisia) score will be summarized, and can range from 0 to 5. Change from randomization in BARS global score will be calculated.

### 11.2.8 Discontinuation Emergent Signs and Symptoms (DESS)

The DESS scale will be used to monitor patients for discontinuation symptoms. It includes 43 signs or symptoms for which the patient indicates whether there has been any change since their last visit—indicating new symptom, old symptom but worse, old symptom but improved, old symptom but unchanged, symptom not present. The DESS total score is calculated as the count of items with new symptoms or old symptoms but worse. The total score can range from 0 to 43.

### 11.2.9 Weight and waist circumference

Change from randomization will be calculated.

### 11.2.10 Abuse potential

Abuse potential includes the following:

- Potential abuse liability
- Euphoria-type AEs, including euphoria, euphoric mood, elevated mood, mood alteration, feeling drunk, feeling abnormal
- Hallucination AEs, visual and auditory
- Inappropriate affect AEs, including elation inappropriate, exhilaration inappropriate, feeling happy inappropriately, inappropriate affect, inappropriate elation, inappropriate laughter and inappropriate mood elevation
- Other pertinent data including measurements of drug accountability, tolerance, physical dependence, withdrawal symptoms, or incidence of drug diversion, and the presence of signs or symptoms of drug abuse, misuse, or overdose

## 11.3 Calculation and derivation of PRO variable(s)

### 11.3.1 Sheehan Disability Scale (SDS)

The SDS total score will be calculated as the sum of the scores for the 3 inter-correlated domains (school/work, social life, and family life/home responsibilities). Each domain score can range from 0 to 10 and the total score can range from 0 to 30. The total score will be calculated only for patients who rate all three domains. Change from randomization will be calculated for the total score and for each domain score.

### 11.3.2 Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)

The Q-LES-Q-SF total score is derived by summing scores from items 1-14, and the fourteen Q-LES-Q-SF items are each scored on a response scale ranging from 1=very poor to 5=very good. The summed score, which can range from 14 to 70, is then expressed as a percentage of the maximum (or % maximum) total score possible (ranging from 0 to 100) for ease of interpretation.

### 11.3.3 Changes in Sexual Functioning Questionnaire (CSFQ)

The CSFQ total score will be calculated as the sum of the 14 individual item scores, and can range from 14 to 70. Change from randomization will be calculated.

### 11.3.4 European Quality of Life (EuroQol) VAS and 5 dimensions (EQ-5D)

- The EQ-5D self-assessment questionnaire provides 2 measures of health status: EQ-5D index score and EQ VAS score. The EQ-5D index score is a weighted linear combination over 5 dimensions of health status. The index score is standardized to range from 0 (worst health state) to 1 (best health state). The EQ VAS is a visual analogue scale of health status, with scores ranging from 0 (worst health state) to 100 (best health state). Change from randomization in both the EQ-5D index score and the EQ-5D VAS score will be calculated.

## 11.4 Calculation or derivation of pharmacokinetic variables

The PK analyses will be performed at AstraZeneca R&D. The actual sampling times will be used in the PK calculations.

Samples for the determination of the concentration of TC-5214 and SSRI/SNRI in plasma will be analyzed by [redacted] on behalf of AstraZeneca Clinical Pharmacology and DMPK (CPD), using liquid chromatography/tandem mass spectrometry LC/MS/MS. Full details of the analytical method used will be detailed in a separate bio-analytical report.

None of the samples from the placebo treated patients will be analyzed unless unusual results are obtained for patients administered TC-5214.

Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites or determine the reproducibility of the analytical results.

PK properties of TC-5214 in patients with MDD using a population PK analysis methodology will be investigated and reported separately from the clinical study report.

# 12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

A comprehensive statistical analysis plan (SAP) will be prepared and finalized before unblinding of the data.

## 12.1 Description of analysis sets

Four analysis sets will be used as defined below. Detailed descriptions of the analysis sets will be described in a comprehensive SAP that will be prepared and finalized before unblinding of the data.

