AstraZeneca

Revised Clinical Study Protocol

Drug Substance	TC-5214 (S-mecamylamine)
Study Code	D4130C00007 (LTSS)
Edition Number	[redacted]
Date	[redacted]

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase III, Long-Term Safety and Tolerability Study of TC-5214 (S-mecamylamine) as an Adjunct to an Antidepressant in Patients with Major Depressive Disorder Who Exhibit an Inadequate response to Antidepressant Therapy

Sponsor:

AstraZeneca [redacted]

Quintiles Global Project Manager [redacted]

Date
(Day Month Year)

[redacted]

Phone: [redacted]

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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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AstraZeneca

REVISED PROTOCOL SYNOPSIS

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase III, Long-term Safety and Tolerability Study of TC-5214 (S-mecamylamine) as an Adjunct to an Antidepressant in Patients with Major Depressive Disorder Who Exhibit an Inadequate response to Antidepressant Therapy

International Co-ordinating Investigator

[redacted]

Phone: [redacted]
Fax: [redacted]

Study center(s) and number of patients planned

This will be a global, multicenter study conducted at approximately 127 centers in the United States (US), with the addition of other countries as needed. A sufficient number of male and female patients, age 18 to 65 years inclusive with an established diagnosis of major depressive disorder (MDD), will be screened to ensure that an adequate number of patients are randomized (3:1) into the study to obtain 400 patients treated for 6 months and 200 patients treated for 1 year within the dose range (1-4 mg twice per day [BID]). Recruitment will be completed once the target number of patients is randomized. It is currently estimated that approximately 800 to 850 subjects will need to be randomized to reach long-term targets.

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

Objectives

Primary Objective:

The primary objective of this study is to evaluate the long-term safety and tolerability 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.

Secondary Safety and Tolerability Objectives:

The secondary safety and tolerability objectives focus on individual safety areas of special interest to this study.

- To evaluate the safety and tolerability of TC-5214 and placebo in combination with an antidepressant (SSRI/SNRI) in patients with MDD by assessing:
  - 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 reduction of blood pressure, orthostatic hypotension, anticholinergic signs and symptoms (including urinary retention), extrapyramidal symptoms (EPS), and increased fasting blood glucose
  - AEs potentially related to abuse, misuse, noncompliance, and diversion
  - Change from randomization in physical examinations, weight, waist circumference, vital signs, clinical laboratory test results, and electrocardiographic (ECG) parameters
  - 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 in EPS as measured by:
    - Barnes Akathisia Rating Scale (BARS)
    - Abnormal Involuntary Movement Scale (AIMS)
- Change from last treatment visit to follow-up visit in the Discontinuation Emergent Signs and Symptoms Scale (DESS)

Secondary Objectives:

The secondary objectives include:

- To evaluate the efficacy of TC-5214 and placebo in combination with an antidepressant (SSRI/SNRI) in patients with MDD by assessing:
  - Montgomery-Åsberg Depression Rating Scale (MADRS) total score
  - Clinical Global Impression-Severity (CGI-S) score
  - Functional impairment by the Sheehan Disability Scale (SDS) score

- Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) % maximum total score
- European Quality of Life (EuroQol) VAS and 5 dimensions (EQ-5D)
- Healthcare Resource Utilization and Work Absence (HRUWA)

Study design

This is a 52-week multicenter, randomized, double-blind, parallel group, placebo-controlled, Phase III safety and tolerability study of TC-5214 flexibly dosed (1-4 mg BID) in combination with an antidepressant in patients with major depressive disorder with an inadequate response to a prior SSRI/SNRI antidepressant therapy. Eligible patients will be randomized to TC-5214 1 mg or matching placebo BID in a 3:1 ratio. Patients will be titrated based on clinical response and tolerability within the range of 1 to 4 mg BID.

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. The current episode of depression must be >6 weeks and not exceed 24 months (2 years) in duration. Additionally, patients may have had an inadequate response to no more than 1 prior 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 prior antidepressant was ≤4 weeks and this treatment was discontinued due to tolerability.

New or screen failure patients who have not been treated with a permitted SSRI/SNRI treatment will be required to have a clinician-rated HAMD-17 total score of ≥15 and CGI-S of ≥4 to enroll into a 6-week prospective open-label SSRI/SNRI period. These patients will receive treatment with an open-label antidepressant (SSRI/SNRI) therapy (citalopram, duloxetine, escitalopram, fluoxetine, paroxetine CR, sertraline, venlafaxine XR) selected by the investigator to demonstrate inadequate response.

Patients who have completed a prospective SSRI/SNRI treatment and have an inadequate response to prospective SSRI/SNRI period will be randomized into the double-blind treatment period. For the purpose of randomization, an inadequate response is strictly defined as a HAMD-17 total score of ≥10 as defined by a clinician-rated HAMD-17 and a CGI-S score ≥3.

Patients in the randomized double-blind study will come from the following three sources:

- Group 1: Patients not receiving treatment with a permitted SSRI/SNRI
- Group 2: Patients receiving treatment with a permitted SSRI/SNRI

- Group 3: Patients completing a TC-5214 Phase III efficacy study and already on a permitted SSRI/SNRI

Investigational product, dosage and mode of administration

TC-5214 1 mg, 2 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

Duration of randomized treatment is 52 weeks.

Outcome variable(s):

- **Safety:**
  - AEs and SAEs, including their severity
  - AEs of special interest including, but not limited to reduction of blood pressure, orthostatic hypotension, anticholinergic signs and symptoms (including urinary retention), EPS symptoms, and increased fasting blood glucose
  - AEs leading to treatment discontinuation or study withdrawal
  - AEs potentially related to abuse, misuse, noncompliance, and diversion
  - Change from randomization in:
    - Clinical laboratory results, vital signs, weight, waist circumference, physical examination, and ECG results
    - BARS
    - AIMS
  - Shifts to clinical important lab, vital sign, ECG values
  - Suicidality as assessed by C-SSRS and AEs of suicidality, suicidal ideation, suicide attempts, suicide completion
  - Change in DESS
  - Other significant adverse events (OAEs)

Safety data, as well as exposure, will be summarized by source and overall. Additional subgroup analyses, including combination with SSRI/SNRI, will be identified in the Statistical Analysis Plan (SAP).

- **Efficacy**

Descriptive statistics will be used to present the following efficacy outcomes:

- Change from randomization in:
  - MADRS total score
  - CGI-S
  - SDS total score
  - Q-LES-Q-SF % maximum total score
  - EQ-5D total score
  - Healthcare Resources Utilization And Work Absence (HRUWA)

- **Pharmacogenetic**
  - Exploratory analysis of the genetic contribution to variance in pharmacodynamics, safety, tolerability and efficacy related to the treatments investigated in this study may be performed. Analyses may also be performed to study the genetics of MDD. Patients who were part of the Phase III pivotal studies for TC-5214 in the preceding 4 months and had a pharmacogenetic sample taken will not have another pharmacogenetic sample taken in the long-term safety study (D4130C00007).

Statistical methods

This is a general evaluation of long-term safety and tolerability. Therefore, no formal inferential statistical analyses are planned. Descriptive statistics will be provided for all safety and efficacy variables to facilitate the evaluation of long-term safety, tolerability, and efficacy. 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). Individual data will be presented in patient listings.

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

Efficacy analyses will be based on the modified intent-to-treat (mITT) analysis set that will include all randomized patients who received at least one dose of investigation product (TC-5214 or placebo) and who have a score at randomization and at least one post-randomization MADRS total score.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study 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
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
CSP	Clinical Study Protocol
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Event
CYP	Cytochrome P450
DAE	Discontinuation of Investigational Product due to Adverse Event

Abbreviation or special term	Explanation
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 (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
eCRF	Electronic case report form
ECT	Electroconvulsive therapy
eDC	Electronic data capture
EDTA	Ethylene diamine tetra acetic acid
EPS	Extrapyramidal symptoms
EQ-5D	European Quality of Life (EuroQol) VAS and 5 dimensions
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GMP	Good manufacturing practice
GRand	Global Randomization system
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
HDL	High-density lipoprotein cholesterol
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HRUWA	Healthcare resource utilization and work absence
IATA	International Airline Transportation Association
ICF	Informed consent form

Abbreviation or special term	Explanation
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 Chromatography/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 Regulatory Activities
MINI	Mini-International Neuropsychiatric Interview
mITT	Modified intent-to-treat
MMRM	Mixed model repeated measures
MRT	Mean residence time
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

Abbreviation or special term	Explanation
PCP	Phencyclidine
PGx	Pharmacogenetic research
PI	Principal Investigator
PRN	Pro-re nata – when necessary
PRO	Patient-reported outcome
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form
QoL	Quality of Life
QTcB	Bazett-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
SSRI	Selective serotonin reuptake inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction
T3	Triiodothyronine
T4	Thyroxine
TCA	Tricyclic antidepressant
TEAE	Treatment-emergent adverse event
THC	Tetrahydrocannabinol
TSH	Thyroid-stimulating hormone
UDS	Urine drug screen
ULN	Upper limit of normal
VAS	Visual analog scale

Abbreviation or special term	Explanation
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 two 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 subjects 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 [redacted]. 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) (Hamilton 1960). Group differences were assessed via an analysis of covariance (ANCOVA) using baseline score as a covariate. There was a 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 Disability Scale [SDS]), Sheehan Irritability Scale [SIS], and Subject Global Impression – 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 (SAEs) 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, 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 objective of this study is to evaluate the long-term safety and tolerability 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. The hypothesis is that the long-term safety and tolerability of TC-5214 in combination with antidepressants (SSRI/SNRI) is similar to that of the antidepressants alone. This hypothesis will be examined by comparing descriptive statistics for safety endpoints between the TC-5214 and placebo groups. No formal inferential statistical analyses are planned.

