NCT02600494

Study ID: ITI-007-401

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study with an Open-Label Extension to Assess the Efficacy and Safety of ITI-007 Monotherapy in the Treatment of Patients with Major Depressive Episodes Associated with Bipolar I or Bipolar II Disorder (Bipolar Depression)

Protocol Version 1.4 Date: 09 March 2018

CLINICAL STUDY PROTOCOL
ITI-007-401

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study with an Open-Label Extension to Assess the Efficacy and Safety of ITI-007 Monotherapy in the Treatment of Patients with Major Depressive Episodes Associated with Bipolar I or Bipolar II Disorder (Bipolar Depression)

Confidential

[redacted]

Version of Protocol: Version 1.4

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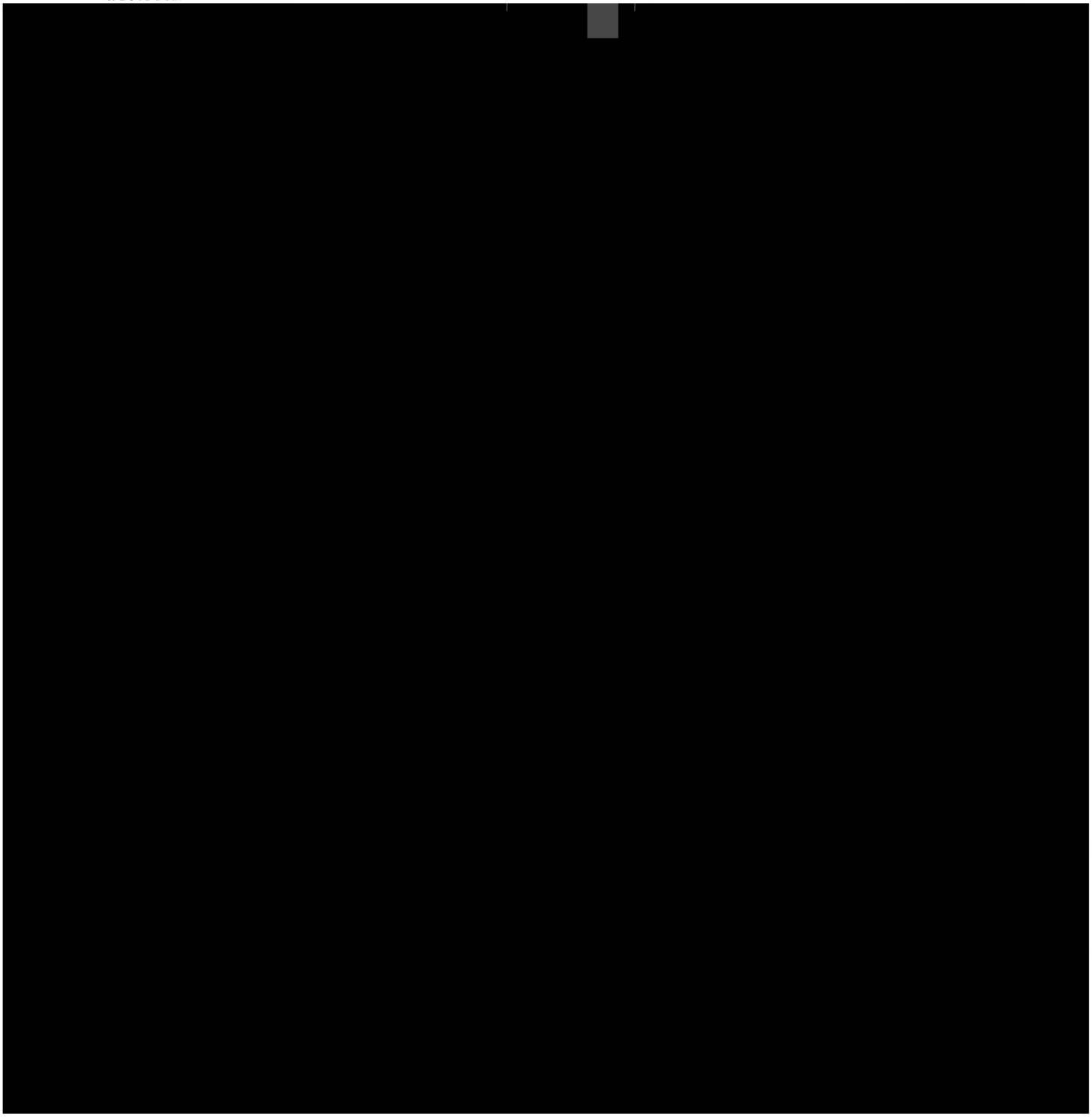
CONFIDENTIAL

All financial and nonfinancial support for this study will be provided by Intra-Cellular Therapies, Inc. (ITI). The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of ITI.

The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice.



Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Phase 3, randomized, double-blind, placebo-controlled, multi-center study with an open-label extension to assess the efficacy and safety of ITI-007 monotherapy in the treatment of patients with major depressive episodes associated with bipolar I or bipolar II disorder (bipolar depression)" and the accompanying investigator's brochure issued 18-May-2017.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Amended Protocol Version 1.4 dated 9 March 2018, the International Council for Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with ITI or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer study treatment only to patients under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without prior authorization from ITI.

Signature of Principal Investigator Date

Printed Name of Principal Investigator

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Protocol Synopsis

Protocol Number:	ITI-007-401
Title:	A Phase 3, randomized, double-blind, placebo-controlled, multi-center study with an open-label extension to assess the efficacy and safety of ITI-007 monotherapy in the treatment of patients with major depressive episodes associated with bipolar I or bipolar II disorder (bipolar depression)
Sponsor:	Intra-Cellular Therapies, Inc. (ITI)
Study Phase:	Phase 3
Study Sites:	Approximately 60 study sites in 1 country (United States)
Indication:	Major depressive episodes associated with bipolar I or bipolar II disorder (bipolar depression)
Rationale:	As a dopamine receptor protein phosphorylation modulator, ITI-007 has dual properties, acting as a post-synaptic antagonist and as a pre-synaptic partial agonist at dopamine 2 (D_2) receptors in vivo, with mesolimbic/mesocortical selectivity. ITI-007 also indirectly modulates glutamatergic activity by increasing the phosphorylation of the NR2B, or GluN2B, subunit of N-methyl-D-aspartate channels in extrastriatal dopamine-rich brain regions (e.g., nucleus accumbens), likely downstream from dopamine 1 receptor activation. ITI-007 has been tested in a number of animal models that suggests efficacy for the treatment of bipolar depression. Evidence supports the use of D_2 receptor antagonists in the treatment of bipolar disorder, including bipolar depression, as both monotherapy and adjunctive therapy to mood stabilizers. The pharmacologic profile of ITI-007 includes both the post-synaptic D_2 antagonism that appears efficacious in bipolar disorder and other pharmacological properties that may confer better safety and tolerability than other D_2 antagonists. As a 5-HT_{2A} receptor antagonist and serotonin reuptake inhibitor, ITI-007 is predicted to have antidepressant efficacy with fewer side effects than selective serotonin reuptake inhibitors. Importantly, ITI-007 lacks potent off-target interactions that have been associated with side effects for other antipsychotic drugs approved for the treatment of bipolar depression. For example, ITI-007 shows relatively weak affinity for 5-HT_{2C} and no measurable affinity for H_1 or muscarinic cholinergic receptors, which predict favorable body weight and metabolic

profile responses to the extent that these receptors mediate such effects.

Nonclinical data suggest that ITI-007 may have the potential to treat depression. Antidepressant-like activity of ITI-007 was measured using the social defeat (resident-intruder) mouse model. In this model, 1 mg/kg ITI-007, administered once daily intraperitoneally for 28 days, reversed the defeat behavior, consistent with antidepressant efficacy.

Brain receptor target engagement was confirmed in healthy male volunteers in the ITI-007-003 positron emission tomography Phase 1 clinical trial. ITI-007 rapidly penetrated the brain, showed long-lasting and dose-related occupancy, and was generally safe and well-tolerated. Cortical 5 HT_{2A} receptors were shown to be fully occupied at 10 mg-ITI-007 (>85% occupancy). A dose of 40-mg ITI-007 achieved up to 39% striatal D_2 occupancy (average of 29%) and up to 31% striatal serotonin transporter occupancy (average of 22%). Together, these data confirm a central mechanism for ITI-007 at dopaminergic and serotonergic brain targets. Projecting occupancy to higher doses based on plasma levels, it was estimated that a dose of 60-mg ITI-007 should achieve approximately 50% striatal D_2 receptor occupancy and similar or slightly less serotonin transporter occupancy.

Clinical data from the ITI-007-005 Phase 2 trial in patients with schizophrenia are consistent with the pharmacological profile and prediction for antidepressant effects with favorable safety and tolerability. Data supporting an improvement in symptoms of depression emerged from a prespecified subgroup analysis of patients with both schizophrenia and comorbid depression in this trial. In addition to meeting the primary efficacy endpoint for improving psychosis in the intent-to-treat population, data in the subgroup of patients with comorbid depression at baseline showed statistically significant reduction in symptoms of depression and in psychosis at the 60-mg ITI-007 dose level.

Safety data from this and other trials with ITI-007 have shown that ITI-007, administered to more than 1600 patients, is generally well tolerated across a dose range from 1 mg to 140 mg and administered once daily for up to 42 days (6 weeks). Additionally, ITI-007 is being evaluated in an open-label safety switching study (ITI-007-303) in patients with schizophrenia for up to 1-year treatment duration; initial data with exposures more than 3 months treatment duration indicate that ITI-007 is generally safe and well-tolerated. These clinical data together

with the nonclinical data and the pharmacological profile support the development of ITI-007 for the treatment of bipolar depression.

Objectives Part A (Double-blind, placebo-controlled phase):

Primary Objective

The primary objective of Part A of this study is to compare the efficacy of 2 doses of ITI-007 administered orally once daily to that of placebo in mean change from baseline in the total score on the rater-administered Montgomery-Åsberg Depression Rating Scale (MADRS) in patients with bipolar depression at Week 6.