### 12.1.1 Modified intent-to-treat analysis set

The modified intent-to-treat (mITT) analysis set will be considered as the full analysis set. This will include all evaluable patients, ie, all randomized patients who receive at least one dose of IP (TC-5214 or placebo) and who have a score at randomization and at least one post-

randomization MADRS total score. Patients will be classified according to the treatment to which they were randomized. Erroneously treated patients (eg, those randomized to treatment A but actually given treatment B) will be accounted for in their randomized treatment group. The mITT analysis set will be used for efficacy analyses.

### 12.1.2 Per-protocol analysis set

The per-protocol (PP) analysis set will include only those mITT patients who have no significant protocol deviations and who received the treatment to which they were randomized. The SAP will provide the exact criteria for determining inclusion in the PP analysis set. Analysis of primary efficacy endpoint will be repeated on the PP analysis set to test for robustness of results.

### 12.1.3 Safety analysis set

All randomized patients who receive at least one dose of IP (TC-5214 or placebo) and for whom any post dose data are available will be included in the safety analysis set. Patients will be classified according to the treatment actually received. Erroneously treated patients (eg, those randomized to treatment A but actually given treatment B) will be accounted for in their actual treatment group. The safety analysis set will be used to assess safety and tolerability variables.

### 12.1.4 DESS analysis set

The DESS analysis set will be used for evaluating discontinuation symptoms. This will include all patients who have a Week 16 assessment and at least one additional follow-up assessment. It will be used for evaluating discontinuation symptoms. Erroneously treated patients (e.g., those randomized to treatment A but actually given treatment B) will be accounted for in their actual treatment group.

## 12.2 Methods of statistical analyses

Detailed methods of statistical analyses will be presented in the SAP.

In general, all efficacy, safety and PK variables will be summarized using descriptive statistics and graphs as appropriate. Continuous variables will be summarized by descriptive statistics (sample size (n), mean, standard deviation (SD), minimum, median and maximum). Categorical variables will be summarized in frequency tables (frequencies and percentages). For AEs, exposure-adjusted incidence will also be presented. For PK variables, the geometric mean and coefficient of variation (CV) will be used instead of the arithmetic mean and SD, if appropriate. Individual data will be presented in patient listings.

All statistical tests will be conducted at a two-sided significance level of 5% unless otherwise specified. In general, each of the TC-5214 dose groups (0.1, 1 and 4 mg BID) will be compared to the placebo group. Where appropriate, model based point estimates, together with their 95% confidence intervals will be presented along with the two-sided p-value for the test.

Two types of datasets, both derived from the mITT analysis set, will be used for efficacy analyses: the observed case (OC) dataset and the last observation carried forward (LOCF) dataset. In general, the OC data for a visit will consist of the actual observations recorded for the visit. If missing, the OC data will remain missing—no data imputation will be performed. The LOCF data will be the corresponding OC data or, if that is missing, the last non-missing data carried forward from the most recent preceding visit. However, randomization values will not be carried forward for LOCF imputation. The calculation of total scores when there are missing item scores will be described in the statistical analysis plan (SAP). No other data imputation will be performed.

For the primary efficacy variable (change from randomization to Week 16 in MADRS total score) and the secondary efficacy variable (change from randomization to Week 16 in SDS total score, a multiple test procedure will be used to control the overall family-wise error rate at $\alpha = 0.025$ (one-sided) for the comparisons of each TC-5214 dose group (0.1, 1, and 4 mg BID) to placebo. Briefly, the procedure only allows a comparison and possible positive result for the 0.1 mg BID group if either the 1 or 4 mg BID dose group demonstrates superiority for the primary efficacy variable—and for the secondary efficacy variables at a particular dose only if the comparison was positive for the primary efficacy variable at the same dose.

It is expected that there will be variation among centers in the number of patients randomized, and that some centers may only randomize a few patients. To remedy this, centers will be pooled on a geographic basis. The detailed pooling plan will be included in the SAP. Pooled center will be used in place of center in all mixed model repeated measures (MMRM) and analysis of covariance (ANCOVA) analyses.

Superiority of TC-5214 over placebo will be shown if, following the multiple test procedure, either the 1 or 4 mg BID dose group demonstrates significantly better efficacy than the placebo group for at least the primary efficacy variable. The details of the multiple test procedure are given in Section 12.2.3.