1.3 Rationale for conducting this study

The rationale for this study is to assess the long-term safety and tolerability of TC-5214 in combination with an antidepressant (SSRI/SNRI) in patients who have not demonstrated an adequate 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 evaluate the long-term safety and tolerability of TC-5214 flexibly dosed of 1-4 mg BID for up to 52 weeks as adjunctive therapy in the treatment of MDD.

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 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

The primary objective of this study is to evaluate the long-term safety and tolerability 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.

2.2 Secondary Safety and Tolerability Objectives

The secondary safety and tolerability objectives focus on individual safety areas of special interest to this study.

To evaluate the long-term safety and tolerability of TC-5214 and placebo in combination with an antidepressant (SSRI/SNRI) in patients with MDD by assessing:

- AEs/SAEs, including their severity
- AEs leading to treatment discontinuation or study withdrawal
- AEs of special interest including, but not limited to reduction of blood pressure, orthostatic hypotension, anticholinergic signs and symptoms (including urinary retention), EPS symptoms, and increased fasting blood glucose
- AEs potentially related to abuse, misuse, noncompliance, and diversion

- Change from randomization in physical examinations, weight, waist circumference, vital signs, clinical laboratory test results, and ECG parameters
- Suicidality as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS) and AEs of suicidality, suicidal ideation, suicide attempts, suicide completion
- Change from randomization in akathisia and abnormal involuntary movements as measured by:
  - Barnes Akathisia Rating Scale (BARS)
  - Abnormal Involuntary Movement Scale (AIMS)
- Change from last treatment visit to follow-up visit in the Discontinuation Emergent Signs and Symptoms Scale (DESS)

2.3 Secondary Efficacy Objectives

The secondary objectives include:

- To evaluate the efficacy of TC-5214 and placebo in combination with an antidepressant (SSRI/SNRI) in patients with MDD by assessing:
  - Montgomery-Åsberg Depression Rating Scale (MADRS) total score
  - Clinical Global Impressions-Severity (CGI-S) score
  - Functional impairment by the Sheehan Disability Scale (SDS) score
  - Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) % maximum total score
  - European Quality of Life (EuroQol) VAS and 5 dimensions (EQ-5D)
  - Healthcare Resource Utilization and Work Absence (HRUWA)

2.4 Exploratory objective

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 subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is a 52-week, multicenter, randomized, double-blind, parallel group, placebo-controlled, Phase III, long-term safety and tolerability study of TC-5214, flexibly dosed (1 to 4 mg BID), in combination with an antidepressant (SSRI/SNRI) in the treatment of patients with MDD with an inadequate response to SSRI/SNRI therapy.

It is estimated that approximately 2000 patients will need to be screened so sufficient number of male and female patients will be randomized to yield data from approximately 400 treated patients at 6 months and 200 treated patients at 1 year. Enrollment in this study will end once the randomization target is met. The study will be conducted at approximately 127 centers in the US, with the addition of other countries as needed. Enrollment is expected to continue for approximately 7 months.

All patients in this study share the randomized treatment period and the 2-week follow-up period in this study. Other preliminary periods are dependent upon the source of patient for this study. The sources of patients in this study are described in Section 3.1.1, while the study periods are described in Section 3.1.2.

3.1.1 Sources of patients

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) in the current depressive episode. The current episode of depression must be >6 weeks and not to exceed 24 months (2 years) in duration. Additionally, patients 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 patient's 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 prior antidepressant was ≤ 4 weeks and this treatment was discontinued due to tolerability.

New or screen failure patients who have not been treated with a permitted SSRI/SNRI treatment will be required to have a clinician-rated HAMD-17 total score of ≥15 and CGI-S of ≥4 to enroll into a 6-week prospective open-label SSRI/SNRI period. These patients will receive treatment with an open-label antidepressant (SSRI/SNRI) therapy (citalopram, duloxetine, escitalopram, fluoxetine, paroxetine CR, sertraline, venlafaxine XR) selected by the investigator to demonstrate inadequate response.

Patients who have completed a prospective SSRI/SNRI treatment and have an inadequate response to the SSRI/SNRI will be randomized into the double-blind treatment period. For

the purpose of randomization, an inadequate response is strictly defined as a HAMD-17 total score of ≥10 as defined by a clinician-rated HAMD-17 and a CGI-S score ≥3.

Patients in the randomized, double-blind 52-week treatment period will come from the following three sources:

- Group 1: Consists of patients who screen failed from a TC-5214 Phase III efficacy study due to not meeting the inclusion criteria for the HAMD-17 or CGI-S score and new patients who have not received treatment with a permitted SSRI/SNRI, see Table 1 for list of permitted SSRI/SNRI treatments.

- Group 2: Consists of patients from a TC-5214 Phase III efficacy study who did not meet randomization criteria and new patients who have received treatment with a permitted SSRI/SNRI for ≥6 weeks, see Table 1 for list of permitted SSRI/SNRI treatments.

- Group 3: Consists of patients who have completed a TC-5214 Phase III efficacy study. These patients will enter the study at the randomization visit.

Figure 3, Figure 4 and Figure 5 show how these 3 groups enter this long-term safety and tolerability study in relation to the TC-5214 Phase III efficacy studies. Note: Group 1 and 2 include new patients who were not part of the TC-5214 Phase III efficacy studies.

Refer to Appendix E for information on the TC-5214 Phase III efficacy studies.

3.1.1.1 GROUP 1 – Patients not receiving treatment with a permitted SSRI/SNRI (SSRI/SNRI)

Group 1 patients are not currently receiving treatment with a permitted SSRI/SNRI (For a list of permitted SSRI/SNRI and doses see Table 1).

Prior to entering the randomized, double-blind, 52-week treatment period and follow-up period common to all patients, Group 1 patients will need to exhibit inadequate response to SSRI/SNRI and complete the:

- A screening period: Visit S1 (up to 21 days)

- A prospective SSRI/SNRI period: Visits S2 to S5 (6 weeks)

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

See Figure 3 for the path of Group 1 patients through this long-term safety and tolerability study.

3.1.1.2 GROUP 2 – Patients receiving treatment with a permitted SSRI/SNRI

Group 2 patients are currently receiving treatment with a permitted SSRI/SNRI for a minimum of 6 weeks (For a list of permitted SSRI/SNRI and doses see Table 1).

In addition to the randomized treatment period and follow-up period common to all patients, Group 2 will include:

Screening Period: Visit P1

See Figure 4 for the path of Group 2 through this long-term safety and tolerability study. Note that some patients had been on a permitted SSRI/SNRI for ≥6 weeks prior to screening for the TC-5214 Phase III efficacy study.

Refer to Appendix E for information on the TC-5214 Phase III efficacy studies.

3.1.1.3 GROUP 3 – Patients completing a Phase III efficacy study

Group 3 patients are currently receiving treatment with a permitted SSRI/SNRI. (For a list of permitted SSRI/SNRI see Table 1).

Group 3 includes:

- Patients who will have completed a TC-5214 Phase III efficacy study

See Figure 5 for the path of Group 3 through this long-term safety and tolerability study.

Refer to Appendix E for information on the TC-5214 Phase III efficacy studies.

3.1.2 Study periods

There are 4 Study Periods in this Study:

- Screening period (up to 21 days)
- Prospective SSRI/SNRI period (6 weeks)
- Randomized Treatment period (52 weeks)
- Follow-up period (2 weeks)

The randomized treatment and follow-up periods are the same for all groups of patients (See Section 3.1.1 for sources of patients). The Screening and Prospective SSRI/SNRI period differ among the groups.

3.1.2.1 Screening period

All groups have a screening period, but the screening procedures differ among the groups.

The screening/washout period will be up to 21 days for current treatment for MDD. 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).

Subjects who are screen failures due to laboratory abnormalities may be re-screened on one additional occasion. Subjects who are screen failures due to taking a prohibited medication may be re-screened one time in order to satisfy the inclusion criteria regarding the washout of the prohibited medication. All cases of re-screening require PRIOR approval by the Study Physician. Subjects requiring re-screening should first be registered as Screen Failures in Interactive Voice Response System (IVRS) and all re-screening procedures must be completed under a new subject E-code. 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. Any extension to the screening period requires approval by the Study Physician.

At screening, all patients will be evaluated to meet the DSM-IV-TR clinical diagnosis of MDD, single episode (296.2x) or recurrent (296.3x) confirmed by the MINI 6.0. Previous ADT treatment in the current episode will be assessed by the Antidepressant Therapy History Form, and requires patients to have received an effective dose according to the prescribing information for ≥ 6 weeks.

1. Group 1– Patients not receiving treatment with a permitted SSRI/SNRI (SSRI/SNRI)

Patients who are taking an ADT not among the 7 ADTs permitted (ie, trazodone 100 mg/day) will be required to washout of the not permitted ADT and complete the 6-weeks of ADT phase on an allowed antidepressant treatment at an appropriate dose.

Group 1 patients, new or screen failures from a TC-5214 Phase III study, must have a HAMD-17 total score ≥15 and CGI-S score ≥4, and will undergo the screening procedures and assessments described in the Study Plan, Table 2.

Screen failure data from Visit 1 in the proceeding TC-5214 Phase III efficacy study may be used as the screening visit data for this study once the patient has signed the D4130C00007 informed consent, as long as the visits are within 7 days. The screening/washout period will be up to 21 days. Patients, not on a permitted SSRI/SNRI, will be required to discontinue current treatment for MDD for up to 14 days prior to the 6-week prospective period. For a list of permitted SSRI/SNRI treatments, see Table 1.

New patients, or either screen failures from the TC-5214 Phase III efficacy study who did not previously participate in the optional pharmacogenetic part of the study, may participate in an optional, exploratory genetic research study, where permitted after signing of consent for collection of genetic sample. A 10 mL sample of blood will be collected from patients who

have provided consent to participate in the optional exploratory genetic research. The blood sample may be collected anytime after a patient has consented to participate in the study, preferably at the baseline/randomization visit.