Secondary Objectives

Key Secondary Objective

The key secondary objective of Part A of this study is to compare the efficacy of 2 doses of ITI-007 administered orally once daily to that of placebo in time to first response, defined as the number of days from first dose of study drug to the earliest date the patient experiences a sustained ≥50% reduction from baseline in the rater-administered MADRS total score.

Other Efficacy Secondary Objectives of Part A of this study are to compare the efficacy of 2 doses of ITI-007 administered orally once daily to that of placebo in relation to:

- MADRS:
    - Time course of improvement, as measured by mean change from baseline in the MADRS total score at each assessment time point;
    - Time course of improvement, as measured by the proportion of treatment responders where response is defined as a ≥50% decrease in the MADRS total score from baseline at each assessment time point, including at Week 6;
    - Time course of improvement, as measured by the proportion of remitters where remission is defined as a MADRS total score ≤12 at each assessment time point, including at Week 6;
    - The improvement in sleep, as measured by Item 4 (reduced sleep) on the MADRS in patients with at least mild sleep disturbance at baseline, defined by a score of ≥2 on Item 4;
    - Change from baseline in MADRS individual item scores at Weeks 1, 2, 3, 4, 5, and 6;

- Clinical Global Impression Scale, Bipolar version (CGI-BP):
    - Time course of improvement, measured by mean change from baseline in the CGI-BP – Severity (CGI-BP-S) score at each assessment time point, including at Week 6;
- Mean change from baseline in the Sheehan Disability Scale (SDS) total score;
- Mean change from baseline in the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF);
- Mean change from baseline in the WHO-5 Well-being Index;
- Mean change from baseline in the Neuroticism, Extraversion, and Openness to Experience-Five Factor Inventory (NEO-FFI).

Safety Secondary Objectives of Part A of this study are to determine the safety and tolerability of 2 doses of ITI-007 via changes in the following:

- Incidence of adverse events (AEs)
- Young Mania Rating Scale (YMRS)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Abnormal Involuntary Movement Scale (AIMS)
- Barnes Akathisia Rating Scale (BARS)
- Simpson Angus Scale (SAS)
- Clinical laboratory evaluations
- Electrocardiograms (ECGs)
- Vital sign measurements
- Physical examination and neurological findings

[redacted]

Exploratory Objectives

The exploratory objective of Part A of this study are to:

- Assess protein biomarkers in blood samples, including but not limited to p11 protein;

[redacted]

Objectives Part B (Open-label extension phase)

Primary Objective

The primary objective of Part B of this study is to determine the safety and tolerability of ITI-007 60 mg administered orally once daily for up to approximately 6 months (175 days) in patients with bipolar disorder. Safety and tolerability will be assessed in relation to:

- Incidence of AEs
- Mean change from baseline in the YMRS
- Mean change from baseline in MADRS
- Mean change from baseline in the C-SSRS
- Mean change from baseline in the AIMS
- Mean change from baseline in the BARS
- Mean change from baseline in the SAS
- Changes from baseline in clinical laboratory evaluations
- Changes from baseline in ECGs
- Changes from baseline in vital sign measurements
- Physical examination and neurological findings

Secondary Effectiveness Objectives

Secondary effectiveness objectives of Part B of this study are to determine whether 60 mg ITI-007, administered once daily for up to approximately 6 months to patients with bipolar disorder who have responded to treatment with ITI-007, improves and/or maintains symptoms, function and quality of life as measured by change from baseline on the following measures:

- MADRS total score;
- CGI-BP-S;
- Q-LES-Q-SF

Patient Population: **Inclusion Criteria (Part A)**

1. Is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.
2. The patient is between the ages of 18 and 75 years, inclusive, at the start of screening (both male and female patients are to be included).
3. Meets the Diagnostic and Statistical Manual of Mental Disorder, 5th Edition (DSM-5) criteria for Bipolar I or Bipolar II Disorder as confirmed by the investigator or sponsor-approved expert site-based rater by a Structured Clinical Interview for DSM-5 Disorders – Clinical Trials Version (SCID-5-CT) and meeting all of the following 5 criteria:
    a. The start of the current MDE is at least 2 weeks but no more than 6 months prior to the screening visit;
    b. Appropriate severity of illness, at least moderately ill, as measured by a rater-administered MADRS total score ≥20 and corresponding to a CGI-BP-S score of ≥4 at the screening and baseline visits;
    c. Sufficient history and/or independent report (such as family member or outside practitioner) verifying that the current major depressive episode is causing clinically significant distress or impairment in social, occupational or other important areas of functioning;
    d. A lifetime history of at least 1 bipolar manic episode or mixed episode (for Bipolar I) or hypomanic episode (for Bipolar II);
    e. A rater-administered YMRS total score of ≤12 at the screening and baseline visits. The presence of psychotic symptoms may result in an increased YMRS without evidence of mania/hypomania. Therefore, a patient with a YMRS > 12 AND psychotic symptoms may be included pending adjudication review by Medical Monitor for diagnostic certainty of the depressive episode.
4. Has a body mass index (BMI) of 18-35 kg/m^2, inclusive.

5. Either must agree to use highly effective methods of birth control (defined as those, alone or in combination, that result in a failure rate less than 1 percent per year when used consistently and correctly) for at least 2 weeks prior to randomization (starting) with signing informed consent) through to the end-of-study follow-up visit or must be of non-childbearing potential (defined as either permanently sterilized or, if female, post-menopausal; the latter is defined as at least 1 year with no menses without an alternative medical explanation).
6. In the opinion of the investigator, the patient is willing and able to comply with study requirements, study visits, and to return to the clinic for follow-up evaluations as specified by the protocol.

Exclusion Criteria (Part A)

1. The patient experiences a decrease in the rater-administered MADRS total score of ≥25% between screening and baseline visits.
2. In the opinion of the investigator, the patient has a significant risk for suicidal behavior during the course of his or her participation in the study or
    a. At screening, the patient scores "yes" on Items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to a 6-month period prior to screening; or
    b. At screening, the patient has had 1 or more suicidal attempts with reference to a 2-year period prior to screening; or
    c. At the baseline visit, the patient scores "yes" on Items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to screening; or
    d. At screening or the baseline visit, scores ≥4 on Item 10 (suicidal thoughts) on the rater-administered MADRS; or
    e. Considered to be an imminent danger to himself, herself, or others.

3. The patient is pregnant or breast-feeding; female patients of childbearing potential must have a negative urine pregnancy test at screening and on Day 1 prior to study treatment administration.
4. The patient has a history within 12 months of screening, based on previous psychiatric evaluation or a confirmed diagnosis upon screening based on the DSM-5 as assessed by the SCID-5-CT, of a psychiatric diagnosis other than bipolar disorder, including:
    a. Schizophrenia or other psychotic disorder;
    b. Anxiety disorders such as panic disorder, general anxiety disorder, or post-traumatic stress disorder as a primary diagnosis (however, anxiety symptoms may be allowed, if secondary to bipolar disorder, provided these symptoms do not require current treatment);
    c. Feeding or eating disorder;
    d. Primary diagnosis of obsessive compulsive disorder;
    e. Personality disorder;
    f. Moderate or severe substance use disorder (including for cannabis, excluding for nicotine);
    g. Any other psychiatric condition (other than bipolar disorder) that has been the main focus of treatment within 12 months of screening;
5. Patients who have experienced hallucinations, delusions, or any other psychotic symptomatology in the current depressive episode may be allowed as long as these symptoms are not attributable to a primary DSM-5 diagnosis other than bipolar disorder as described in Exclusion #4. The presence of these symptoms should be reviewed with the medical monitor and adjudication team prior to inclusion. The presence of psychotic symptoms may result in an increase in YMRS to > 12 in the absence of impending mania/hypomania, therefore these patients will be reviewed on a case by case basis to rule out possible impending mania/hypomania.

6. The patient has been hospitalized for mania associated with Bipolar I disorder within 30 days of screening.
   Note: This criterion is included to ensure that any manic phase has completely resolved before enrollment in the study.
7. The patient has received electroconvulsive therapy, vagal nerve stimulation, or repetitive trans-cranial magnetic stimulation within the last 5 years or received more than 1 course of electroconvulsive therapy during the patient's lifetime.
8. The patient is considered a rapid cycler, defined by the occurrence of at least 6 major depressive, manic, hypomanic, or mixed episodes during the previous year. These episodes must be demarcated either by a partial or full remission of at least 2 months' duration or by a switch to an episode of opposite polarity. (Each MDE must have lasted at least 2 weeks, each manic or mixed episode must have lasted at least 1 week, and each hypomanic episode must have lasted at least 4 days, as validated by a reliable informant).
   Note: This criterion is included to avoid spontaneous remission during participation in the study that might confound treatment results.
9. The patient is considered treatment-resistant, defined as having a lifetime history of treatment resistance (no remission) to ≥2 treatments with FDA-approved medications for Bipolar depression (lurasidone, quetiapine or Symbyax) at an adequate dose (per FDA-approved label) for an adequate duration (at least 6 weeks).
10. The patient is currently receiving formal cognitive or behavioral therapy, systematic psychotherapy, or plans to initiate such therapy during the study.
11. The patient presents with a lifetime history of epilepsy, seizure or convulsion, or electroencephalogram with clinically significant abnormalities, delirium, dementia, amnestic, or other cognitive disorder or significant brain trauma.

12. The patient has a positive test for drugs of abuse or alcohol test at the screening or baseline visits, or presents evidence of either withdrawal from or acute intoxication with cocaine, opiates, amphetamines (including methamphetamine), alcohol, barbiturates, or hallucinogens or similar compounds. The urine drug screen may be repeated once based on investigator judgment and reviewed for medical appropriateness by the medical monitor as part of the screening adjudication process.

    Note: Previous occasional use of alcohol or cannabis (but not synthetic marijuana/K2/Spice) or prescribed psychotropic (e.g., benzodiazepine, opiate) is allowed as long as the level of use does not meet DSM-5 criteria for any moderate or severe substance use disorder within the 12 months prior to screening and the use of alcohol or cannabis is not considered to be the precipitating factor of the current depressive episode, in the opinion of the investigator and any prescribed psychotropic is accompanied by evidence of prescription; patients are required to abstain from alcohol and cannabis use during the study.