### 12.2.1 Primary efficacy variable

The primary efficacy variable, the change from randomization in MADRS total score to Week 16 (end of treatment period) will be analyzed using a MMRM analysis of all of the post-randomization OC MADRS total scores through Week 16. The MMRM model will include treatment, pooled center, visit and treatment by visit interaction as explanatory variables and randomization MADRS total score as covariate. Treatment, visit and treatment by visit interaction will be fixed effects in the model; pooled center will be a random effect. Robust variance estimates for the fixed effects will be used for testing the treatment the effect of TC-5214 versus placebo. An unstructured covariance matrix will be used. Model based point estimates, 95% confidence intervals, and p-values will be calculated.

An ANCOVA with randomization MADRS total score as covariate, treatment as a fixed effect and pooled center as a random effect will be used as a robustness analysis using the last-observation-carried-forward (LOCF) approach.

Subgroup analyses will be performed by age, gender, race, and background antidepressant.

A test for dose-response will be performed using linear contrasts.

### 12.2.2 Secondary efficacy variables

The following continuous secondary efficacy variables will be analyzed using a MMRM analysis, which is described in Section 12.2.1:

- Change from randomization in HAMD-17 total score
- Change from randomization in the CGI-S score
- Change from randomization in the HAM-A total score
- Change from randomization in the MADRS total score at each assessment
- Change from randomization in functional impairment as assessed by SDS total score and 3 domain scores
- Change in Q-LES-Q-SF, items 15 and 16
- Change in EQ-5D index score and the EQ VAS score

Change from randomization to end of treatment in overall quality of life and satisfaction as assessed by Q-LES-Q-SF % maximum total score will be analyzed using an ANCOVA model with the baseline Q-LES-Q-SF % maximum total score as a covariate, treatment as a fixed effect, and pooled center as a random effect.

The following binary variables will be analyzed using a logistic regression model using treatment and pooled center as factors. For response and remission in depressive symptoms of MDD, Early and Sustained Response, Sustained Response, and Sustained Remission, the randomization MADRS total score will be used as a covariate and for analyzing CGI-I, the randomization CGI-S will be used as covariate.

- Response in depressive symptoms of MDD at Week 16
- Remission in depressive symptoms of MDD at Week 16
- Early and Sustained Response
- Sustained Response
- Sustained Remission
- Response in CGI-I at Week 16

No subgroup analyses or test for dose response of the secondary efficacy variables are planned.