- **Group 2– Patients receiving treatment with a permitted SSRI/SNRI (SSRI/SNRI)**

Group 2 consists of patients who meet the DSM-IV-TR clinical diagnosis of MDD, single episode (296.2x) or recurrent (296.3x) confirmed by the MINI 6.0 who are currently on a permitted SSRI/SNRI. Patients who are receiving one of the seven permitted ADTs at a dose not allowed per the protocol are required to complete the 6-weeks of ADT phase on an allowed antidepressant treatment at an appropriate dose. These patients will fall under the Group 1 category.

Patients or screen failure patients from a TC-5214 Phase III efficacy study who are receiving treatment with a permitted SSRI/SNRI, for a minimum of 6 weeks, must have a HAMD-17 total score ≥10 and CGI-S score ≥3 at randomization.

Screen failure data from Visit 1 in the proceeding TC-5214 Phase III efficacy study may be used as the screening visit data for this study once the patient has signed the D4130C00007 informed consent. Patients who are partial responders from a TC-5214 Phase III efficacy study must have a HAMD-17 total score ≥10 and CGI-S score ≥3, and undergo the screening procedures and assessments described in the Study Plan, Table 3. The screening/washout period will be up to 21 days.

New patients, or screen failures or partial responders from the TC-5214 Phase III efficacy study who did not previously participate in the optional pharmacogenetic part of the study, may participate in an optional, exploratory genetic research study, where permitted after signing of consent for collection of genetic sample. A 10 mL sample of blood will be collected from patients who have provided consent to participate in the optional exploratory genetic research. The blood sample may be collected anytime after a patient has consented to participate in the study, preferably at the baseline/randomization visit.

- **Group 3– Patients completing a Phase III efficacy study**

All patients who have completed one of the TC-5214 Phase III pivotal studies are eligible for participation in this study. The screening period (to determine whether patients still meet the inclusion and exclusion criteria Section 4) and randomization occur at the same visit.

Patient data from Visit 14 in the proceeding TC-5214 Phase III efficacy study may be used as the baseline randomization visit data for this study once the patient has signed the D4130C00007 informed consent, if both visits are within 7 days.

3.1.2.2 Prospective SSRI/SNRI period

From a study level, efforts will be made to ensure that no more than 40% of the patients will be treated with the same background SSRI/SNRI.

Only Group 1 patients have a prospective SSRI/SNRI period.

1. Group 1– Patients not receiving treatment with a permitted SSRI/SNRI (SSRI/SNRI)

The Principal Investigator (PI) will select the background SSRI/SNRI treatment for the patient during the SSRI/SNRI period from Table 1. The administration of background therapy will be recorded in the electronic Case Report Form (eCRF).

The investigator should increase the dose of the background SSRI/SNRI based on tolerability and per package insert instructions. Dose up-titration after week 4 of the open label prospective period is not allowed. Investigators are allowed one dose reduction of SSRI/SNRI depending on tolerability. Patients who do not tolerate a reduced SSRI/SNRI dose are withdrawn from the study.

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

Table 1 Administration of background SSRI/SNRI during prospective SSRI/SNRI period

	SSRI/SNRI Period			
SSRI/SNRI[a]	**Day 1 (S2) (mg/day)**	**Week 1 (Between S2+ S3) (mg/day)**	**Week 2 S3 (mg/day)**	**Week 4 and after S4 (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.

3.1.2.3 Randomized treatment period

The randomized treatment period is common for all groups, except for the entrance criteria.

The SSRI/SNRI therapy selected for the 6-week open-label SSRI/SNRI period cannot be modified during the 52-week randomized treatment period.

1. Group 1– Patients not receiving treatment with a permitted SSRI/SNRI (SSRI/SNRI)

At the randomization visit, eligible patients with a HAMD-17 total score ≥10 and a CGI-S score ≥3, will continue into the randomized treatment period.

2. Group 2– Patients receiving treatment with a permitted SSRI/SNRI (SSRI/SNRI)

At the randomization visit, eligible patients must have a HAMD-17 total score ≥10 and CGI-S score ≥3, will continue into the randomized treatment period.

3. Group 3– Patients completing a Phase III efficacy study

Eligible patients completing a TC-5214 Phase III efficacy study may proceed into the randomized treatment period.

The randomization and screening visit are the same for Group 3.

Refer to Appendix E for information on the TC-5214 Phase III efficacy studies.

The randomized treatment period is the same for all groups after entrance into this period.

The SSRI/SNRI therapy selected for the 6-week open-label SSRI/SNRI period cannot be modified during the 52-week randomized treatment period. Patients will continue the background SSRI/SNRI at the final dose of the previous period and will be randomized to TC-5214 1 mg BID or matching placebo in a 3:1 ratio.

The study center will call the IVRS at Weeks 2, 4, and 8 of treatment to provide the patients MADRS score and provide a response to the question whether the patient is tolerating treatment. Based on this information, the central IVRS will indicate which bottle of the IP to be dispensed. The study center, investigator, and the patient will remain blinded to the IP. According to pre-defined criteria in the IVRS, patients randomized to TC-5214 may remain at the same dose, have their dose increased (up to 4 mg BID), or have their dose decreased. Down titration can occur only once. A patient who otherwise would be down-titrated a second time will be withdrawn from treatment by the IVRS. The dose cannot be increased subsequent to a down titration. Patients who experience intolerability following an up-titration should be encouraged to contact the site to be evaluated for a down-titration and dispensation of study medication. Patients who are not tolerating treatment during the first

randomized treatment period will be withdrawn from the study via IVRS. The specifications for titration will be described in the CSR.

Patients who complete treatment will have an End of Treatment Visit (R17) completed according to Study Plan, Table 4. Patients who discontinue prior to completing 52 weeks of double-blind treatment should also complete the end of treatment assessments (Visit R17).

At the end-of-treatment visit (Visit R17), all patients should be advised to contact the study center if new AEs emerge.

3.1.2.4 Follow-up period

All groups share a common follow-up period.

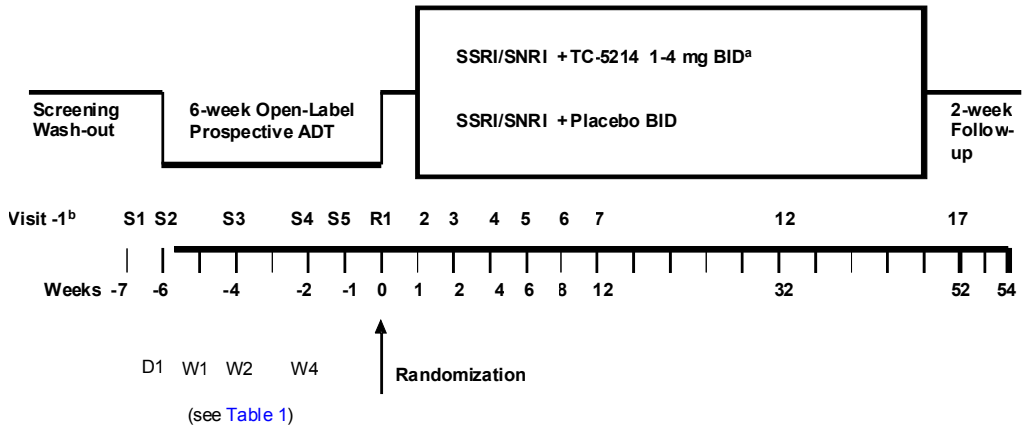
All randomized patients who complete the 52-week double-blind treatment period will enter the 2-week post-treatment phase of the study. The post-treatment follow-up period will allow for a measure of investigational drug effect washout. Patients will continue on background therapy throughout this period and will receive a 30-day SSRI/SNRI prescription.

A telephone visit will be performed on Day 3 after completion of the randomized, double-blind, treatment period, at which time the C-SSRS, DESS, AE and concomitant medications will be assessed.

A one week post randomized, double-blind, treatment visit will be performed at which time the vital signs, C-SSRS, DESS, AE and concomitant medications will be assessed.

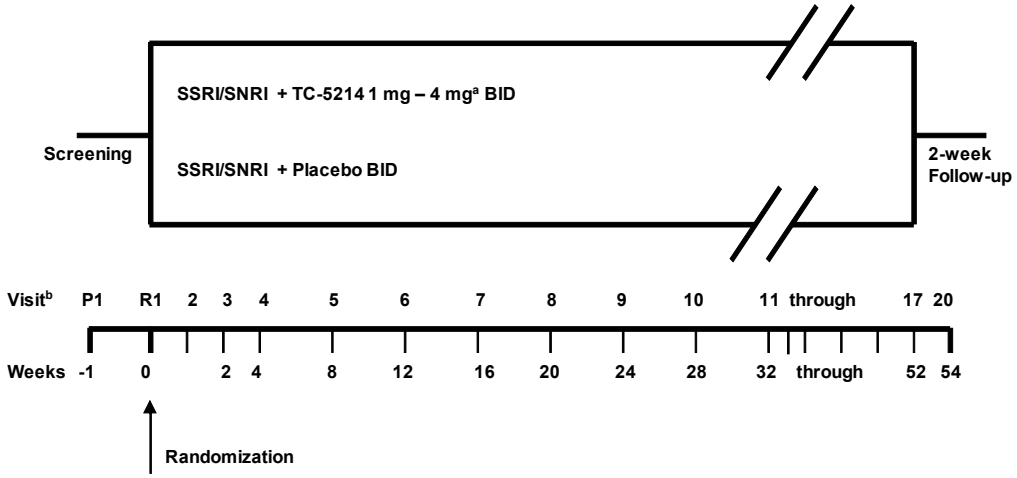
At the final study visit, which is 2 weeks after the final randomized, double-blind treatment visit (Visit 20), all patients will return to the study center to complete vital signs, C-SSRS, DESS, AE and concomitant medications. Refer to Study Plan, Table 4.