13. The patient has used 1 of the following agents under the specified conditions:

    a. Lifetime exposure to ITI-007 (i.e., participated in previous clinical study with ITI-007 as verified by DupCheck) or who has had exposure to any investigational product within 3 months of the baseline visit or participated in the past 4 years in >2 clinical studies of an investigational product with a central nervous system indication.

    b. Any strong or moderate cytochrome P450 3A4 inhibitor or inducer within 7 days prior to the baseline visit.

    c. Use of any long-acting anxiolytics within 5 half-lives of the baseline visit.

d. Drugs with known psychotropic properties or any non-psychotropic drugs with known or potentially significant central nervous system effects within the last 28 days or 5 half-lives before the baseline visit, whichever is less, as reviewed by the medical monitor including, but not limited to:

   i. sedative hypnotics (with the exception of zolpidem and zolpidem CR as noted in the concomitant medication section, allowed during the screening period and the first 2 weeks of the treatment period);

   ii. central opioid agonists/antagonists including tramadol (Ultram);

   iii. anticonvulsants;

   iv. mood stabilizers, antipsychotics, antidepressants; EXCEPTION: long acting injectable antipsychotics must be washed out 1.5 cycles or 28 days, whichever is LONGER, before baseline

   v. methotrexate;

   vi. Any known 5-HT_{2A} receptor antagonist or inverse agonist including but not limited to mianserin, mirtazapine, nefazodone, cyproheptadine, pimavanserin, or fluvoxamine;

   vii. Immunosuppressants;

   viii. dietary supplements, or medical foods must be approved by the Medical Monitor. Daily multivitamin use is not excluded.

14. The patient has abnormal laboratory values or clinical findings at screening that are judged clinically significant and confirmed upon re-test (1 re-test prior to baseline visit is allowed and results must be available prior to the baseline visit and must have returned to within normal range), including, but not limited to:

a. Aspartate aminotransferase (AST) >2.0 × the upper limit of normal (ULN)

b. Alanine aminotransferase (ALT) >2.0 × the ULN

c. Alkaline phosphatase >2.0 × the ULN

d. Gamma-glutamyl transpeptidase >2.0 × the ULN

e. Total bilirubin >1.5 × the ULN

f. Serum creatinine >1.5 × the ULN

g. Blood urea nitrogen >1.5 × the ULN

h. Thyroid-stimulating hormone outside of the normal limits and clinically significant, as determined by the investigator. Free thyroxine levels may be measured if thyroid-stimulating hormone level is high. The patient will be excluded if the free thyroxine level is clinically significant.

i. 12-lead ECG (in a supine position at rest at the screening or baseline visit) corrected QT interval using the Fridericia formula (QTcF) >450 ms, and/or heart rate ≤50 beats per minute, or evidence of clinically significant bundle-branch blocks. The ECG may be repeated one time at the investigator's discretion to ensure the reproducibility of results.

j. Any other clinically significant abnormal laboratory result at the time of the screening examination.

   Note: medical conditions that are stable with medication (e.g., hypertension, high cholesterol, and hyperthyroidism) are allowed as long as the condition has been stable for at least 3 months prior to screening, the medications are documented and kept stable during the study, and the condition is not thought to affect safe participation in the study in the opinion of the investigator and confirmed by the medical monitor as part of the screening adjudication process

15. The patient has clinically significant cardiovascular (including but not limited to uncontrolled angina, or history of a myocardial infarction within 3 months prior to screening, or history of a clinically significant cardiac arrhythmia including antipsychotic drug-induced corrected QT interval prolongation), endocrine (including poorly controlled diabetes defined as glycated hemoglobin A1c [HbA1c] >53 mmol/mol [7.0%] at screening with no re-test allowed for HbA1c), hepatic, renal, pulmonary, gastrointestinal, neurological, malignancy (including any malignancy and/or chemotherapy within the 2 years prior to screening; malignancy more than 2 years prior to screening must have been local and without metastasis and/or recurrence, and if treated with chemotherapy, without nervous system complications; some malignancies, such as basal cell carcinoma, may not preclude participation and will be individually reviewed), pheochromocytoma, metabolic, psychiatric or other condition that might be detrimental to the patient if he or she participates in the study (in the opinion of the investigator).
16. The patient has a history of human immunodeficiency virus (HIV) infection or has HIV antibodies in blood at screening.
17. At Screening, the patient has a history of Hepatitis B or Hepatitis C infection (or demonstrated Hepatitis B surface antigen or Hepatitis C antibodies), AND evidence of active disease defined as elevated ALT, AST or bilirubin levels as specified in Exclusion 14.
18. The patient is an employee of the investigator or study center, or immediate family (i.e., spouse, parent, child, or sibling, whether biological or legally adopted) of such employees, the investigator, ITI, or contract research organizations conducting the study.
19. The patient is unable to be safely discontinued from current antidepressant medication, mood stabilizers, anticholinergics, or other psychotropic medications (in the opinion of the investigator).
20. The patient is judged by the investigator to be inappropriate for the study.

Inclusion Criteria (Part B)

Each patient continuing into Part B of the study must meet all of the following criteria:

1. Patient must have safely (in the opinion of the investigator and confirmed by the Medical Monitor) completed Part A and in the opinion of the investigator is willing and able to comply with study requirements as specified by the protocol.
1. [Note: patients who had experienced significant AEs which were thought to be possibly related to blinded study medication, should not be enrolled into the open-label extension];
2. Patients must be capable of understanding the written informed consent, providing signed and witnessed written informed consent, and agreeing to comply with protocol requirements for Part B of the study; a separate written informed consent must be provided for continuation into the open-label extension after treatment in Part A has been completed.
3. Patients must agree to use highly effective methods of birth control (as defined in Part A Inclusion #5) for at least 2 weeks prior to randomization (starting with informed consent) through to the end of study visit, or, patients must be of non-childbearing potential (as defined in Part A Inclusion #5).

Exclusion Criteria (Part B) Re-Screening

Since all prior participants in Part A were required to satisfy exclusion criteria for participation in that part of the study, the investigator should assess where there has been any change of status. In the event of a recently emerged new medical condition, this should be evaluated carefully and discussed with the Medical Monitor before including the patient in Part B.

Patients who safely completed Part A of the study prior to the open-label extension becoming available, will undergo screening procedures and must be eligible according to the abbreviated Part A exclusion criteria as described below. Any references to adjudication in Part B will be limited to review by the Medical Monitor.

Please note these Part B Exclusion Criteria are numbered to coincide with the Part A Exclusion Criteria for consistency of reference.

Patients meeting any of the following criteria will be excluded from the study:

2. In the opinion of the investigator, the patient has a significant risk for suicidal behavior during the course of his or her participation in the study or
    a. At Visit 10 Screening, the patient scores "yes" on Items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to the last visit; or
    b. At Visit 10 Screening, the patient has had 1 or more suicidal attempts with reference to a 2-year period prior to screening; or
    c. At the Visit 11 Baseline Visit, the patient scores "yes" on Items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to the last visit; or
    d. At Visit 10 Screening or the Visit 11 Baseline Visit, scores $\geq$4 on Item 10 (suicidal thoughts) on the *self*-administered MADRS; or
    e. Considered to be an imminent danger to himself, herself, or others.
3. The patient is pregnant or breast-feeding; female patients of childbearing potential must have a negative urine pregnancy test at Visit 10 Screening and on Visit 11 Baseline Visit prior to study treatment administration.
4. The patient is assessed by the investigator as not having had a change in primary diagnosis at Visit 10 Screening, as compared to Visit 1 Screening.
7. The patient has received electroconvulsive therapy, vagal nerve stimulation, or repetitive trans-cranial magnetic stimulation within the last 5 years or received more than 1 course of electroconvulsive therapy during the patient's lifetime.

9. The patient is considered treatment-resistant, defined as having a lifetime history of treatment resistance (no remission) to ≥2 treatments with FDA-approved medications for Bipolar depression (lurasidone, quetiapine or Symbyax) at an adequate dose (per FDA-approved label) for an adequate duration (at least 6 weeks).

11. The patient presents with a lifetime history of epilepsy, seizure or convulsion, or electroencephalogram with clinically significant abnormalities, delirium, dementia, amnestic, or other cognitive disorder or significant brain trauma.

12. The patient has a positive test for drugs of abuse or alcohol test at the Visit 10 Screening or Visit 11 Baseline visits, or presents evidence of either withdrawal from or acute intoxication with cocaine, opiates, amphetamines (including methamphetamine), alcohol, barbiturates, or hallucinogens or similar compounds. The urine drug screen may be repeated once based on investigator judgment and reviewed for medical appropriateness by the medical monitor as part of the Screening adjudication process.

    Note: Previous occasional use of alcohol or cannabis (but not synthetic marijuana/K2/Spice) or prescribed psychotropic (e.g., benzodiazepine, opiate) is allowed as long as the level of use does not meet DSM-5 criteria for any moderate or severe substance use disorder within the 12 months prior to screening and the use of alcohol or cannabis is not considered to be the precipitating factor of the current depressive episode, in the opinion of the investigator and any prescribed psychotropic is accompanied by evidence of prescription; patients are required to abstain from alcohol and cannabis use during the study.

13. The patient has used 1 of the following agents under the specified conditions:

    b. Any strong or moderate cytochrome P450 3A4 inhibitor or inducer within 7 days prior to the Visit 11 Baseline Visit.

c. Use of any long-acting anxiolytics within 5 half-lives of the Visit 11 Baseline Visit.

d. Drugs with known psychotropic properties or any non-psychotropic drugs with known or potentially significant central nervous system effects within the last 28 days or 5 half-lives before the Visit 11 Baseline Visit, whichever is less, as reviewed by the medical monitor including, but not limited to:

    i. sedative hypnotics (with the exception of zolpidem and zolpidem CR as noted in the concomitant medication section)

    ii. central opioid agonists/antagonists including tramadol (Ultram);

    iii. anticonvulsants;

    iv. mood stabilizers, antipsychotics, antidepressants; EXCEPTION: long acting injectable antipsychotics must be washed out 1.5 cycles or 28 days, whichever is LONGER, before baseline

    v. methotrexate;

    vi. Any known 5-HT_{2A} receptor antagonist or inverse agonist including but not limited to mianserin, mirtazapine, nefazodone, cyproheptadine, pimavanserin, or fluvoxamine;

    vii. Immunosuppressants;

    viii. dietary supplements, or medical foods must be approved by the Medical Monitor. Daily multivitamin use is not excluded.