### 12.2.3 Multiplicity adjustments for the primary and the important secondary objective of special interest

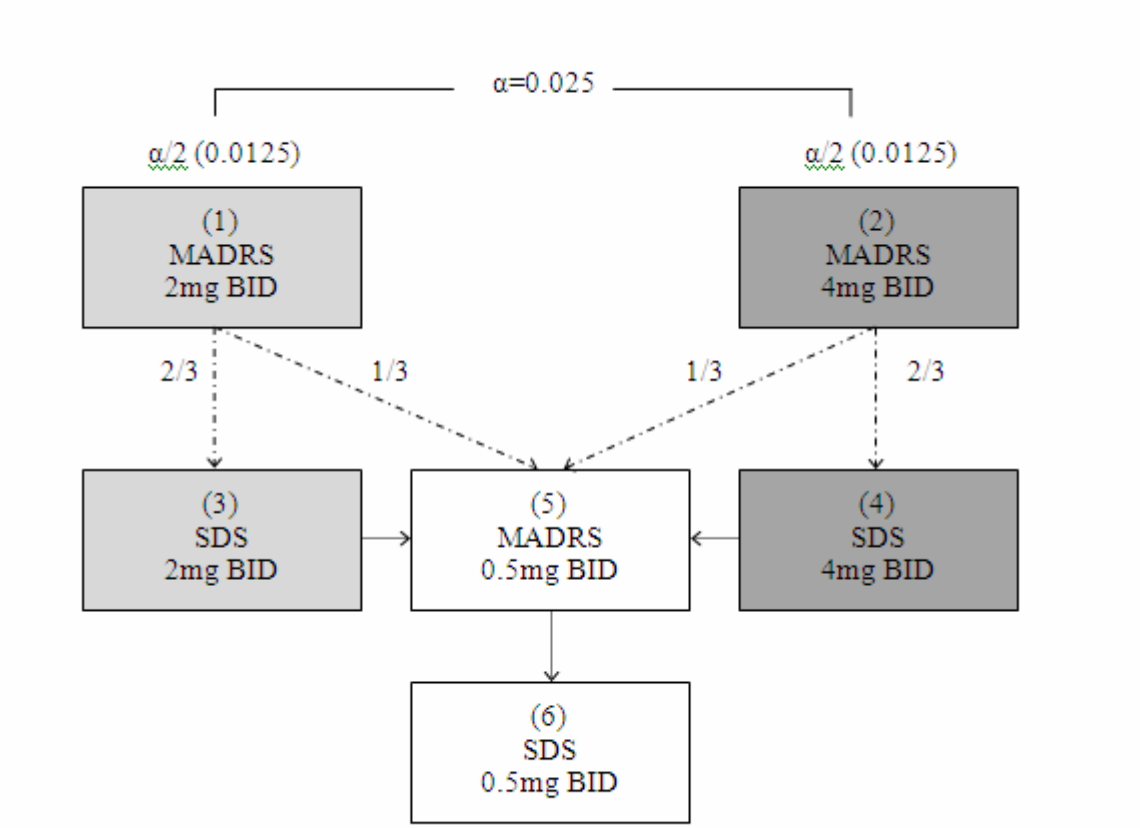
Each TC-5214 dose group (0.1, 1 and 4 mg BID) will be compared to placebo with respect to two variables; change from randomization to Week 16 in MADRS total score and change from randomization to Week 16 in SDS total score. The one-sided p-values for these 6 comparisons (from the MMRM analyses) will be used for the multiple test procedure.

For the primary objective, the null hypotheses are that the TC-5214 treatments, compared to placebo, do not reduce MADRS total score, when co-administered with an antidepressant for 8 weeks.

For the secondary objective, the null hypothesis is that the TC-5214 treatments, compared to placebo, do not reduce SDS total score, when co-administered with an antidepressant for 8 weeks.

In order to take account of these 6 comparisons and to control the overall family-wise type-I error rate at $\alpha$=0.025 (one-sided) in the strong sense, a recycling procedure (Burman et al 2009) will be used, as illustrated in the figure below (Figure 2). This procedure satisfies the matching restriction that a positive result for a secondary outcome variable with a certain dose is possible only if the result is positive for the primary outcome variable with the same dose.

**Figure 2 Graphical display of the recycling procedure**




If neither primary hypothesis (1) for the mid dose or (2) for the high dose can be rejected, the procedure stops and no further confirmatory hypothesis tests will be performed.

If hypothesis (1) is rejected, 2/3 of its test mass is recycled to test the secondary hypotheses for the mid dose, (3), and 1/3 of its test mass is recycled to test the primary hypothesis for the low dose (5). Similarly, if hypothesis (2) is rejected, 2/3 of its test mass is recycled to test the secondary hypotheses for the high dose, (4), and 1/3 of its test mass is recycled to test the primary hypothesis for the low dose (5).

If hypothesis (1) is rejected, secondary hypothesis (3) will be tested at level $\alpha/2 \times 2/3$ (approximately 0.008333). If hypothesis (3) is not rejected, no test mass is recycled. If hypothesis (3) is rejected, the test mass equal to $\alpha/2 \times 2/3$ is recycled to hypothesis (5). Similarly, if hypothesis (2) is rejected, the secondary hypothesis (4) will be tested and the test mass recycled accordingly.

Hypothesis (5) will be tested at a level equal to the sum of recycled test masses from hypotheses (1), (2), (3) and (4), if at least one of those hypotheses is rejected; i.e., the available test mass will range from $\alpha/2 \times 1/3$ (approximately 0.004167) to $\alpha/2 \times 2$ (0.025), depending on the outcomes of the preceding tests.

The secondary hypotheses for the low dose (6) will only be tested if hypothesis (5) is rejected. In that case, all of the test mass from hypothesis (5) will be recycled to hypothesis (6).