Figure 1 **Study flow chart (Group 1- new patients and screen failures from pivotal Phase III efficacy studies)**



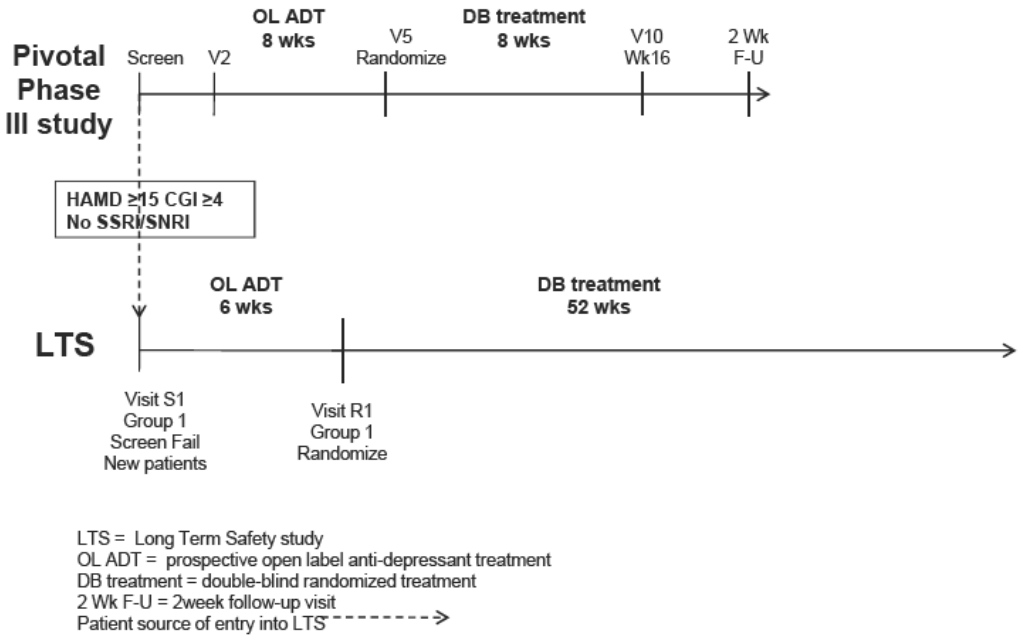
a SSRI/SNRI + TC-5214 start on 1 mg BID, up-titrated to 4 mg BID based on protocol-defined criteria.
b Visits occur biweekly for the 1st 8 weeks, then at 4 week intervals.

Figure 2 Study flow chart (Group 2 & Group 3)



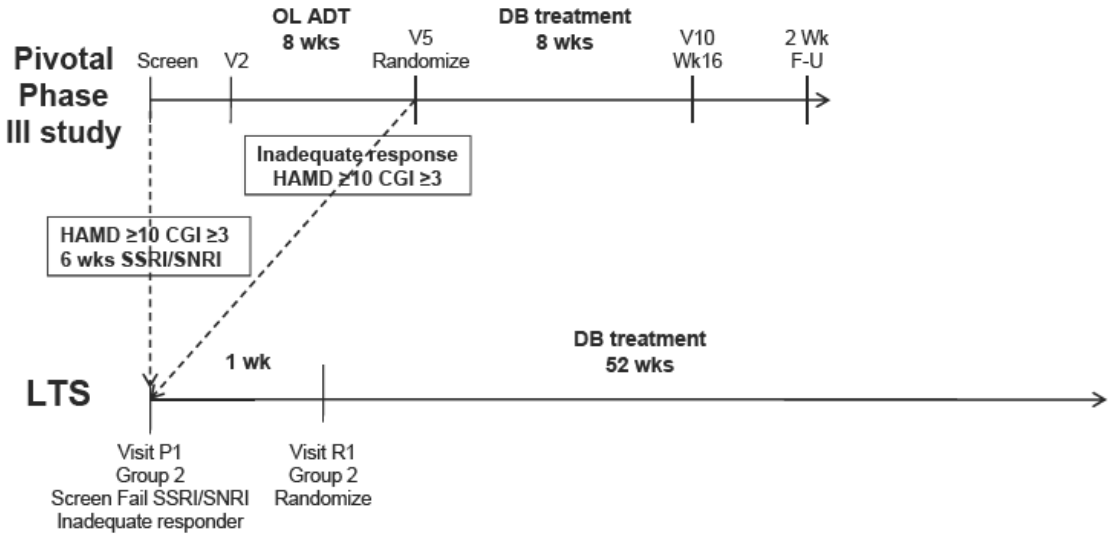
a SSRI/SNRI + TC-5214 start on 1 mg BID, up-titrated to 4 mg BID based on protocol-defined criteria.
b Visits occur biweekly for the 1st 8 weeks, then at 4 week intervals.

Figure 3 Group 1 – Patient source for long-term safety study (LTS)



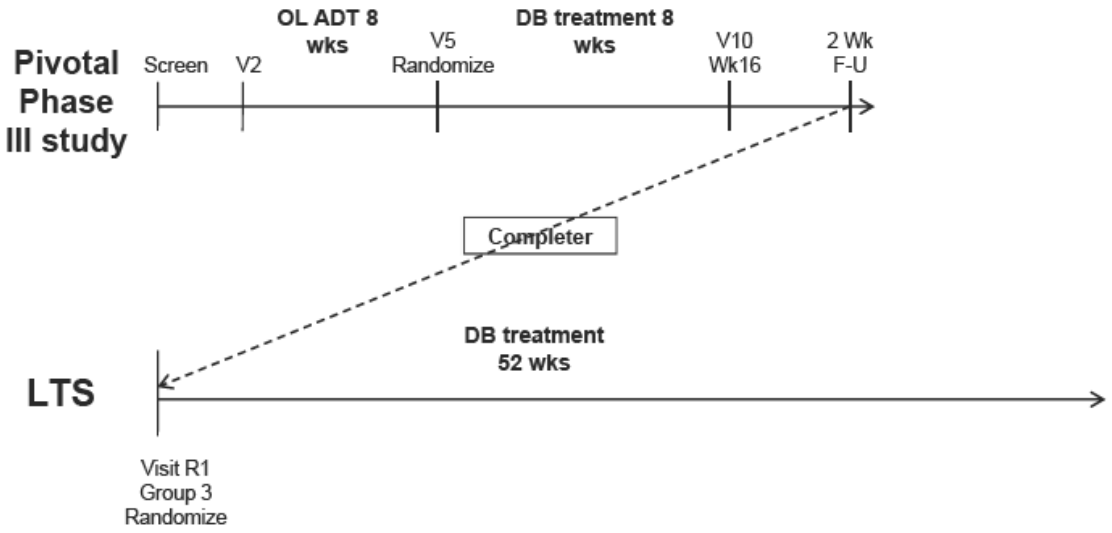
LTS = Long Term Safety study
OL ADT = prospective open label anti-depressant treatment
DB treatment = double-blind randomized treatment
2 Wk F-U = 2week follow-up visit
Patient source of entry into LTS ---------->

Figure 4 Group 2 – Patient source for long-term safety study (LTS)



LTS = Long Term Safety study
OL ADT = prospective open label anti-depressant treatment
DB treatment = double-blind randomized treatment
2 Wk F-U = 2-week follow-up visit
Patient source of entry into LTS ---------->

Figure 5 Group 3 – Patient source for long-term safety study (LTS)



LTS = Long Term Safety study
OL ADT = prospective open label anti-depressant treatment
DB treatment = double-blind randomized treatment
2 Wk F-U = 2week follow-up visit
Patient source of entry into LTS ---------->

Table 2 Study plan (Group 1 - New patients or screen failures not on a permitted SSRI/SNRI treatment)

	Screening	6-week open-label SSRI/SNRI period			
Visit	**S1**	**S2**	**S3**	**S4**	**S5**
Week	**-8**	**-6**	**-4**	**-2**	**-1**
Day (±3 days)	**Up to 21 days**	**-43**	**-29**	**-15**	**-8**
Informed consent	X				
Pharmacogenetics informed consent	X				
Inclusion/Exclusion criteria	X	X			
Medical, Psychiatric & Surgical History	X				
ATHF	X				
Employment status	X				
DSM-IV-TR diagnosis (MINI v6.0)	X				
Demography	X				
Prohibited medication washout period	X				
HIV, HBV, HbsAg, and HCV serology	X				
Hematology & clinical chemistry	X	X			
Glucose and lipids (fasting 12 hours)		X			
HbA_{1C}	X				
FSH, LH (for all female patients to determine menopausal status)	X				
PGx sample (optional)		X			
Urinalysis	X	X			
Urine pregnancy test (WOCBP)	X				
Urine drug screen	X				
Physical examination	X				
Height and weight [a]	X	X			
Waist circumference	X	X			

Table 2 Study plan (Group 1 - New patients or screen failures not on a permitted SSRI/SNRI treatment)

	Screening	6-week open-label SSRI/SNRI period			
Visit	**S1**	**S2**	**S3**	**S4**	**S5**
Week	**-8**	**-6**	**-4**	**-2**	**-1**
Day (±3 days)	**Up to 21 days**	**-43**	**-29**	**-15**	**-8**
Vital signs (supine and standing blood pressure and pulse) [b]	X	X	X	X	X
12-lead ECG	X		X		
AEs	X	X	X	X	X
Prior & concomitant medication[c]	X	X	X	X	X
Rating scales					
BARS		X			
AIMS		X			
HAMD-17	X	X			
CGI-S	X	X			
C-SSRS	X	X	X	X	X
MADRS		X			
PROs					
SDS		X			
Q-LES-Q-SF		X			
EQ-5D		X		X	
HRUWA		X		X	

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

a Height should only be measured at screening (S1).

b Blood pressure measurements are to be performed in the following order: sitting, supine, immediately after standing, 3 minutes after standing.

c Prior medications will be collected for 1 month prior to enrollment.