14. The patient has abnormal laboratory values or clinical findings at screening that are judged clinically significant and confirmed upon re-test (1 re-test prior to Visit 11 Baseline visit is allowed and results must be available prior to the Visit 11 Baseline Visit and must have returned to within normal range), including, but not limited to:

    a) Aspartate aminotransferase (AST) >2.0 × the upper limit of normal (ULN)

    b) Alanine aminotransferase (ALT) >2.0 × the ULN

    c) Alkaline phosphatase >2.0 × the ULN

    d) Gamma-glutamyl transpeptidase >2.0 × the ULN

    e) Total bilirubin >1.5 × the ULN

    f) Serum creatinine >1.5 × the ULN

    g) Blood urea nitrogen >1.5 × the ULN

    h) Thyroid-stimulating hormone outside of the normal limits and clinically significant, as determined by the investigator. Free thyroxine levels may be measured if thyroid-stimulating hormone level is high. The patient will be excluded if the free thyroxine level is clinically significant.

    i) 12-lead ECG (in a supine position at rest at the Visit 10 Screening or Visit 11 Baseline visit) corrected QT interval using the Fridericia formula (QTcF) >450 ms, and/or heart rate $\leq$50 beats per minute, or evidence of clinically significant bundle-branch blocks. The ECG may be repeated one time at the investigator's discretion to ensure the reproducibility of results.

j) Any other clinically significant abnormal laboratory result at the time of the Visit 10 Screening examination. Note: medical conditions that are stable with medication (e.g., hypertension, high cholesterol, and hyperthyroidism) are allowed as long as the condition has been stable for at least 3 months prior to Visit 10 Screening, the medications are documented and kept stable during the study, and the condition is not thought to affect safe participation in the study in the opinion of the investigator and confirmed by the medical monitor as part of the screening adjudication process

15. The patient has clinically significant cardiovascular (including but not limited to uncontrolled angina, or history of a myocardial infarction within 3 months prior to Visit 10 Screening, or history of a clinically significant cardiac arrhythmia including antipsychotic drug-induced corrected QT interval prolongation), endocrine (including poorly controlled diabetes defined as glycated hemoglobin A1c [HbA1c] >53 mmol/mol [7.0%] at screening with no re-test allowed for HbA1c), hepatic, renal, pulmonary, gastrointestinal, neurological, malignancy (including any malignancy and/or chemotherapy within the 2 years prior to Visit 10 Screening; malignancy more than 2 years prior to Visit 10 Screening must have been local and without metastasis and/or recurrence, and if treated with chemotherapy, without nervous system complications; some malignancies, such as basal cell carcinoma, may not preclude participation and will be individually reviewed), pheochromocytoma, metabolic, psychiatric or other condition that might be detrimental to the patient if he or she participates in the study (in the opinion of the investigator).
16. The patient has a history of human immunodeficiency virus (HIV) infection or has HIV antibodies in blood at screening.

17. The patient has a history of hepatitis B or hepatitis C infection (or demonstrated Hepatitis B surface antigen or Hepatitis C antibodies), AND evidence of active disease defined as elevated ALT, AST or bilirubin levels as specified in Exclusion 14.
18. The patient is an employee of the investigator or study center, or immediate family (i.e., spouse, parent, child, or sibling, whether biological or legally adopted) of such employees, the investigator, ITI, or contract research organizations conducting the study.
19. The patient is unable to be safely discontinued from current antidepressant medication, mood stabilizers, anticholinergics, or other psychotropic medications (in the opinion of the investigator).
20. The patient is judged by the investigator to be inappropriate for the study.

Exclusion Criteria (Part B) Direct Rollover

Patients directly enrolling into the open-label extension upon completing Part A, presenting at the Day 43 visit with any of the following characteristics, will be excluded from the study:

1. Is, in the opinion of the investigator, unable to comply with study procedures;
2. Has a significant risk for suicidal behavior during the course of their participation in the study or is considered to be an imminent danger to themselves or others, in the opinion of the investigator, and/or as assessed by the C-SSRS; or <u>≥ 4 on item 10 of the subject-rated MADRS</u>
3. Clinically significant (in the investigator's judgement) abnormal laboratory results at the time of the last study evaluation.

<u>Note</u>: medical conditions are allowed as long as the condition has been stable during Part A, the medications are documented and kept stable during the study, and the condition is not thought to affect safe participation in the study in the opinion of the investigator;

4. The patient is pregnant or breast-feeding; female patients of childbearing potential must have a negative pregnancy test at rescreening (if applicable) and upon entry to Part B of the study prior to treatment administration;

5. Has a positive qualitative urine drug or alcohol test (which may be confirmed with additional testing) at the last evaluation, or evidence of either withdrawal from, or acute intoxication with cocaine, opiates, amphetamines (including methamphetamine), alcohol, barbiturates, or hallucinogens or similar compounds;

   Note: Previous occasional use of alcohol or cannabis (but not synthetic marijuana/K2/Spice) or prescribed psychotropic (e.g., benzodiazepine, opiate) is allowed as long as the level of use does not meet DSM-5 criteria for any moderate or severe substance use disorder within the 12 months prior to screening and the use of alcohol or cannabis is not considered to be the precipitating factor of the current depressive episode, in the opinion of the investigator and any prescribed psychotropic is accompanied by evidence of prescription; patients are required to abstain from alcohol and cannabis use during the study.;

6. Is judged by the investigator to be inappropriate for the study.

Study Design:

This study will be conducted in 2 parts, Part A and Part B. Part A is a randomized, double-blind, placebo-controlled, two-stage adaptive design with a single interim analysis (IA) and a final analysis. In Part B, patients who safely completed participation in Part A may be enrolled in an open-label extension.

Part A Study Periods (up to 10 Weeks, Including Screening/Baseline)

Part A of the study consists of the following periods: screening period, on-treatment period, and safety follow-up period. Patients who roll directly over into Part B will not have a unique safety follow-up visit after the 6-week treatment.

Screening Period (2 Weeks)

Potential patients will be evaluated during a screening period lasting up to 2 weeks, unless confirmed by the medical monitor that a longer screening phase, lasting no longer than 28 days, is appropriate to ensure washout of excluded medications with long half-lives (e.g., fluoxetine), under the supervision of the investigator before baseline.

After obtaining written informed consent, diagnostic interviews and physical examinations will be conducted, vital signs and

ECGs will be assessed, and blood samples for laboratory assessments will be collected. Patients considered potentially eligible for participation will be required to discontinue their current antidepressant treatment and/or other psychotropic drugs.

Adjudication of patient eligibility will be determined by remote, independent expert raters and medical monitor(s).

At baseline (Visit 2), patients who continue to meet all eligibility criteria will be randomly assigned to 1 of the 3 treatment arms for a 6-week, double-blind treatment period. Patients will be randomly assigned to 1 of the following groups: 40-mg ITI-007, 60-mg ITI-007, or matching placebo.

On-Treatment Period (6 Weeks)

Patients will take their first dose of study medication the evening of their baseline randomization visit. A single dose will be taken each day in the evening for the duration of the on-treatment period.

Following randomization, patients will attend the clinic at Weeks 1, 2, 3, 4, 5, and 6.

The on-study treatment period will be a total of 6 weeks.

Safety Follow-up Period (2 Weeks)

For those patients not continuing on to Part B, a return to the clinic for a safety follow-up visit will occur at Week 8, approximately 2 weeks following the last dose of study medication. If possible, patients who discontinue treatment prematurely will be seen for an early termination visit (within 1 week of last dose, when possible) and will be asked to return to the clinic for a safety follow-up visit 2 weeks following withdrawal.

Part B Study Periods (Up to Approximately 6 Months [175 Days])

Part B of the study will be an open-label extension. Patients enrolling directly into the open-label extension will have their baseline visit on Visit 8 (Study Day 43 of Part A). Patients who safely complete Part A of the study prior to the open-label extension becoming available will undergo screening procedures for determination of their eligibility for Part B. Subsequent post-dose clinical evaluations will occur on Study Days 8, 15, and 25, then every 25 ± 3 days (Study Days 50, 75, 100, 125, 150, and 175) of Part B. Evaluations on Days 75, 125, and 150 will be conducted by telephone. A safety follow-up visit will be completed at approximately Day 189. Patients must undergo these scheduled clinical evaluations in order to continue to receive study drug. Unscheduled clinical evaluations may occur at any time if deemed appropriate by the investigator, to discontinue patient participation, and/or for safety follow up. Patients will return for a final safety follow-up visit approximately 2 weeks after their last dose of study drug.

Concomitant Medications

The use of concomitant medications has some restrictions in both Part A and Part B of the protocol. Details of these restrictions are listed in Section 5.8 of the protocol.

Estimated Study Duration:

In Part A, the study will last a maximum of approximately 10-12 weeks (9 visits).

In Part B, the duration of individual patient participation in the study will be determined based on clinical grounds, but may continue for up to approximately 6 months (175 days) plus the safety follow-up visit (6.5 months). After the final treatment visit, patients will return to prior therapy or standard of care therapy as determined by the investigator.

Analysis Sets:

The following analysis sets will be used for the analyses: The All Patients Enrolled (ENR) Set will contain all patients who signed informed consent for the study.

The All Patients Randomized (RND) Set will contain all patients who signed the informed consent and were randomized to study drug.

Primary, secondary, and exploratory efficacy analyses of Part A data will be performed using the Intent-to-Treat (ITT) Set, which will contain all randomly assigned patients who received at least one dose of study drug and who had a valid baseline (pre-dose) measurement and at least one valid post-baseline measurement of MADRS.

For Part A, the Per-protocol (PP) Set will contain all ITT patients who did not have any major protocol deviations. Patients will be classified according to the randomized treatment. For part B, the PP Set will contain all patients in the Safety Analysis Set who did not have any major protocol deviations.

The Safety Analysis Set will contain all patients who received at least 1 dose of study drug. In Part A, patients will be classified according to the treatment received.