### 12.2.4 Safety variables

All safety data will be listed. Descriptive statistics will be used to summarize the following safety outcomes in the randomized double-blind treatment period by TC-5214 dose as well as for all TC-5214 doses combined:

- AEs and 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 related to abuse, misuse, noncompliance, and diversion
- Change from randomization (Week 8) to each assessment timepoint in:
  - Physical examination results, clinical laboratory test results , vital signs, weight, waist circumference, and ECG results
  - BARS and AIMS
  - CSFQ total score
- Suicidal behavior as assessed by C-SSRS and AEs of suicidality, suicidal ideation, suicide attempts, and suicide completion
- Occurrences of clinically important laboratory results, vital sign and ECG results (The criteria for these will be specified in the SAP)

Individual items of the DESS scale will be summarized by proportion of patients with treatment emergent symptoms at each assessment. The total score of the DESS scale will be summarized with descriptive statistics and with proportion of patients experiencing one or more symptoms at each assessment. Similar data presentations will be provided for by-item summaries across all assessments during the follow-up period.

## 12.3 Determination of sample size

The sample size calculation in this study is based for demonstrating the superiority of TC-5214 as adjunct to antidepressant versus placebo as add on to antidepressant with respect to the primary outcome variable change from randomization (Week 8) to Week 16 (end of treatment) in MADRS total score. A multiplicity procedure will be utilized implying that testing the lowest dose versus placebo with respect to primary endpoint only is only done if at

least one of the two higher doses is statistically significant. Thus, sample size is based on a Bonferroni adjustment for two comparisons versus placebo.

Assuming a standard deviation of 9 (based on historical data), a true difference of 3.5 between the treatment groups, 664 evaluable patients (166 per arm) are needed to reject the null hypothesis of no difference (for any dose) with a power of 90% using a significance level of 5% (2.5% for each of the 2 higher doses versus placebo). The choice of detecting a difference of 3.5 is based on what has been used for other studies and is considered to be clinically relevant. This implies that 684 patients need to be randomized assuming 2.5% of the randomized population will not qualify for the mITT analysis set. Assuming that 45% of the enrolled population treated with antidepressant will enter the randomized part, 1520 patients need to enter the open label ADT period. Assuming a screening failure rate of 32%, 2236 patients need to be screened.

| | **As specified** |
|---|---|
| **Power** | 90% |
| **Anticipated difference to be detected compared to placebo** | 3.5 |
| **Standard deviation** | 9 |
| **Significance level** | 5% |
| **Sample size (evaluable)** | 664 (166 per arm) |
| **Number of randomized patients** | 684 (171 per arm) |
| **Number of patients entering open label treatment with antidepressant** | 1520 |
| **Number of patients to be screened/enrolled** | 2236 |

# 13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

## 13.1 Medical emergencies and AstraZeneca contacts

The PI is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4.**

In the case of a medical emergency, the investigator should contact the following personnel below:

| **Name** | **Role in the study** | **Address & telephone number** |
|---|---|---|
| [redacted] | Global Study Physician | [redacted]<br>Tel: [redacted]<br>Fax: [redacted]<br>24 hour urgent medical contact:<br>Tel: [redacted] |
| [redacted] | SAE reporting | Refer to the study reference manual for country-specific SAE reporting numbers |
| **Other contact information** | | |
| **Name** | **Role in the study** | **Address & telephone number** |
| [redacted] | Central laboratory (Europe) | [redacted]<br>Phone: [redacted]<br>Fax: [redacted] |
| [redacted] | Central laboratory (Chile, Columbia) | [redacted]<br>Phone: [redacted]<br>Fax: [redacted] |

| Name | Role in the study | Address & telephone number |
|---|---|---|
| [redacted] | Central laboratory (Argentina) | [redacted] Phone: [redacted] |
| [redacted] | Central laboratory (Brazil) | [redacted] |
| [redacted] | Central laboratory (South Africa) | [redacted] Phone: Fax: [redacted] |
| [redacted] | Central ECG laboratory | [redacted] |
| [redacted] | IVRS | [redacted] Tel: Fax: [redacted] |
| [redacted] | PK sampling | [redacted] Fax: Phone: [redacted] |

## 13.2 Overdose

For the TC-5214 program, any overdoses of TC-5214, placebo, or ADT in the interval from Visit 2 to the end of follow-up should be recorded. Overdose is defined as a dose ingested (or taken via any other route), confirmed by the patient (if possible), in excess of the total daily dose specified for the patient in their treatment group of the protocol (including prospective ADT treatment**)**. All reports of overdose (with or without associated adverse events) are to be collected.