Table 3 Study plan (Group 2 – New Patients, Screen Failures or Partial responders on a permitted SSRI/SNRI treatment)

	SCR
Visit	**P1**
Week	**–1**
Day (±3 days)	**1**
Informed consent	X
Pharmacogenetics informed consent	X
Inclusion/Exclusion criteria	X
Medical, Psychiatric & Surgical History	X
ATHF	X
Employment status	X
DSM-IV-TR diagnosis (MINI v6.0)[a]	X
Demography	X
HIV, HBV, HbsAg, and HCV serology[b]	X
Hematology & clinical chemistry	X
HbA_{1C}	X
FSH, LH (for all female patients to determine menopausal status)	X
PGx sample (optional)	X
Urinalysis	X
Urine drug screen	X
Urine pregnancy test (WOCBP)	X
Physical examination	X
Height, weight, and waist circumference	X
Vital signs (supine and standing blood pressure and pulse)[d]	X
12-lead ECG	X
AEs	X
Prior & concomitant medication[c]	X
Rating scales	
HAMD-17	X
CGI-S	X
C-SSRS	X

a MINI will not need to be reassessed for patients that are partial responders from the open-label SSRI/SNRI period of the TC-5214 Phase III efficacy study.
b HIV, HBV, HbsAg, and HCV serology will not need to be reassessed for patients that are partial responders from the open-label SSRI/SNRI period of the TC-5214 Phase III efficacy study.
c Prior medications will be collected for 1 month prior to enrollment.
d Blood pressure measurements are to be performed in the following order: sitting, supine, immediately after standing, 3 minutes after standing.

Table 4 Study plan (All patients, Group 1, Group 2, Group 3)

	52-week double-blind treatment period																	Post-treatment Follow-Up		
Visit	**R[a] 1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18[c]**	**19**	**20**
Week	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**52**	**53**	**54**
Day (±x days)	**1 (±2)**	**8 (±2)**	**15 (±2)**	**29 (±2)**	**43 (±2)**	**57 (±2)**	**85 (±5)**	**113 (±5)**	**141 (±5)**	**169 (±5)**	**197 (±5)**	**225 (±5)**	**253 (±5)**	**281 (±5)**	**309 (±5)**	**337 (±5)**	**365 (±5)**	**368 (±2)**	**372 (±2)**	**379 (±2)**
Informed consent	X																			
Inclusion/Exclusion criteria	X																			
Medical, Psychiatric & Surgical History	X																			
Demography	X																			
ATHF	X																			
Smoking History	X									X							X			
Employment status	X			X		X	X	X	X	X	X	X	X	X	X	X	X			
Hematology & clinical chemistry	X	X		X		X			X			X			X		X			X
Urine drug screen[d]	X																			
Glucose, lipids (fasting 12 hours)	X	X		X		X			X			X			X		X			X
HbA_{1C}	X					X			X			X					X			X
Urinalysis	X						X					X								X
Urine pregnancy test (WOCBP)	X						X		X			X					X			X
Physical examination[f]	X									X[e]							X			X

Table 4 Study plan (All patients, Group 1, Group 2, Group 3)

	52-week double-blind treatment period																	Post-treatment Follow-Up		
Visit	**R[a] 1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18[c]**	**19**	**20**
Week	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**52**	**53**	**54**
Day (±x days)	**1 (±2)**	**8 (±2)**	**15 (±2)**	**29 (±2)**	**43 (±2)**	**57 (±2)**	**85 (±5)**	**113 (±5)**	**141 (±5)**	**169 (±5)**	**197 (±5)**	**225 (±5)**	**253 (±5)**	**281 (±5)**	**309 (±5)**	**337 (±5)**	**365 (±5)**	**368 (±2)**	**372 (±2)**	**379 (±2)**
Weight, Waist circumference	X					X						X					X			X
Vital signs (sitting, supine and standing) [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
12-lead ECG									X			X			X					
12-lead ECG (triplicate)	X[b]					X											X			
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Rating scales																				
BARS	X			X		X			X				X				X			X
AIMS	X			X		X			X				X				X			X[e]
HAMD-17	X																			
CGI-S	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X			X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MADRS	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X			X
DESS																	X	X	X	X
PROs																				
SDS	X						X			X			X				X			
Q-LES-Q-SF	X						X			X			X				X			

Table 4 Study plan (All patients, Group 1, Group 2, Group 3)

	52-week double-blind treatment period																	Post-treatment Follow-Up		
Visit	**R[a] 1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18[c]**	**19**	**20**
Week	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**52**	**53**	**54**
Day (±x days)	**1 (±2)**	**8 (±2)**	**15 (±2)**	**29 (±2)**	**43 (±2)**	**57 (±2)**	**85 (±5)**	**113 (±5)**	**141 (±5)**	**169 (±5)**	**197 (±5)**	**225 (±5)**	**253 (±5)**	**281 (±5)**	**309 (±5)**	**337 (±5)**	**365 (±5)**	**368 (±2)**	**372 (±2)**	**379 (±2)**
EQ-5D	X			X		X	X	X	X	X	X	X	X	X	X	X	X			
Healthcare Resource Utilization and Work Absence	X			X		X	X	X	X	X	X	X	X	X	X	X	X			
IP																				
Dispense IP (double-blind) [i]	X [f, g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Collect IP (double-blind)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

R randomization

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

Note: The physical examination will be conducted after the rating scales and questionnaires.

Note: For patients who withdraw early from the study, Week 52 (R17) assessments should be performed.

a For a patient who completed a TC-5214 Phase III efficacy study, the screening assessments will be performed at the randomization visit.

b At Visit 1 (randomization), ECG will be performed in triplicate (3 readings in rapid succession and not more than 2 minutes apart) at predose and 2-3 hours postdose.

c Visit 18 will be a telephone call to assess patient well-being.

d The urine drug screen will be performed at randomization for the patients who completed a TC-5214 Phase III efficacy study. The investigator may also order a urine drug screen at any time during the study in order to confirm suspected drug abuse.

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

f Physical examination should be conducted **after** psychiatric assessments have been completed.

g Following dosing at randomization, patients will remain at the center for up to 4 hours of observation.

h Blood pressure measurements are to be performed in the following order: sitting, supine, immediately after standing, 3 minutes after standing.

i Patients should take IP in the morning and evening.

3.2 Rationale for study design, doses and control groups

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

The doses chosen for this study are based on results of information gained from previous clinical studies, as well as from toxicological, pharmacological and PK studies. The dosing regimen is similar to concurrent efficacy studies in the TC-5214 program.

The duration and sample size of this study are based on ICH exposure guidance for long-term safety evaluation that at least 300 patients on TC-5214 are treated for 6 months and of those at least 100 patients on TC-5214 need to complete a 12-month treatment.

This study utilizes a randomized (3:1 ratio), double-blind, placebo-controlled design to minimize bias in comparing the safety profiles of TC-5214 combined with antidepressants (SSRI/SNRI) and the antidepressants alone, respectively.

The primary objective regarding overall safety and tolerability relies on typical safety variables, as well as some safety areas of special interest that have been identified as secondary objectives. These secondary safety variables include:

- The C-SSRS (Posner et al 2007) is a validated scale for suicidality that is recommended by the FDA and will be assessed prior to and after treatment.
- Extrapyramidal symptoms (EPS), which have been associated with the treatment of MDD, will be measured by AIMS (Guy 1976a) and BARS (Barnes 1989) scales.

MADRS and CGI-S will be used during the course of this 52-week study to monitor and evaluate the patient's depressive symptoms.

For this long-term safety and tolerability study, the criteria for randomization were chosen to provide safety information from a broad group of patients with an inadequate response to prior SSRI/SNRI who could potentially benefit from TC-5214 as an adjunct therapy to SSRI/SNRI for MDD, as well as to facilitate recruitment. The criteria for randomization regarding inadequate response to prior SSRI/SNRI were defined more strictly in the 8-week TC-5214 Phase III studies (see Appendix E) designed to assess efficacy (from HAMD-17 total score <50 of Day 1 for the prospective ADT, HAMD-17 total score ≥16, CGI-S ≥4 compared with HAMD-17 total score ≥10 and CGI-S ≥3).

4. SUBJECT SELECTION CRITERIA

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

Each patient should 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 postmenopausal 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 postmenopausal 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 luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in the postmenopausal range.

4. Primary clinical diagnosis in the current episode with a duration of < 2 years meeting criteria 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 patients history (ATHF). A patient needs to be on an antidepressant treatment for at least 6 weeks at a dose range listed on the label for depression in order for it to be classified as an inadequate response. Antidepressant treatment/medications discontinued within four weeks of initiation due to intolerance would not count towards this number. Patients who are not currently receiving treatment with antidepressant drugs during this current depressive episode are not allowed to proceed to randomization; however, they may enroll into a 6-week prospective open-label SSRI/SNRI period to demonstrate inadequate response.

   This criterion does not apply to patients who have completed a TC-5214 Phase III efficacy study.

6. Documented Clinician-rated total score HAMD-17 total score at screening/randomization as follows:

   - SSRI/SNRI Screening (Visit S1): Clinician-rated ≥15
   - Randomization (Visit R1): Clinician rated total score ≥10

   This criterion does not apply to patients who have completed a TC-5214 Phase III efficacy study.

7. Documented CGI-S at screening/randomization as follows:

   - SSRI/SNRI Screening (Visit S1): ≥4
   - Randomization (Visit R1): ≥3

This criterion does not apply to patients who have completed a TC-5214 Phase III efficacy study.

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

9. Out-patient status at enrollment and randomization.

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

10. 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 and confirmed by the investigator; c) current (within 12 months before open-label baseline [Visit 2]) generalized anxiety disorder, panic disorder, obsessive compulsive disorder, social anxiety disorder, ADHD or dysthymic 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

4. Patients whose current episode of depression is greater than 24 months in duration

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

6. Substance or alcohol abuse or dependence within 6 months prior to enrollment (except dependence in full remission, and except for caffeine or nicotine dependence), as defined in DSM-IV criteria. Patients with a positive urine drug screen will be excluded, with the exception of patients testing positive only for

cannabinoids or for prescription medications with supporting prescription documentation (see Section 6.4.5.3). Patients can be re-tested once if the initial urine drug screen is positive for cannabinoids (THC) or if the prescription medication is to be discontinued and an adequate washout time of the prohibited prescription medication has elapsed prior to the end of the screening period. Positive UDS results not meeting these criteria ~~but~~ should be excluded if the results are still positive at the second test.