[redacted]

The following analysis sets will be used for the analyses of Part B data: ENR, Safety Analysis, and Part B PP Sets. The classification of patients according to study drug does not apply to Part B.

Efficacy Assessments:

For Part A, the efficacy assessments will include: the MADRS, the CGI-BP-S, the SDS, the Q-LES-Q-SF, the WHO-5 Well-being Index and the NEO-FFI.

For Part B, effectiveness assessments will include: MADRS. CGI-BP-S, and Q-LES-Q.

[redacted]

[redacted]

Safety Assessments: Safety assessments for both study parts will include incidence of AEs; suicidality assessment by the C-SSRS; mania assessment by the YMRS; movement disorder assessment by the AIMS, the BARS, and the SAS; clinical laboratory evaluations; ECG evaluations; vital sign measurements; physical examination; and neurological findings.

Study Drug, Dosage, and Route of Administration: In Part A, patients will be assigned to receive either ITI-007 (40- or 60-mg doses) or placebo. Patients will self-administer all doses orally, once daily, at home, each evening, for the duration of the on-treatment period. Treatments will be provided in dose cards containing 2 strips of over-encapsulated tablets, and patients will be instructed to take 2 capsules (1 capsule from each strip) per dose.

In Part B, all patients will receive ITI-007 60 mg. Patients will self-administer all doses orally, once daily, at home, each evening for up to 6 months. Treatment will be provided in dose cards containing 28 tablets and patients will be instructed to take 1 tablet per dose. A one-time dose reduction to 40 mg will be allowed if the 60 mg dose is not tolerated. If the patient does not tolerate the 40 mg dose, the patient should be withdrawn from the study.

Sample Size:

In Part A, approximately 549 patients will be randomly assigned in a 1:1:1 ratio to 1 of the 3 treatment arms, which will provide approximately 471 evaluable patients, assuming an approximate 14% early discontinuation rate before a post-dose assessment in the primary efficacy endpoint.

In Part B, up to approximately 549 patients will be enrolled. The sample size is not based on statistical considerations, rather on the number of patients who may be eligible based on participation in Part A of the study. It is estimated that the majority of patients will continue treatment for the full 6 months.

Statistical Methods:

Patient Disposition, Demographics, and Other Baseline Data

Patient disposition will be summarized for each Part by treatment group, when applicable, and overall, including incidence of screening, screening failure and incidence of treatment or study discontinuation and the corresponding reasons for discontinuation. Time to treatment discontinuation due to all reasons, adverse events, lack of efficacy, or due to any other reason of special interest will be evaluated separately using the Kaplan-Meier method, where patients who complete the On-Treatment Period or who discontinue for a reason other than the one being evaluated will be censored. The Log-rank test will be used to compare the time to discontinuation between each treatment group and the placebo group (Part A).

Demographic and baseline characteristics, including bipolar disorder diagnosis and bipolar disorder baseline efficacy measures, will be summarized for each Part and by treatment group for Part A only. No inferential statistics will be presented.

Prior and Concomitant Medications

Prior, prior concomitant, concomitant, and post-treatment medications, defined by start and stop dates relative to study medication administration, will be summarized by preferred term for each Part and by treatment group for Part A only.

Additionally, for Part A, the number and percent of patients in the ITT Set receiving concomitant medications of special interest, such as zolpidem, and the total number of days on each medication will be summarized by treatment group for the Screening Period, for each week during the On-Treatment Period and for post treatment. Other medications will be summarized by treatment group and study period if deemed necessary.

Study Medication Exposure and Treatment Compliance

Exposure to study medication and treatment compliance will be presented for each Part using the Safety Analysis Set and additionally, for Part A, using the ITT Set. Duration of exposure (days) and dosing compliance (%) will be calculated and summarized for each Part and by treatment group for Part A only. In addition, the number and percentage of patients exposed to study medication will be presented.

Efficacy Analysis – Part A

The primary efficacy endpoint will be evaluated using a mixed model repeated measures (MMRM) method. The model will include the change from baseline at each pre-specified time point in the rater-administered MADRS total score as the response variable and visit, treatment, site, and the stratification variable, bipolar disorder at screening (I or II), as factors, the baseline MADRS total score as a covariate, and interaction terms for treatment-by-visit, visit-by-baseline MADRS total score, and treatment-by-site. Estimates for change from baseline in MADRS total score, standard errors and 95% confidence intervals (CIs) will be presented by treatment group and time point. The least-squares mean difference between ITI-007 groups and placebo along with the corresponding 95% confidence intervals (CIs), effect sizes, and p-values will be presented for each visit.

The key secondary efficacy endpoint, time to first response, defined as ≥50% reduction from baseline in rater-administered MADRS total score and maintaining it through the end of the 6-week treatment, will be analyzed using time-to-event methods. Time to the first response for treatment responders will be analyzed using the Cox's Proportional Hazards model with terms for treatment, site, baseline MADRS total score, the bipolar disorder stratification variable and treatment-by-site interaction. Patients who do not experience at least 50% reduction from baseline in the rater-administered MADRS total score, or do not maintain it through the end of the 6-week treatment, and patients who discontinue treatment, will be considered non-responders and will be censored.

Time to first response will be compared between treatment groups using the Kaplan-Meier product limit method.

The primary and key secondary efficacy endpoints will be evaluated using a gatekeeping procedure to adjust for multiplicity while controlling the overall Type I error rate in the strong sense at a two-sided alpha=0.05. The primary endpoint will serve as a gatekeeper for the key secondary endpoint in the sense that a key secondary endpoint will be tested only if at least one primary test is significant, as described in Section 7.5.4 of the protocol and detailed in the Statistical Analysis Plan (SAP).

[redacted]

Binary secondary endpoints (proportion of treatment responders, proportion of remitters) will be analyzed using a logistic regression model with terms for treatment and the bipolar disorder at screening (I or II) stratification variable. An estimate and 95% CI for the odds ratio between each dose of ITI-007 and placebo will be presented for each of the proportions evaluated.

The CGI-BP-S, improvement in sleep, SDS, Q-LES-Q-SF, WHO-5 and NEO-FFI scores and the changes from baseline will be summarized by treatment and visit.

The analyses of secondary efficacy endpoints, other than the key secondary one, will not be adjusted for multiple comparisons.

Analysis of Secondary Effectiveness Endpoints – Part B

Analyses of effectiveness endpoints in Part B will be performed on the Safety Analysis Set and will primarily consist of change from baseline descriptive summaries of MADRS, CGI-BP-S, and Q-LES-Q-SF.

Safety Analyses – Parts A and B

All safety parameters will be summarized using the Safety Analysis Set.

Medical history, prior medications, concomitant medications, and compliance/exposure will be summarized using descriptive statistics. Safety data such as reported and observed AEs, treatment emergent AEs (TEAEs) and serious AEs (SAEs), clinical laboratory results, vital signs, physical examinations and neurological findings, ECGs, and the different rating scales will be summarized by visit (Part A and Part B) and treatment group

(Part A). Parameters planned to be collected more than once at pre-specified time points will be analyzed as an average of the measures for the relevant time point, including screening or baseline.

Reported AE terms will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MeDRA). TEAEs and SAEs will be listed and summarized by system organ class (SOC), preferred term (PT), relationship to study drug, intensity (Part A and Part B) and by treatment group (Part A).

Patients who discontinued study or study drug due to an AE will be listed and summarized by SOC and PT (Parts A and B) and by treatment group (Part A).

Laboratory assessments, including hematology and chemistry, vital signs, and ECGs, will be listed and summarized by visit and time point (Parts A and B) and by treatment group (Part A). Summaries will include actual and change values, incidence of abnormal values according to normal range criteria, shifts from baseline to each visit and time point according to markedly abnormal criteria, and listings of patients meeting markedly abnormal criteria.

The observed and change in YMRS, AIMS, BARS, SAS, and C-SSRS scores will be summarized by visit (Parts A and B) and by treatment group (Part A).

[redacted]

Subgroup Analyses – Parts A and B

Subgroup analyses of efficacy and safety variables may be conducted as deemed necessary and will be detailed in the Statistical Analysis Plan (SAP).

Interim Analysis – Part A

One Interim Analysis (IA) is planned during Part A of the study, after 375 patients have completed the 6-week treatment period or confirmed to have discontinued treatment or study prior to first post-baseline assessment of MADRS. The IA will be conducted such that the ongoing study integrity is maintained, and the interim data will be reviewed by an independent external unblinded Data Monitoring Committee (DMC).

The IA will be used to review interim safety and efficacy data and reassess the assumptions of variability and effect size. It may be used for a decision to terminate the study due to superior efficacy or to adjust the sample size.

Date of Protocol: 9 March 2018

List of Abbreviations

Abbreviation	Definition
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BLQ	below the limit of quantification
BMI	body mass index
BPI	Bipolarity Index
CFR	Code of Federal Regulations
CGI-BP	Clinical Global Impression Scale, Bipolar version
CGI-BP-S	Clinical Global Impression Scale, Bipolar version – Severity
CI	confidence interval
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
C-VISA™	Clinical Validation Inventory for Study Admission (Bracket)
D_2	dopamine 2 receptor
DMC	Data Monitoring Committee
DSM-5	Diagnostic and Statistical Manual, 5th Edition
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
FWER	familywise error rate
GCP	Good Clinical Practice
HbA_{1c}	glycated hemoglobin A_{1c}
HIV	human immunodeficiency virus
IA	interim analysis
ICF	informed consent form
ICH	International Council for Harmonisation

Abbreviation	Definition
IRB	Institutional Review Board
ITI	Intra-Cellular Therapies, Inc.
ITT	intent-to-treat
IVRS	interactive voice response system
IWRS	interactive web response system
LDL	low-density lipoprotein
LOCF	Last observation carried forward
MADRS	Montgomery-Åsberg Depression Rating Scale
MDE	major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
NEO-FFI	Neuroticism, Extraversion, and Openness to Experience-Five Factor Inventory
NMDA	N-methyl-D-aspartate
PET	positron emission tomography
PK	pharmacokinetic
PP	per-protocol
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form
QTcF	corrected QT interval using the Fridericia formula
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson Angus Scale
SCID-5-CT	Structured Clinical Interview for DSM-5 Disorders – Clinical Trials Version
SDS	Sheehan Disability Scale
SERT	serotonin transporter
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
YMRS	Young Mania Rating Scale

1 Introduction

Bipolar disorder is a serious psychiatric disorder associated with shifts in mood including manic or hypomanic episodes, depressed episodes, or mixed episodes. Bipolar I Disorder is defined by the presence of manic or mixed episodes, whereas Bipolar II Disorder is defined by hypomania, but both are often associated with major depressive episodes. Bipolar disorder affects approximately 5.7 million adult Americans, or about 2.6% of the U.S. population age 18 and older, every year according to the National Institute of Mental Health. Depressive episodes associated with bipolar disorder tend to last longer, recur more often, and are associated with a worse prognosis than manic/hypomanic episodes. Bipolar depression, the predominant presentation of bipolar disorder, remains a significantly underserved medical need, with only a few Food and Drug Administration (FDA)-approved treatment options available.