There is no specific antidote to TC-5214. In cases of severe intoxication, intensive care procedures are recommended. Close medical supervision and monitoring should be continued until the patient recovers.

Signs of overdose with mecamylamine include hypotension (which may lead to peripheral vascular collapse), postural hypotension, nausea, vomiting, diarrhea, constipation, paralytic ileus, urinary retention, dizziness, anxiety, dry mouth, mydriasis, blurred vision, or palpitations. A rise in intraocular pressure may occur.

Pressor amines may be used to counteract excessive hypotension. Since patients being treated with ganglion blockers are more than normally reactive to pressor amines, smaller doses of the later are recommended to avoid excessive response.

For recording purposes:

- If an overdose is reported during the course of a study, the patient is evaluated by the investigator/site staff to determine whether an SAE, non-serious AE, or no symptoms have been experienced after the overdose has been taken
- If the patient experiences an overdose with an associated SAE, the investigator/site staff will capture details of the SAE and associated information on OVERDOSE, AELOG, and SAE modules in the CRF
- If the patient experiences an overdose with an associated non-serious AE, the investigator/site staff will capture details of the non-serious AE and associated information on OVERDOSE and AELOG modules in the CRF
- If the patient experiences an overdose with no symptoms, the investigator/site staff will capture details of the overdose and associated information on OVERDOSE module only in the CRF
- The OVERDOSE module in the eCRF will be used for collecting the overdose information.

For reporting purposes:

- If an overdose occurs in the course of an AstraZeneca study, the investigators/site staff must inform appropriate **AstraZeneca representatives immediately, but no**

**later than the end of the next business day** of when he or she becomes aware of it.

- The designated AstraZeneca representative or its representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety Data Entry Site (DES)

The following timelines will apply on reports of overdose:

- Fatal/life threatening SAEs are sent to DES **within one calendar day** of initial notification of the overdose
- Other SAEs are sent to DES **within four calendar days** of initial notification of the overdose
- Overdoses with no symptoms or with associated non-serious AEs are sent to DES **within five calendar days** of initial notification of the overdose

For overdoses associated with a SAE, standard reporting timelines apply, see Section 6.4.4. All overdoses must be reported. In all instances, the overdose substance and amount ingested if known, must be stated and an assessment whether the overdose was accidental or intentional should be recorded. If the overdose was a suicide attempt, this should be clearly stated.

## 13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca or its representative on the pregnancy form.

### 13.3.1 Maternal exposure

Requirements for contraception in females of childbearing potential are specified in inclusion criteria #3 (see Section 4.1).

If a patient becomes pregnant during the course of the study, the IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one calendar day**, ie, immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.4.4, and within 30 days for all other pregnancies

The same timelines apply when outcome information is available.

The Pregnancy module in the eCRF is used to report the pregnancy and Astra Zeneca's Pregnancy Outcome Report, part 2, is used to report the outcome of the pregnancy.

If the pregnancy was known before the patient received investigational treatment, the outcome is not reported or followed-up as long as the patient was subsequently withdrawn from the study before receiving any investigational treatment or procedures. The outcome of any pregnancy occurring from the date of the first dose and for 30 days post-treatment (or last dose) should be followed up and documented.

### 13.3.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 12 weeks following the last dose.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

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AstraZeneca

**Clinical Study Protocol Appendix B**

| | |
|---|---|
| Drug Substance | TC-5214 (S-mecamylamine) |
| Study Code | D4130C00005 |
| Edition [redacted] | [redacted] |
| Date | [redacted] |

# Appendix B
# Additional Safety Information

# FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)



## Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

## Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

## Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

# A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

# Appendix C
# International Airline Transportation Association (IATA) 6.2 Guidance Document

# LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES



International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

**Category B Infectious Substances** are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

**Exempt** - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

**Clinical Study Protocol Appendix D**

| | |
|---|---|
| Drug Substance | TC-5214 (S-mecamylamine) |
| Study Code | D4130C00005 |
| Edition | [redacted] |
| Date | [redacted] |