7. Subjects 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.

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

9. Any significant unstable hepatic infection and/or condition (including Hepatitis B [HBV] and Hepatitis C [HCV]) or a newly diagnosed Hepatitis B or C identified at screening

10. 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 subject at greater risk during study participation.

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

12. 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.

13. Patients on thyroid medication unless at a stable dose for ≥3 months; thyroid level must be within normal range.

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

15. Any other severe progressive or uncontrolled medical condition, or chronic medical illness (eg, fibromyalgia, chronic pain conditions, obstructive sleep apnea).

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

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

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

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

20. History of stroke or transient ischemic attack.

21. Myocardial infarction within 180 days before Screening (Visit 1).

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

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

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

25. Use of prohibited treatments (refer to Table 6 and Table 7 for additional information on prohibited medications).

26. 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 60 days prior to study start.

27. Pregnancy or lactation.

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

29. 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).

30. History of orthostatic hypotension.

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

32. QTcF (Fridericia-corrected) ≥450 msec (on repeated tests) at screening (Visit S1) or randomization (Visit R1), or a medical or family history of long QT syndrome.

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

34. Previous randomization in this study.

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

    This criterion does not apply to patients who have completed a TC-5214 Phase III efficacy study.

36. Randomization in another clinical trial currently or within 3 months of screening for this study or screening in more than 2 trials in the 12 months prior to screening for this study.

37. 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:

38. Have had previous allogeneic bone marrow transplant.

39. 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.

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.

If a patient withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused.

Patients entering the long-term safety study from a TC-5214 Phase III efficacy study will not be assigned a new unique enrollment number but will use the same number from those studies.

5.2.1 Procedures for randomization

This study will be established with a non-center-specific-labeling randomization. Patient eligibility will be established before treatment randomization. Randomization codes will be assigned strictly sequentially as patients become eligible for randomization by the IVRS system.

Eligible patients will be randomized to receive either TC-5214 1 mg or matching placebo BID in a 3:1 ratio.

The actual treatment given to individual patients will be determined by a randomization scheme that has been loaded into the (IVRS) database. The randomization scheme will be produced by a computer software program called GRand (AstraZeneca's Global Randomization system) that incorporates a standard procedure for generating random numbers. If a patient is discontinued from the study, his/her patient enrollment number will not be reused, and the patient will not be allowed to re-enter the study. Randomized patients who discontinue early from the study will not be replaced.

If a randomization number is allocated incorrectly (randomized to the wrong treatment, not due to the patient not meeting the inclusion/exclusion criteria), no attempt should be made to remedy the error once study material has been dispensed. The patient will continue with the allocated number and study material. AstraZeneca or its representative should be notified as soon as the error is discovered and the error should be adequately documented. Subsequent patients will continue using the first unallocated randomization number in the original numbering sequence.

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 randomized. 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 contract research organization (CRO) handling data will have access to the randomization scheme during the conduct of the study with the exception of AstraZeneca's IPS and Patient Safety.

Where patients that do not meet the selection criteria are randomized in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post

initiation, a discussion should occur between the Study Physician and the Investigator regarding whether to continue or discontinue the patient from treatment.

The Study Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have their study therapy stopped.

Patients who have entered the 6-week open-label ADT period and are discontinued prior to randomization solely because randomization is halted (not because they have subsequently become ineligible) may complete the 6-week ADT period and will be provided with an additional 30-day supply of their open-label ADT after the conclusion of the 6-week open-label period.

Patients who are withdrawn during the ADT period for any reason should have their vital signs assessed and be assessed for any ongoing or new AEs. Patients should be asked to complete the C-SSRS prior to study exit. If the provider has concerns about the patient's status based on the results of study assessments (eg, labs or ECGs) at the time of study termination, then the assessments of concern (eg, labs or ECGs) should be repeated and the results recorded as an unscheduled visit.

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.

The data from any patient for whom the code is broken at the site will be included in the safety analysis up to the date and time of code break. From that point on, the patient must be withdrawn from the study and followed-up, as appropriate.

5.5 Treatments

5.5.1 Identity of investigational product(s)

The IP will consist of 1 mg, 2 mg, 4 mg TC-5214 and matching placebo tablets, as add-on 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 5. Patients will be supplied with sufficient drug for each visit period.

The SSRI/SNRI used in this study will be prescribed and filled through normal prescribing methods, and will be reimbursed by AstraZeneca.

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

Table 5 Investigational Product

Investigational product	Dosage form and strength	Manufacturer
TC-5214	1 mg tablets	[redacted]
TC-5214	2 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

Patients will be randomized to receive either TC-5214 1 mg BID or matching placebo BID orally in a 3:1 ratio.

During the double-blind treatment period, for patients randomized to TC-5214, the dose of TC-5214 will be flexibly adjusted from 1, 2 or 4 mg BID. The total TC-5214 add-on treatment period is 52 weeks. Patients will continue to take the background SSRI/SNRI at the final dose of the previous period.

After randomization, patients assigned to the TC-5214 treatment group will start taking 1 mg TC-5214 tablet orally BID. After 2, 4 and 8 weeks of treatment, based on efficacy and

safety/tolerability information entered into the IVRS, the individual patient's dose may remain the same, be increased to a maximum of 4 mg BID, or be decreased. Down-titration may occur only once.

Patients randomized to placebo will take matching placebo along with the background SSRI/SNRI.

5.5.3 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.

5.5.4 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 this 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 use of medicines either prescribed or over the counter used to treat symptoms of the common cold is permitted (sympathomimetic cold medicines 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:

- Alprazolam max 1 mg/day
- Lorezapam max 2 mg/day
- Zolpidem tartrate 10 mg
- Zaleplon 20 mg
- Zopiclone 7.5 mg

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

Patients taking trazodone ≤ 150 mg/night for insomnia will be allowed to enroll if they are willing to stop the trazodone to allow for a sufficient washout period of 7 days and are willing to substitute a different benzodiazepine or non- benzodiazepine sleep aid at a 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 6 for information regarding approved sleep aids during the study.

5.6.1 Prohibited/restricted medications

A list of prohibited medications and their washout periods are shown in Table 6.

Table 6 Prohibited/restricted medications and treatments

Excluded treatments	**Number of days before first day of open-label antidepressant treatment**				
	2 years	**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
Anxiolytics (benzodiazepines (except for alprazolam and lorezapam[e]) and nonbenzodiazepines)					X

Table 6 Prohibited/restricted medications and treatments

Excluded treatments	Number of days before first day of open-label antidepressant treatment				
	2 years	60	30	14	7
Antidepressants other than the designated 7 SSRIs and SNRIs [f]					X
Cimetidine					X
Herbal products intended to treat anxiety, insomnia, and depression				X	
Monoamine oxidase inhibitors, including Linezolid				X	
Sumatriptan, naratriptan, zolmitriptan[g]				X	
Antipsychotics				X	
Smoking cessation agents			X		
ECT therapy	X				
Stimulants [h]					X
Isotretinoin [i]		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 administered for the diagnosis of insomnia are permitted but not greater than 4 times per week. Patients will be instructed not to take alprazolam: max 1mg/day or lorezapam: max 2 mg/day, 24 hours before any visit.
f Designated SSRIs includes any of the following: citalopram, duloxetine, escitalopram, fluoxetine, paroxetine CR, sertraline, venlafaxine XR
g Including drugs that have a similar mechanism of action.
h 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.
i Subjects requiring medications that have a >21 day washout would be excluded from the study.

The list of medications and cytochrome P450 (CYP)-influencing medications prohibited during screening and treatment periods is shown in Table 7.

Table 7 Prohibited medications and treatments during the study

Drug Classification or Treatment	Drug Names
Acne medication	Isotretinoin
Analgesics, opioid type	For example, morphine, fentanyl, methadone
Sympathomimetic cold medicines or cough medicines	For example, contains ephedrine or dextromethorphan
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 1 year prior to screening
Psychotherapy	Unless stable appointments that began at least 90 days before screening
P450 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 site 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 site 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 site 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 10mins) 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 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.

Patients who withdraw outside of the double-blind treatment period with AEs, SAEs or clinically significant abnormal results should be followed up through completion/resolution of the event (See Sections 6.4.3 and 6.4.4).

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.

If a patient discontinues during the prospective, open-label ADT period, the following assessments should be conducted: review of any AEs/SAEs, review of concomitant medications, completion of the C-SSRS, AIMS, and BARS. 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 R17) 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 20) 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's case will need to be discussed with a study physician. If this discussion leads to discontinuation of the patient, all assessments and procedures required at Week 52/Visit 17 will be conducted. Refer to Study Plan, Table 4.

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

For new patients or screen failures enrolling in this long-term safety and tolerability study, the following data will be collected and recorded in the appropriate sections of the eCRF at the time of the screening visit (refer to Study Plan, Table 2).

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
- A collection of standard medical and surgical history
- History of prescription and over the counter medication usage
- Inadequate response to antidepressant therapy as assessed by the ATHF
- Employment status
- 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, and waist circumference
- Seated blood pressure and pulse (the patient should be resting in the seated position for at least 5 minutes prior to the evaluation)
- Supine blood pressure and pulse (the patient should be resting in a supine position for at least 10 minutes prior to the evaluation)
- Standing blood pressure and pulse (this evaluation will follow the supine blood pressure assessment). The patient should stand for 3 minutes prior to the evaluation.
- Recording of a resting 12-lead ECG (the patient should be resting in the supine position for at least 10 minutes prior to the evaluation)

- A blood sample for standard clinical chemistry, hematology, and a mid-stream urine sample for urinalysis and drugs of abuse
- A blood sample for glucose, lipids, and HbA_{1c}
- A urine sample for pregnancy testing on all female patients
- A blood sample to determine menopausal status (LH and FSH)
- A blood sample for HBV, HCV, and HIV serology evaluations
- HAMD-17, CGI-S, C-SSRS

The urine drug screen is part of a general assessment for the presence of substance abuse disorders. Patients can be re-tested if the initial urine drug screen is positive, however, patients will be excluded, with the exception of patients testing positive for cannabinoids, if the results are still positive at the second test. For patients testing positive for cannabinoids at enrollment, they must not meet abuse or dependence criteria and, in the judgment of the investigator, will not use cannabinoids or other illegal or non-prescribed drugs during the study.