Intra-Cellular Therapies (ITI) is developing ITI-007, a new chemical entity, for the treatment of patients with major depressive episodes (MDEs) associated with bipolar I or bipolar II disorder (bipolar depression). ITI-007 is currently in Phase 3 clinical development in the United States for the treatment of schizophrenia.

ITI-007 is a novel small molecule therapeutic agent designed specifically to combine, in a dose-dependent manner, potent serotonin 5-HT_{2A} receptor antagonism with both mesolimbic/mesocortical selective modulation of phosphoprotein pathways downstream of dopamine receptors and serotonin reuptake inhibition (Snyder, 2015). As a dopamine receptor protein phosphorylation modulator, ITI-007 has dual properties, acting as a post-synaptic antagonist and as a pre-synaptic partial agonist at dopamine 2 (D_2) receptors in vivo, with mesolimbic/mesocortical selectivity. ITI-007 also indirectly enhances glutamatergic activity by increasing the phosphorylation of the NR2B, or GluN2B, subunit of N-methyl-D-aspartate channels in extrastriatal dopamine-rich brain regions (e.g., nucleus accumbens), via N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) currents downstream from dopamine 1 receptor activation. ITI-007 has been tested in a number of animal models that suggests efficacy for the treatment of bipolar depression.

Evidence supports the use of D_2 receptor antagonists in the treatment of bipolar disorder, including bipolar depression (Young, 2013; Loebel, 2014a; Loebel, 2014b), as both monotherapy and adjunctive therapy to mood stabilizers. The pharmacologic profile of

ITI-007 includes both the post-synaptic D_2 antagonism that appears efficacious in bipolar disorder and other pharmacological properties that may confer better safety and tolerability than other D_2 antagonists. As a 5-HT_{2A} receptor antagonist and serotonin reuptake inhibitor, ITI-007 is predicted to have antidepressant efficacy with fewer side effects than selective serotonin reuptake inhibitors. Importantly, ITI-007 lacks potent off-target interactions that have been associated with side effects for other antipsychotic drugs approved for the treatment of bipolar depression. For example, ITI-007 shows relatively weak affinity for 5-HT_{2C} and no measurable affinity for H_1 or muscarinic cholinergic receptors, which predict favorable body weight and metabolic profile responses to the extent that these receptors mediate such effects. Additional details of the pharmacologic profile of ITI-007 can be found in the most recent version of the investigator's brochure.

Nonclinical data suggest that ITI-007 may have the potential to treat depression (Snyder, 2015). Antidepressant-like activity of ITI-007 was measured using the social defeat (resident-intruder) mouse model. Mice exposed to repeated social defeat conditions display a reduced amount of time in contact with unfamiliar non-aggressive mice than normal controls. Such defeat behavior is reversed by chronic (but not acute) treatment with clinically effective antidepressant drugs. In this model, 1 mg/kg ITI-007, administered once daily intraperitoneally for 28 days, reversed the defeat behavior, consistent with antidepressant efficacy. 5-HT_{2A} receptor antagonism in vivo combined with antidepressant and antipsychotic efficacy in animal models predicts efficacy in bipolar depression. Moreover, indirect glutamatergic enhancement via both NMDA and AMPA currents following D_1 receptor activation predicts a rapid-acting antidepressant response.

Brain receptor target engagement was confirmed in healthy male volunteers in the ITI-007-003 positron emission tomography (PET) Phase 1 clinical trial (Davis, 2015). Positron emission tomography was used to determine dopamine D_2 receptor, serotonin transporter (SERT), and serotonin 5-HT_{2A} receptor occupancy in the brain at various times following single dose oral ITI-007 administration. ITI-007 rapidly penetrated the brain, showed long-lasting and dose-related occupancy, and was generally safe and well-tolerated. Cortical 5-HT_{2A} receptors were shown to be fully occupied at 10-mg ITI-007 (>85% occupancy). A dose of 40-mg ITI-007 achieved up to 39% striatal D_2 occupancy (average of 29%) and up to 31% striatal SERT occupancy (average of 22%). Together, these data confirm a central mechanism for ITI-007 at dopaminergic and serotonergic brain targets. Projecting occupancy to higher doses based on plasma levels, it was estimated that a dose of

60-mg ITI-007 should achieve approximately 50% striatal D_2 receptor occupancy and similar or slightly less SERT occupancy.

Clinical data from the ITI-007-005 Phase 2 trial in patients with schizophrenia are consistent with the pharmacological profile and prediction for antidepressant effects with favorable safety and tolerability. Data supporting an improvement in symptoms of depression emerged from a prespecified subgroup analysis of patients with both schizophrenia and comorbid depression in this trial. In addition to meeting the primary efficacy endpoint for improving psychosis in the intent-to-treat population, data in the subgroup of patients with comorbid depression at baseline showed statistically significant reduction in symptoms of depression and in psychosis at the 60-mg ITI-007 dose level. Safety data from this and other trials with ITI-007 have shown that ITI-007, administered to more than 1600 patients, is generally well tolerated across a dose range from 1 mg to 140 mg and administered once daily for up to 6 weeks. Additionally, ITI-007 is being evaluated in an open-label safety switching study (ITI-007-303) in patients with schizophrenia for up to a 1-year treatment duration; initial data with exposures more than 3 months treatment duration indicate that ITI-007 is generally safe and well-tolerated. These clinical data together with the nonclinical data and the pharmacological profile support the development of ITI-007 for the treatment of bipolar depression.

2 Study Objectives

2.1 Primary Objectives

2.1.1 Part A Primary Objectives

The primary objective of Part A of this study is to compare the efficacy of 2 doses of ITI-007 administered orally once daily to that of placebo in mean change from baseline in the total score on the rater-administered Montgomery-Åsberg Depression Rating Scale (MADRS) in patients with bipolar depression at Week 6.

2.1.2 Part B Primary Objective

The primary objective of Part B of this study is to determine the safety and tolerability of ITI-007 60 mg administered orally once daily for 6 months in patients with bipolar disorder. Safety and tolerability will be assessed in relation to:

- Incidence of AEs
- Mean change from baseline in the YMRS
- Mean change from baseline in MADRS
- Mean change from baseline in the C-SSRS
- Mean change from baseline in the AIMS
- Mean change from baseline in the BARS
- Mean change from baseline in the SAS
- Changes from baseline in clinical laboratory evaluations
- Changes from baseline in ECGs
- Changes from baseline in vital sign measurements
- Physical examination and neurological findings

2.2 Secondary Objectives

2.2.1 Part A Secondary Objectives - Efficacy

2.2.1.1 Key Secondary Objectives - Efficacy (Part A)

The key secondary objective of Part A of this study is to compare the efficacy of 2 doses of ITI-007 administered orally once daily to that of placebo in time to first response, defined as the number of days from first dose of study drug to the earliest date the patient experiences a sustained ≥50% reduction from baseline in the rater-administered MADRS total score.

[redacted]

[redacted]

2.2.2 Part A Secondary Objectives - Safety

The safety objectives of Part A of this study are to determine the safety and tolerability of 2 doses of ITI-007 via change in the following safety endpoints:

- Incidence of adverse events (AEs)
- Young Mania Rating Scale (YMRS)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Abnormal Involuntary Movement Scale (AIMS)
- Barnes Akathisia Rating Scale (BARS)
- Simpson Angus Scale (SAS)
- Clinical laboratory evaluations
- Electrocardiograms (ECGs)
- Vital sign measurements
- Physical examination and neurological findings.

[redacted]

[redacted]

[redacted] Part B Secondary Objectives – Effectiveness

Secondary effectiveness objectives of Part B of this study are to determine whether 60 mg ITI-007, administered once daily for up to approximately 6 months to patients with bipolar disorder who have responded to treatment with ITI-007, improves and/or maintains symptoms, function, and quality of life as measured by change from baseline on the following measures:

- MADRS total score
- CGI-BP-S
- Q-LES-Q-SF.

[redacted]

[redacted]

[redacted]

3 Investigational Plan

3.1 Study Design

This study will be conducted in 2 parts: Part A and Part B. Part A is a randomized, double-blind, placebo-controlled, two-stage adaptive design study comparing the efficacy and safety of ITI-007 versus placebo administered orally once daily in patients with bipolar depression. For Part A, there will be a single interim analysis (IA) and a final analysis. In Part B, patients who safely completed participation in Part A may be enrolled in an open-label extension.

3.1.1 Part A Study Periods (up to 10 Weeks, Including Screening/Baseline)

Part A of the study consists of the following periods: screening period, on-treatment period, and safety follow-up period. Patients who rollover directly into Part B will not have a unique safety follow-up visit after the 6-week treatment.

Screening Period (2 Weeks)

Potential patients will be evaluated during a screening period lasting up to 2 weeks, unless confirmed by the medical monitor that a longer screening phase, lasting no longer than 28 days, is appropriate to ensure washout of excluded medications with long half-lives (e.g., fluoxetine), under the supervision of the investigator before baseline.

After obtaining written informed consent, diagnostic interviews and physical examinations will be conducted, vital signs and ECGs will be assessed, and blood samples for laboratory assessments will be collected. Patients considered potentially eligible for participation will be required to discontinue their current antidepressant treatment and/or other psychotropic drugs.