# Appendix D
# Pharmacogenetics Research

# TABLE OF CONTENTS PAGE

# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation or special term | Explanation |
|---|---|
| CSR | Clinical Study Report |
| DNA | Deoxyribonucleic acid |
| LIMS | Laboratory information management system |
| PGx | Pharmacogenetics |

# 1. BACKGROUND AND RATIONALE

AstraZeneca intends to perform genetic research in the TC-5214 clinical development programme to explore how genetic variations may affect the clinical parameters associated with TC-5214 and/or agents used in combination or as comparators. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies. Studies may also be performed on the underlying genetic contribution to MDD.

# 2. GENETIC RESEARCH OBJECTIVES

The objective of this research is 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.

# 3. GENETIC RESEARCH PLAN AND PROCEDURES

## 3.1 Selection of genetic research population

### 3.1.1 Study selection record

All subjects who did not participate or were screen failures in the Phase III efficacy studies (D4130C00002, D4130C00003, D4130C00004, or D4130C00005) will be asked to participate in this genetic research. Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

### 3.1.2 Inclusion criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

### 3.1.3 Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

### 3.1.4 Discontinuation of subjects from this genetic research

Specific reasons for discontinuing a subject from this genetic research are:

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 7.5 of the main Clinical Study Protocol.

## 3.2 Collection of samples for genetic research

The blood sample for genetic research will be obtained from the subjects at Visit 2 or after randomisation. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume, see Section 7.1 of the Clinical Study Protocol.

## 3.3 Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 25 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible. Residual DNA will be destroyed at or before a 25-year maximum retention time has been reached.

For all samples, irrespective of the type of coding used, the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the subject enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

# 4. ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 8 of the main Clinical Study Protocol.

## 4.1 Informed consent

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue from the genetic aspect of the study at any time.

## 4.2 Subject data protection

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

# 5. DATA MANAGEMENT

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze the samples.

The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

# 6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

# 7. LIST OF REFERENCES

Not Applicable.

# Appendix E
# Study designs and treatment regimes used in the phase III efficacy studies

## Summary of Phase III efficacy studies

| Study number | Study Design | No. of patients | Patient population | Dose and route (p.o.) | Objective |
|---|---|---|---|---|---|
| D4130C00002 (US and Canada) | This is a multicenter, randomized, double-blind, parallel group, placebo-controlled, Phase III study of the efficacy and safety of 8 weeks of treatment with TC-5214 in flexible doses of 1, 2, and 4 mg twice a day (BID) in combination with an antidepressant (SSRI/SNRI) in the treatment of patients with MDD with an inadequate response to an antidepressant (SSRI/SNRI) therapy. Following the screening, washout and antidepressant treatment (ADT) periods, eligible patients will be randomized to 1 of 2 treatment regimens (TC-5214 or placebo) and assigned in a 1:1 ratio. | 288 (144 on TC-5214 and 144 on placebo) | MDD | Dose to be titrated in 2 week intervals starting at randomization<br>1 mg TC-5214<br>2 mg TC-5214<br>4 mg TC-5214<br>Placebo | To evaluate the efficacy of TC-5214 compared with placebo as an adjunct to antidepressant selective serotonin reuptake inhibitor [SSRI]/serotonin/norepinephrine reuptake inhibitor [SNRI]) therapy in patients with major depressive disorder (MDD) who exhibit an inadequate response to antidepressant therapy, as assessed by change in Montgomery-Åsberg Depression Rating Scale (MADRS) total score from randomization (Week 8) to end of treatment (Week 16).<br>• Change from randomization to end of treatment:<br>o HAMD-17<br>o CGI-S<br>o CGI-I<br>o HAM-A<br>o MADRS<br>o SDS<br>o Q-LES-Q-SF<br>o QIDS-SR-16 |