For patients enrolling in this long-term safety and tolerability study from a TC-5214 Phase III efficacy study, the following data will be collected and recorded in the appropriate sections of the eCRF at the time of the screening/randomization visit (refer to Study Plan, Table 3 and Table 4).

- Signed informed consent
- Recording demographic data–date of birth, sex, race, ethnicity
- Inclusion/exclusion criteria
- A collection of standard medical, psychiatric and surgical history. Ongoing AEs from the TC-5214 Phase III efficacy study is to be recorded on the medical history
- History of prescription and over the counter medication usage (prior and concomitant medication)
- A complete physical examination including general appearance, skin, head, neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular system, respiratory system, abdomen, and neurological examination. A brief physical examination will be conducted for patients completing the pivotal Phase III studies
- Height, weight and waist circumference
- Supine blood pressure

- Standing blood pressure and pulse (this evaluation will follow the supine blood pressure assessment). The patient should stand for 3 minutes prior to the evaluation.
- Seated blood pressure and pulse (the patient should be resting in the seated position for at least 5 minutes prior to the evaluation)
- Recording of a resting 12-lead ECG. The patient should be resting in the supine position for at least 10 minutes prior to the evaluation.
- A blood sample (fasting) for standard clinical chemistry and hematology for patients from the TC-5214 Phase III efficacy study that did not have a sample taken within the past 7 days
- A fasting blood sample for glucose, lipids, and HbA_{1c} for patients from the TC-5214 Phase III efficacy study that did not have a sample taken within the past 7 days
- A urinalysis and urine drug sample (for partial responders) for drug abuse
- A urine sample for pregnancy testing on all female patients
- HAMD-17
- C-SSRS
- BARS, AIMS, CGI-S, MADRS, Q-LES-Q-SF, EQ-5D

6.2.2 Post-treatment procedures

The 2-week follow-up period, post the completion of the double-blind period, will consist of 2 clinic visits and 1 telephone visit. A medical examination will be performed at the end of the randomized treatment period. This will be similar to the one performed at screening and will include:

- A blood sample collection for clinical chemistry, and hematology
- A urine sample for urinalysis
- A fasting blood sample for glucose, lipids, and HbA_{1c}
- A urine sample for pregnancy testing on all female patients
- A complete physical examination including general appearance, skin, head, neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular system, respiratory system, abdomen, and neurological examination

- Weight evaluation
- Seated blood pressure and pulse (the patient should be resting in the seated position for at least 5 minutes prior to the evaluation)
- Supine blood pressure and pulse (the patient should be resting in a supine position for at least 10 minutes prior to the evaluation)
- Standing blood pressure and pulse (this evaluation will follow the supine blood pressure assessment).
    - The patient will stand and immediately measure blood pressure and heart rate. The patient should stand for 3 minutes prior to the evaluation)
    - After patient remains standing for 3 minutes, measure blood pressure and heart rate
- Recording of a resting 12-lead ECG (the patient should be resting in the supine position for at least 10 minutes prior to the evaluation). ECGs will be recorded in triplicate.
- MADRS, C-SSRS, and CGI-S
- BARS and AIMS
- Adverse events and concomitant medication usage
- DESS

6.3 Efficacy

For the timing of individual assessments for patients enrolling from a TC-5214 Phase III efficacy study, refer to the Study Plan, Table 3 and Table 4.

For the timing of individual assessments for new patients or screen failures from the pivotal Phase III studies, refer to the Study Plan, Table 2.

The efficacy of TC-5214 will be assessed using the following rating scales: MADRS and CGI-S. To ensure consistency throughout the study, the same rater should 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 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 scale will be used.

The first part, the Severity of Illness item (CGI-S), is scored to rate the patient's current clinical state.

Each CGI-S 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". Higher CGI-S scores indicate greater illness severity.

The CGI-S 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 is familiar with the content of this section.

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

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 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:

1. mild (awareness of sign or symptom, but easily tolerated)

2. moderate (discomfort sufficient to cause interference with normal activities)

3. 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-S 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. The investigator should complete the Healthcare utilization form and report hospitalization and other resource use if and whenever an adverse event occurs.

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 electronic Data Capture (eDC) system.

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 Section 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 taken at the times indicated in the Study Plans (Table 2, Table 3, and Table 4). The date and time of collection will be recorded in the appropriate eCRF. The following laboratory variables will be measured.

For the timing of individual measurements refer to the Study Plans, Table 2, Table 3 and Table 4.

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.

Table 8 Laboratory assessments

Clinical chemistry (serum)	Hematology (blood)	Urinalysis (urine)
Alanine aminotransferase (ALT)	Red blood cell (RBC)	Color
Aspartate aminotransferase (AST)	HIV	Specific gravity
Alkaline phosphatase	HbsAg	pH
Bilirubin, total (direct and indirect)	HBV, HCV	Glucose
Blood urea nitrogen (BUN)	Hematocrit (Hct), hemoglobin (Hgb)	Blood
Calcium	MCH, MCHC, MCV, RDW	Protein
Chloride	White blood cell (WBC)	Nitrites
CO_2 (Bicarbonate)	WBC differential (%) including: lymphocytes, basophils, monocytes, neutrophils and eosinophils (absolute and percentages)	Leukocyte esterase
Creatinine	Platelet count	
Creatinine phosphokinase (CPK)		**Urine drug screen**
Glucose (fasting)		

Table 8 Laboratory assessments

Clinical chemistry (serum)	Hematology (blood)	Urinalysis (urine)
FSH, LH[a]		**Urine pregnancy test[c]**
HbA_{1c}		
LDH		
Potassium		
Sodium		
Total protein		
Lipid panel – Fasting		
Total cholesterol		
Triglycerides		
High-density lipoprotein (HDL) cholesterol		
Low-density lipoprotein (LDL) cholesterol		
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.
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 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".

6.4.5.1 Serology

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, 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 female patients. If the urine pregnancy test is positive it must be confirmed with a serum pregnancy test. A patient with a confirmed pregnancy will be terminated.

For timing of measurements, refer to the Study Plans, Table 2, Table 3 and Table 4.

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 UDS will be excluded, with the exception of patients testing positive for only cannabinoids (THC) or for drugs legally available by valid prescription. Patients testing positive for THC can be included if, in the opinion of the investigator, they are not chronic abusers and have not used THC-containing substances in the week prior to Day 1 and the pattern of use has not changed.

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 complete physical examination will be performed at times indicated in the Study Plans (Table 2, Table 3, and Table 4) 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 baseline 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 baseline assessment will be reported as an AE.

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 for new patients are to be recorded. For patients who were part of a TC-5214 Phase III efficacy study, any medications that are ongoing at the time informed consent is signed for the long-term safety and tolerability study will 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 Study Plan, Table 2, Table 3, and Table 4. 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.

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 Study Plan, Table 2, Table 3, and Table 4.

The ECGs performed at randomization and end of treatment will be performed in triplicate. Each subsequent recording must be performed within 2-3 minutes of the previous recording.

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 72 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 Plans, Table 2, Table 3, and Table 4.

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. This will be documented in the source documents at the investigative site.

6.4.9.2 Orthostatic blood pressure and pulse

To assess for orthostatic hypotension, the following will be performed.

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 (eg, 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 will be measured in centimeters (cm). 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 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 is outlined in Study Plan, Table 2, Table 3, and Table 4. 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 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 Plans, Table 2 and Table 4.

6.4.11.2 Barnes Akathisia Rating Scale (BARS)

The BARS is the most widely used comprehensive rating scale for akathisia. 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 Plans, Table 2 and Table 4.

6.4.12 Discontinuation-Emergent Signs and Symptoms (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 Day 3 post dose (by telephone interview), at Week 1 follow-up (on-site visit) and at the Week-2 follow-up onsite visit. At each visit, 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 (PRO)

The methods for collecting PRO data are presented below. For the timing of individual assessments, refer to the Study Plans, Table 2 and Table 4. All PRO evaluations will be assessed first before the clinician-reported efficacy scales discussed in Section 6.3. The order of administration of the questionnaires is: SDS, Q-LES-Q-SF, 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 is some "heading information" such as E-code and patient number.

6.5.1 Sheehan Disability Scale (SDS)

The SDS consists of three items designed to measure the severity of functioning impairments due to illness symptoms in the area of work/school, family life/home responsibilities, and social life (Sheehan 1983, Sheehan et al 1996). 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 0-10. 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 is an often used standard short form assessment of quality of life satisfaction (Endicott et al 1993). 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 to 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 European Quality of Life (EuroQol) VAS and 5 dimensions (EQ-5D)

The EQ-5D is a validated measure of health-related quality of life (EuroQol 1990). The descriptive system of health-related quality of life states consisting of five dimensions: (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of three responses. The responses record three levels of severity (no problems/some or moderate problems/extreme problems) within a particular EQ-5D dimension. Standard vertical 20 cm visual analogue scale (similar to a thermometer) is used for recording an individual's rating for their current health-related quality of life state (often referred to as page 3 of the EQ-5D questionnaire). EQ-5D scores can be converted to utility measures. Utility measures are used in analysis where the consequences of treatment are measured in terms of quality adjusted life years.

6.5.4 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 Pharmacogenetics

AstraZeneca intends to perform genetic research in the TC-5214 clinical development program to explore how genetic variations may affect the clinical parameters associated with TC-5214. Collection of DNA samples from populations with well described clinical characteristics may aid in the identification of future drug targets and projects to validate identified targets.

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

For blood volume, see Section 7.1.