[redacted]

At baseline (Visit 2), patients who continue to meet all eligibility criteria will be randomly assigned to 1 of the 3 treatment arms for a 6-week, double-blind treatment period. Patients will be randomly assigned to 1 of the following groups: 40-mg ITI-007, 60-mg ITI-007, or matching placebo.

On-Treatment Period (6 Weeks)

Patients will take their first dose of study medication the evening of their baseline randomization visit. A single dose will be taken each day in the evening for the duration of the on-treatment period.

Following randomization, patients will attend the clinic at Weeks 1, 2, 3, 4, 5, and 6.

The on-study treatment period will be a total of 6 weeks.

Safety Follow-up Period (2 Weeks)

For those patients not continuing on to Part B, a return to the clinic for a safety follow-up visit will occur at Week 8, approximately 2 weeks following the last dose of study medication. If possible, patients who discontinue treatment prematurely will be seen for an early termination visit (within 1 week of the last dose of study drug when possible) and will be asked to return to the clinic for a safety follow-up visit 2 weeks following withdrawal.

3.1.2 Part B Study Periods (up to Approximately 6 months [175 days])

Part B of the study will be an open-label extension. Patients enrolling directly into the open-label extension will have their baseline visit at Visit 8 (Study Day 43) of Part A. Patients who safely completed Part A of the study prior to open-label extension becoming available, will undergo screening procedures for determination of their eligibility for Part B. Subsequent post-dose clinical evaluations will occur on Study Days 8, 15, and 25, then every 25 ± 3 days (Study Days 50, 75, 100, 125, 150, and 175) of Part B. Evaluations on Days 75, 125, and 150 will be conducted by telephone. Patients must undergo these scheduled clinical evaluations in order to continue to receive study treatment. Unscheduled clinical evaluations may occur at any time if deemed appropriate by the investigator, to discontinue patient participation, and/or for safety follow-up. Patients will return for a final safety follow-up visit approximately 2 weeks after their last dose of study treatment.

3.1.3 Rationale of Study Design

In Part A, the screening phase permits evaluation of the laboratory and ECG assessments and enables confirmation of eligibility for inclusion into the study. The screening phase will be no longer than 14 days, unless confirmed by the medical monitor that a longer screening phase, not to exceed 28 days, is appropriate to ensure washout of excluded medication with

long half-life (e.g., fluoxetine), under the supervision of the investigator before baseline. Patients will be randomly assigned to 1 of 3 treatment groups (1:1:1) at the baseline visit and will receive treatment for up to 6 weeks. In order to ensure patient safety, a mandatory 14-day follow-up visit will be performed after administration of the last dose of study medication. Any ongoing AEs at the follow-up visit must be followed until resolution, until the AE stabilizes, until it is determined to be non-clinically significant, or until the patient is lost to follow-up.

In Part B, patients who safely completed participation in Part A may enroll in an open-label extension. Patients enrolling into the open-label extension upon completing treatment in Part A will have their Part B baseline visit on Visit 8 (Study Day 43) of Part A. Patients who safely (in the opinion of the investigator and confirmed by the Medical Monitor) completed Part A of the study prior to the open-label extension becoming available, will undergo re-screening procedures for determination of their eligibility for Part B.

For Part A, 2 ITI-007 doses were selected to deliver full occupancy of the cortical 5-HT_{2A} receptors (>85% occupancy) at both doses. Data from a human PET brain receptor occupancy study in healthy male volunteers indicates that 40-mg ITI-007 is associated with up to 39% striatal D_2 receptor occupancy (average of 29%) and up to 31% striatal SERT occupancy (average of 22%) while the 60-mg dose is projected to achieve up to 50% striatal D_2 receptor occupancy and similar or slightly less SERT occupancy. These doses have been shown to be generally safe and well tolerated and enable an exploration of the dose required to achieve efficacy in this patient population.

The doses to be administered in Part A of the present study, 40- and 60-mg ITI-007, were shown to be generally well tolerated in prior studies with no evidence of a need for drug titration. Therefore, a fixed-dose design will be employed in this study.

In Part A, the placebo control group is needed to establish the efficacy of a new compound.

For Part A, the treatment duration of 6 weeks has been chosen because this is considered an acceptable period to demonstrate efficacy in this patient population.

Part B of the study is to determine the safety and effectiveness of ITI-007 (60 mg) administered daily for up to approximately 6 months (175 days) in patients with bipolar depression who safely completed Part A of the study.

4 Patient Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 549 patients (183 patients/arm in Part A) will be enrolled at approximately 60 study sites in the United States. In Part A, patients will be randomly assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria. In Part B, up to 549 patients who safely completed Part A may receive ITI-007 60 mg.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the criteria, as specified in the protocol, is essential.

In Part A, appropriateness of patient eligibility will be assessed by expert site-based raters and investigators and confirmed by remote, independent expert raters and/or medical monitor(s) by a systematic adjudication process in concert with the sponsor. In Part B, appropriateness of patient eligibility will be assessed by the investigator. In the event of a recently emerged new medical condition, this should be evaluated carefully and discussed with the Medical Monitor prior to participation in Part B of the study. Once a final decision is made, no waivers for exceptions will be provided.

4.1.1 Part A Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in this study:

1. Is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.
2. Is between the ages of 18 and 75 years, inclusive, at the start of screening (both male and female patients are to be included).
3. Meets the Diagnostic and Statistical Manual of Mental Disorder, 5th Edition (DSM-5) criteria for Bipolar I or Bipolar II Disorder as confirmed by the investigator or sponsor-approved expert site-based rater by a Structured Clinical Interview for DSM-5 Disorders – Clinical Trials Version (SCID-5-CT) and meeting all of the following 5 criteria:

a. The start of the current MDE is at least 2 weeks but no more than 6 months prior to the screening visit;

b. Appropriate severity of illness, at least moderately ill, as measured by a rater-administered MADRS total score ≥20 and corresponding to a CGI-BP-S score of ≥4 at the screening and baseline visits;

c. Sufficient history and/or independent report (such as family member or outside practitioner) verifying that the current MDE is causing clinically significant distress or impairment in social, occupational, or other important areas of functioning;

d. A lifetime history of at least 1 bipolar manic episode or mixed episode (for Bipolar I) or hypomanic episode (for Bipolar II);

e. A rater-administered YMRS total score of ≤12 at the screening and baseline visits. The presence of psychotic symptoms may result in an increased YMRS without evidence of mania/hypomania. Therefore, a patient with a YMRS >12 AND psychotic symptoms may be included pending adjudication review for diagnostic certainty of the depressive episode.

4. Has a body mass index (BMI) of 18 – 35 kg/m^2, inclusive.
5. Either must agree to use highly effective methods of birth control (defined as those, alone or in combination, that result in a failure rate less than 1 percent per year when used consistently and correctly) for at least 2 weeks prior to randomization (starting with signing informed consent) through to the end-of-study follow-up visit or must be of non-childbearing potential (defined as either permanently sterilized or, if female, post-menopausal; the latter is defined as at least 1 year with no menses without an alternative medical explanation).
6. In the opinion of the investigator, the patient is willing and able to comply with study requirements, study visits, and to return to the clinic for follow-up evaluations as specified by the protocol.

4.1.2 Part A Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. The patient experiences a decrease in the rater-administered MADRS total score of ≥25% between screening and baseline visits.

2. In the opinion of the investigator, the patient has a significant risk for suicidal behavior during the course of his or her participation in the study or
    a. At screening, the patient scores "yes" on Items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to a 6-month period prior to screening; or
    b. At screening, the patient has had 1 or more suicidal attempts with reference to a 2-year period prior to screening; or
    c. At the baseline visit, the patient scores "yes" on Items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to screening; or
    d. At screening or the baseline visit, scores ≥4 on Item 10 (suicidal thoughts) on the rater-administered MADRS; or
    e. Considered to be an imminent danger to himself, herself, or others.
3. The patient is pregnant or breast-feeding; female patients of childbearing potential must have a negative urine pregnancy test at screening and on Day 1 prior to study treatment administration.
4. The patient has a history within 12 months of screening, based on previous psychiatric evaluation or a confirmed diagnosis upon screening based on the DSM-5 as assessed by the SCID-5-CT, of a psychiatric diagnosis other than bipolar disorder, including:
    a. Schizophrenia or other psychotic disorder;
    b. Anxiety disorders such as panic disorder, general anxiety disorder, or post-traumatic stress disorder as a primary diagnosis (however, anxiety symptoms may be allowed, if secondary to bipolar disorder, provided these symptoms do not require current treatment);
    c. Feeding or eating disorder;
    d. Primary diagnosis of obsessive compulsive disorder;
    e. Personality disorder;
    f. Moderate or severe substance use disorder (including for cannabis, excluding for nicotine);
    g. Any other psychiatric condition (other than bipolar disorder) that has been the main focus of treatment within 12 months of screening;

5. Patients who have experienced hallucinations, delusions, or any other psychotic symptomatology in the current depressive episode may be allowed as long as these symptoms are not attributable to a primary DSM-5 diagnosis other than bipolar disorder as described in Exclusion #4. The presence of these symptoms should be reviewed with the medical monitor and adjudication team prior to inclusion. The presence of psychotic symptoms may result in an increase in YMRS to > 12 in the absence of impending mania/hypomania, therefore these patients will be reviewed on a case by case basis to rule out possible impending mania/hypomania.
6. The patient has been hospitalized for mania associated with Bipolar I disorder within 30 days of screening.
   Note: This criterion is included to ensure that any manic phase has completely resolved before enrollment in the study.
7. The patient has received electroconvulsive therapy, vagal nerve stimulation, or repetitive trans-cranial magnetic stimulation within the last 5 years or received more than 1 course of electroconvulsive therapy during the patient's lifetime.
8. The patient is considered a rapid cycler, defined by the occurrence of at least 6 major depressive, manic, hypomanic, or mixed episodes during the previous year. These episodes must be demarcated either by a partial or full remission of at least 2 months' duration or by a switch to an episode of opposite polarity. (Each MDE must have lasted at least 2 weeks, each manic or mixed episode must have lasted at least 1 week, and each hypomanic episode must have lasted at least 4 days, as validated by a reliable informant).
   Note: This criterion is included to avoid spontaneous remission during participation in the study that might confound treatment results.
9. The patient is considered treatment-resistant, defined as having a lifetime history of treatment resistance (no remission) to ≥2 treatments with FDA-approved medications for Bipolar depression (lurasidone, quetiapine or Symbyax) at an adequate dose (per FDA-approved label) for an adequate duration (at least 6 weeks).
10. The patient is currently receiving formal cognitive or behavioral therapy, systematic psychotherapy, or plans to initiate such therapy during the study.