## Summary of Phase III efficacy studies

| Study number | Study Design | No. of patients | Patient population | Dose and route (p.o.) | Objective |
|---|---|---|---|---|---|
| D4130C00003 (RoW countries) | This is a multicenter, randomized, double-blind, parallel group, placebo-controlled, Phase III study of the efficacy and safety of 8 weeks of treatment with TC-5214 in flexible doses of 1, 2, and 4 mg twice a day (BID) in combination with an antidepressant (SSRI/SNRI) in the treatment of patients with MDD with an inadequate response to an antidepressant (SSRI/SNRI) therapy. Following the screening, washout and antidepressant treatment (ADT) periods, eligible patients will be randomized to 1 of 2 treatment regimens (TC-5214 or placebo) and assigned in a 1:1 ratio. | 288 (144 on TC-5214 and 144 on placebo) | MDD | Dose to be titrated in 2 week intervals starting at randomization<br>1 mg TC-5214<br>2 mg TC-5214<br>4 mg TC-5214<br>Placebo | To evaluate the efficacy of TC-5214 compared with placebo as an adjunct to antidepressant selective serotonin reuptake inhibitor [SSRI]/serotonin/norepinephrine reuptake inhibitor [SNRI]) therapy in patients with major depressive disorder (MDD) who exhibit an inadequate response to antidepressant therapy, as assessed by change in Montgomery-Åsberg Depression Rating Scale (MADRS) total score from randomization (Week 8) to end of treatment (Week 16).<br>• Change from randomization to end of treatment:<br>o HAMD-17<br>o CGI-S<br>o CGI-I<br>o HAM-A<br>o MADRS<br>o SDS<br>o Q-LES-Q-SF<br>o QIDS-SR-16 |

## Summary of Phase III efficacy studies

| Study number | Study Design | No. of patients | Patient population | Dose and route (p.o.) | Objective |
|---|---|---|---|---|---|
| D4130C00004 (US, Canada and India) | This is a multicenter, randomized, double-blind, parallel group, placebo-controlled, Phase III study of the efficacy and safety of 8 weeks of treatment with TC-5214 in fixed doses of 0.5, 2 and 4 mg twice daily (BID); in combination with an antidepressant (SSRI/SNRI) in the treatment of patients with MDD with an inadequate response to an antidepressant (SSRI/SNRI) therapy. Following the screening, washout and open-label antidepressant treatment (ADT) periods, eligible patients will be randomized to 1 of 4 treatment regimens and assigned in a 1:1:1:1 ratio. | 684 (166 per group) | MDD | 0.5 mg TC-5214<br>2 mg TC-5214<br>4 mg TC-5214<br>Placebo | To evaluate the efficacy of TC-5214 compared with placebo as an adjunct to antidepressant (selective serotonin reuptake inhibitor [SSRI]/serotonin/norepinephrine reuptake inhibitor [SNRI]) therapy in patients with major depressive disorder (MDD) who exhibit an inadequate response to antidepressant therapy, as assessed by change in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score from randomization (Week 8) to end of treatment (Week 16). |

## Summary of Phase III efficacy studies

| Study number | Study Design | No. of patients | Patient population | Dose and route (p.o.) | Objective |
|---|---|---|---|---|---|
| D4130C00005 (RoW countries) | This is a multicenter, randomized, double-blind, parallel group, placebo-controlled, Phase III study of the efficacy and safety of 8 weeks of treatment with TC-5214 in fixed doses of 0.1, 1 and 4 mg twice daily (BID); in combination with an antidepressant (SSRI/SNRI) in the treatment of patients with MDD with an inadequate response to an antidepressant (SSRI/SNRI) therapy. Following the screening, washout and open-label antidepressant treatment (ADT) periods, eligible patients will be randomized to 1 of 4 treatment regimens and assigned in a 1:1:1:1 ratio. | 720 (180 per group) | MDD | 0.1 mg TC-5214<br>1 mg TC-5214<br>4 mg TC-5214<br>Placebo | To evaluate the efficacy of TC-5214 compared with placebo as an adjunct to antidepressant (selective serotonin reuptake inhibitor [SSRI]/serotonin/norepinephrine reuptake inhibitor [SNRI]) therapy in patients with major depressive disorder (MDD) who exhibit an inadequate response to antidepressant therapy, as assessed by change in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score from randomization (Week 8) to end of treatment (Week 16). |