6.6.1 Collection of pharmacogenetic samples

Patients will be offered the possibility to participate in optional genetic exploratory research. After signing a separate consent for optional genetic research, a blood sample will be collected as per the inclusion criteria.

The blood sample for genetic research will preferably be obtained from the patient at Visit 2 after randomization. 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 patient for genetics during the study.

A single venous blood sample (10 mL) will be collected into a polypropylene tube containing EDTA and gently inverted a minimum of 5 times to mix thoroughly. Tubes will be labeled with the study number, enrollment code and/or randomization code and date of sample collection. No personal identifiers (patient name, initials, or date of birth) will be placed on the tube or accompanying documentation. A record of the date of patient consent to the genetic research and the date of the blood sample collection will be recorded in the appropriate sections of the eCRF.

For blood volume, see Section 7.1.

6.7 Health economics

6.7.1 Healthcare Resource Utilization and Work Absence (HRUWA)

The HRUWA form captures data for evaluation of the burden of illness to the healthcare system and loss of work productivity. It captures the frequency of direct healthcare resource utilization for both in-patient and out-patient care caused by patients' MDD or otherwise. This form also captures work productivity (less the number of paid or unpaid hours that the patient missed work) due to the patient's MDD or due to other reasons. It also captures the productivity loss of patients' spouse/family member/friend caused by the patients' MDD (the number of paid or unpaid hours giving care to the patient). The investigators complete this form during an interview with the patient every 4 weeks in order to be consistent with the 4 week recall period of the form.

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

The total volume of blood that will be drawn from each patient enrolling in this study from the pivotal Phase III efficacy studies (Study Codes D4130C00002, D4130C00003, D4130C00004 or D4130C00005) for completers:

Table 9 Volume of blood to be drawn from completers of the Phase III pivotal study

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry (including lipid panel, thyroid, serum pregnancy[a])	8.5	9	76.5
	Hematology	2	9	18
	Bicarbonate	3.5	9	31.5
Total				**126**

a If urine pregnancy test is positive, a serum pregnancy test will be performed to confirm results.

The total volume of blood that will be drawn from each new patient, screen failures, or partial responders enrolling in this study from the pivotal Phase III efficacy studies (Study Codes D4130C00002, D4130C00003, D4130C00004 or D4130C00005) is as follows:

Table 10 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry (including lipid panel, thyroid, serum pregnancy[a])	8.5	11	93.5
	Hematology	2	11	22
	Bicarbonate	3.5	11	38.5
HIV, HBV, HbsAg, HCV		8.5	1	8.5
Pharmacogenetics (optional)		10	1	10
Total				**172.5**

a If urine pregnancy test is positive, a serum pregnancy test will be performed to confirm results.

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 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 representatives 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 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 Informed Consent Form (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 follows 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

11.1 Calculation or derivation of efficacy variable(s)

Change from randomization 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.

11.1.2 Clinical Global Impression (CGI)

CGI-S is a single item score. Change from randomization will be calculated.

11.2 Calculation or derivation of safety variable(s)

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

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: systolic blood pressure (SBP), diastolic blood pressure (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. The global clinical assessment of akathisia score will be reported, 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 or derivation of PRO variable(s)

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

11.3.1 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 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 in randomization in both the EQ-5D index score and the EQ VAS score will be calculated.

11.4 Calculation or derivation of health economic variables

11.4.1 Healthcare Resource Utilization and Work Absence (HRUWA)

Resource use will be abstracted during visits every 4 weeks for the duration of the study and the following individual items will be described descriptively for each assessment point on group level by geographic region and overall on individual level as well as on group level by geographic region.

Healthcare Resource Utilization and Work Absence Form Section 1

- Hospitalization due to MDD or due to other reasons: number of days in intensive care, intermediate care, and general care, if due to an adverse event
- Emergency room visits due to MDD or due to other reasons: classified by if arriving in ambulance, if due to an adverse event

- Primary care (general practitioner) office visits due to MDD or due to other reasons: frequency of visit(s)
- Specialist care (Psychiatrist, Psychologist/Counselor) office visits due to MDD or due to other reasons: frequency of visit(s)
- Social worker office visits due to MDD or due to other reasons: frequency of visit(s)
- Other health care provider (Nurse, Physiotherapist, Occupational Therapist, Massage Therapist, Acupuncturist, Chiropractor) office visits due to MDD or due to other reasons: frequency of visit(s)
- Telephone contact with a medical professional (not including calling to make an appointment) due to MDD or due to other reasons: frequency of contacts
- Time to hospitalization or ER visit (calculated as days from randomization to hospitalization or ER visit)

Healthcare Resource Utilization and Work Absence Form Section 2

The individual items will be summarized using descriptive statistics.

Healthcare Resource Utilization and Work Absence Form Section 3

Calculations of percent of total work time loss and number of hours work productivity loss for patients and caregivers. Items in the employment status module need to be considered for calculation of percentage of the total work time loss due to MDD and due to other reasons. The following assessments can be conducted using items in this section alone.

- Number of paid and/or unpaid hours missed work due to MDD or due to other reasons
- Number of paid and/or unpaid hours a caregiver (spouse/ family member/ friends) missed work due to patients' MDD

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

Three 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 Safety analysis set

The safety analysis set will include all randomized patients who receive at least one dose of investigational product (TC-5214 or placebo) and for whom post-dose data are available after randomization in this study. 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.

12.1.2 Modified intent-to-treat analysis set (mITT)

The mITT analysis set will include all randomized patients who receive at least one dose of investigational product (TC-5214 or placebo) and who have a score at randomization and at least one post-randomization total MADRS 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 the efficacy variables.

12.1.3 DESS analysis

The DESS analysis set will include all patients who have a Week 52 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.

This is a general evaluation of long-term safety and tolerability. Therefore, no formal inferential statistical analyses are planned. In general, all safety and efficacy 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 adverse events and other event type of endpoints, exposure adjusted incidence will also be presented beside frequency and percentages. For adverse events of special interest as well as AEs leading to discontinuation of investigational product Kaplan-Maier plots will be presented.

Exposure will be summarized (number of patients and percentage) by timepoint.

The calculation of total scores when there are missing item scores will be described in the SAP. No other data imputation will be performed.

12.2.1 Safety variables

The primary objective includes typical safety variables, as well as those of special interest that are identified individually as part of secondary safety objectives.

- **Safety:**
  - AEs and SAEs, including severity
  - AEs of special interest including, but not limited to reduction of blood pressure, orthostatic hypotension, anticholinergic signs and symptoms (including urinary retention), EPS symptoms, and increased fasting blood glucose
  - AEs leading to treatment discontinuation or study withdrawal
  - AEs potentially related to abuse, misuse, noncompliance, and diversion
  - Change from randomization in:
    - Clinical laboratory results, vital signs, weight, waist circumference, physical examinations, and ECG results
    - BARS and AIMS
  - Suicidal behavior as assessed by C-SSRS and AEs of suicidality, suicidal ideation, suicide attempts, suicide completion
  - DESS
  - OAEs

Safety data, as well as exposure, will be summarized by source and overall. Additional subgroup analyses, including combination with SSRI/SNRI, will be identified in the SAP

12.2.2 Secondary Efficacy variables

Descriptive statistics will be used to present the following efficacy outcomes:

- Efficacy
  - Change from randomization in:
    - MADRS total score
    - CGI-S

- SDS total score
- Q-LES-Q-SF % maximum total score
- EQ-5D total score

- HRUWA

12.3 Determination of sample size

No formal sample size calculation is performed for this long-term safety trial. The sample size determination is based on the regulatory exposure requirement that at least 300 patients need to complete a 6-month TC-5214 treatment and of those at least 100 patients need to complete a 12-month TC-5214 treatment within the dose range 1-4 mg BID.

It is expected approximately 50% of patients who receive active treatment will complete 26 weeks and approximately 25% of patients who receive active treatment will complete 52 weeks. Based on these assumptions and a randomization ratio of 3:1, the trial will randomize 800 patients with 600 to receive S-mecamylamine and 200 to receive placebo. Assuming the above drop-out rate 400 patients are expected to complete 6 months of treatment (300 patients on TC-5214) and 200 patients are expected to complete 12 months of treatment (150 on TC-5214).

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]	North America (NA) Study Medical Monitor - Responsible for protocol implementation in US/Canada	[redacted] 24 hour urgent medical content Tel: [redacted]
Other contact information		
Name	**Role in the study**	**Address & telephone number**
[redacted]	Central laboratory	[redacted] Tel: [redacted]
[redacted]	Central ECG laboratory	[redacted] Tel: [redacted]
[redacted]	IVRS	[redacted] Tel: [redacted] Fax: [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

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.

For overdoses associated with a SAE, standard reporting timelines apply, see Section 6.4.4.

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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Clinical Study Protocol Appendix B

Drug Substance	TC-5214 (S-mecamylamine)
Study Code	D4130C00007
Edition Number	[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.

Clinical Study Protocol Appendix C

Drug Substance	TC-5214 (S-mecamylamine)
Study Code	D4130C00007
Edition Number	[redacted]
Date	[redacted]

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	D4130C00007
Appendix Edition Number	[redacted]
Appendix Date	[redacted]

Appendix D
Pharmacogenetics Research

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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.

Clinical Study Protocol Appendix E

Drug Substance	TC-5214 (S-mecamylamine)
Study Code	D4130C00007
Appendix Edition Number	[redacted]
Appendix Date	[redacted]

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 1 mg TC-5214 2 mg TC-5214 4 mg TC-5214 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). •Change from randomization to end of treatment: o HAMD-17 o CGI-S o CGI-I o HAM-A o MADRS o SDS o Q-LES-Q-SF 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 1 mg TC-5214 2 mg TC-5214 4 mg TC-5214 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). • Change from randomization to end of treatment: o HAMD-17 o CGI-S o CGI-I o HAM-A o MADRS o SDS o Q-LES-Q-SF 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 2 mg TC-5214 4 mg TC-5214 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 1 mg TC-5214 4 mg TC-5214 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).