11. The patient presents with a lifetime history of epilepsy, seizure or convulsion, or electroencephalogram with clinically significant abnormalities, delirium, dementia, amnestic, or other cognitive disorder or significant brain trauma.

12. The patient has a positive test for drugs of abuse or alcohol test at the screening or baseline visits, or presents evidence of either withdrawal from or acute intoxication with cocaine, opiates, amphetamines (including methamphetamine), alcohol, barbiturates, or hallucinogens or similar compounds. The urine drug screen may be repeated once based on investigator judgment and reviewed for medical appropriateness by the medical monitor as part of the screening adjudication process.

    Note: Previous occasional use of alcohol or cannabis (but not synthetic marijuana/K2/Spice) or prescribed psychotropic (e.g., benzodiazepine, opiate) is allowed as long as the level of use does not meet DSM-5 criteria for any moderate or severe substance use disorder within the 12 months prior to screening and the use of alcohol or cannabis is not considered to be the precipitating factor of the current depressive episode, in the opinion of the investigator and any prescribed psychotropic is accompanied by evidence of prescription; patients are required to abstain from alcohol and cannabis use during the study.

13. The patient has used 1 of the following agents under the specified conditions:

    a. Lifetime exposure to ITI-007 (i.e., participated in previous clinical study with ITI-007 as verified by DupCheck) or who has had exposure to any investigational product within 3 months of the baseline visit or participated in the past 4 years in >2 clinical studies of an investigational product with a central nervous system indication.

    b. Any strong or moderate cytochrome P450 3A4 inhibitor or inducer within 7 days prior to the baseline visit.

    c. Use of any long-acting anxiolytics within 5 half-lives of the baseline visit.

    d. Drugs with known psychotropic properties or any non-psychotropic drugs with known or potentially significant central nervous system effects within the last 28 days or 5 half-lives before the baseline visit, whichever is less, as reviewed by the medical monitor including, but not limited to:

i. sedative hypnotics (with the exception of zolpidem and zolpidem CR as noted in the concomitant medication section, allowed during the screening period and the first 2 weeks of the treatment period);

ii. central opioid agonists/antagonists including tramadol (Ultram);

iii. anticonvulsants;

iv. mood stabilizers, antipsychotics, antidepressants; EXCEPTION: long acting injectable antipsychotics must be washed out 1.5 cycles or 28 days, whichever is LONGER, before baseline

v. methotrexate;

vi. Any known 5-HT_{2A} receptor antagonist or inverse agonist including but not limited to mianserin, mirtazapine, nefazodone, cyproheptadine, pimavanserin, or fluvoxamine;

vii. Immunosuppressants;

viii. dietary supplements, or medical foods must be approved by the Medical Monitor. Daily multivitamin use is not excluded.

14. The patient has abnormal laboratory values or clinical findings at screening that are judged clinically significant and confirmed upon re-test (1 re-test prior to baseline visit is allowed and results must be available prior to the baseline visit and must have returned to within normal range), including, but not limited to:

    a. Aspartate aminotransferase (AST) >2.0 × the upper limit of normal (ULN)

    b. Alanine aminotransferase (ALT) >2.0 × the ULN

    c. Alkaline phosphatase >2.0 × the ULN

    d. Gamma-glutamyl transpeptidase >2.0 × the ULN

    e. Total bilirubin >1.5 × the ULN

    f. Serum creatinine >1.5 × the ULN

    g. Blood urea nitrogen >1.5 × the ULN

h. Thyroid-stimulating hormone outside of the normal limits and clinically significant, as determined by the investigator. Free thyroxine levels may be measured if thyroid-stimulating hormone level is high. The patient will be excluded if the free thyroxine level is clinically significant.

i. 12-lead ECG (in a supine position at rest at the screening or baseline visit) corrected QT interval using the Fridericia formula (QTcF) >450 ms, and/or heart rate ≤50 beats per minute, or evidence of clinically significant bundle-branch blocks. The ECG may be repeated one time at the investigator's discretion to ensure the reproducibility of results.

j. Any other clinically significant abnormal laboratory result at the time of the screening examination. Note: medical conditions that are stable with medication (e.g., hypertension, high cholesterol, and hyperthyroidism) are allowed as long as the condition has been stable for at least 3 months prior to screening, the medications are documented and kept stable during the study, and the condition is not thought to affect safe participation in the study in the opinion of the investigator and confirmed by the medical monitor as part of the screening adjudication process

15. The patient has clinically significant cardiovascular (including but not limited to uncontrolled angina, or history of a myocardial infarction within 3 months prior to screening, or history of a clinically significant cardiac arrhythmia including antipsychotic drug-induced corrected QT interval prolongation), endocrine (including poorly controlled diabetes defined as glycated hemoglobin A1c [HbA1c] >53 mmol/mol [7.0%] at screening with no re-test allowed for HbA1c), hepatic, renal, pulmonary, gastrointestinal, neurological, malignancy (including any malignancy and/or chemotherapy within the 2 years prior to screening; malignancy more than 2 years prior to screening must have been local and without metastasis and/or recurrence, and if treated with chemotherapy, without nervous system complications; some malignancies, such as basal cell carcinoma, may not preclude participation and will be individually reviewed), pheochromocytoma, metabolic, psychiatric or other condition that might be detrimental to the patient if he or she participates in the study (in the opinion of the investigator).
16. The patient has a history of human immunodeficiency virus (HIV) infection or has HIV antibodies in blood at screening.

17. At Screening, the patient has a history of Hepatitis B or Hepatitis C infection (or demonstrates Hepatitis B surface antigens or Hepatitis C antibodies), AND evidence of active disease defined as elevated ALT, AST or bilirubin levels as specified in Exclusion 14.
18. The patient is an employee of the investigator or study center, or immediate family (i.e., spouse, parent, child, or sibling, whether biological or legally adopted) of such employees, the investigator, ITI, or contract research organizations conducting the study.
19. The patient is unable to be safely discontinued from current antidepressant medication, mood stabilizers, anticholinergics, or other psychotropic medications (in the opinion of the investigator).
20. The patient is judged by the investigator to be inappropriate for the study.

4.1.3 Part B Inclusion Criteria

Each patient continuing into Part B of the study must meet all of the following criteria:

1. Patients must have safely (in the opinion of the investigator, and confirmed by the Medical Monitor) completed Part A.

   [Note: patients who had experienced significant AEs which were thought to be possibly related to blinded study medication, should not be enrolled into the open-label extension];
2. Patients must be capable of understanding the written informed consent, providing signed and witnessed written informed consent, and agreeing to comply with protocol requirements for Part B of the study; a separate written informed consent must be provided for continuation into the open-label extension after treatment in Part A has been completed.
3. Patients must agree to use highly effective methods of birth control (as defined in Part A Inclusion #5) for at least 2 weeks prior to randomization (starting with informed consent) through to the end of study visit, or, patients must be of non-childbearing potential (as defined in Part A Inclusion #5).

4.1.4 Part B Exclusion Criteria

Exclusion Criteria (Part B) Re-Screening

Since all prior participants in Part A were required to satisfy exclusion criteria for participation in that part of the study, the investigator should assess where there has been any change of status. In the event of a recently emerged new medical condition, this should be evaluated carefully and discussed with the Medical Monitor before including the patient in Part B.

Patients who safely completed Part A of the study prior to the open-label extension becoming available, will undergo screening procedures and must be eligible according to the abbreviated Part A exclusion criteria as described below. Any references to adjudication in Part B refer to a review by the Medical Monitor.

Please note these Part B Exclusion Criteria are numbered to coincide with the Part A Exclusion Criteria for consistency of reference.

Patients meeting any of the following criteria will be excluded from the study:

2. In the opinion of the investigator, the patient has a significant risk for suicidal behavior during the course of his or her participation in the study or
    a. At Visit 10 screening, the patient scores "yes" on Items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to the last visit; or
    b. At Visit 10 screening, the patient has had 1 or more suicidal attempts with reference to a 2-year period prior to screening; or
    c. At the Visit 11 Baseline Visit, the patient scores "yes" on Items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to the last visit; or
    d. At Visit 10 Screening or the Visit 11 Baseline Visit, scores $\geq$4 on Item 10 (suicidal thoughts) on the *self*-administered MADRS; or
    e. Considered to be an imminent danger to himself, herself, or others.
3. The patient is pregnant or breast-feeding; female patients of childbearing potential must have a negative urine pregnancy test at Visit 10 Screening and on Visit 11 Baseline Visit prior to study treatment administration.
4. The patient is assessed by the investigator as not having had a change in primary diagnosis at Visit 10 Screening, as compared to Visit 1 Screening.

7. The patient has received electroconvulsive therapy, vagal nerve stimulation, or repetitive trans-cranial magnetic stimulation within the last 5 years or received more than 1 course of electroconvulsive therapy during the patient's lifetime.

9. The patient is considered treatment-resistant, defined as having a lifetime history of treatment resistance (no remission) to ≥2 treatments with FDA-approved medications for Bipolar depression (lurasidone, quetiapine or Symbyax) at an adequate dose (per FDA-approved label) for an adequate duration (at least 6 weeks).

11. The patient presents with a lifetime history of epilepsy, seizure or convulsion, or electroencephalogram with clinically significant abnormalities, delirium, dementia, amnestic, or other cognitive disorder or significant brain trauma.

12. The patient has a positive test for drugs of abuse or alcohol test at the Visit 10 Screening or Visit 11 Baseline visits, or presents evidence of either withdrawal from or acute intoxication with cocaine, opiates, amphetamines (including methamphetamine), alcohol, barbiturates, or hallucinogens or similar compounds. The urine drug screen may be repeated once based on investigator judgment and reviewed for medical appropriateness by the medical monitor as part of the Screening adjudication process.

    Note: Previous occasional use of alcohol or cannabis (but not synthetic marijuana/K2/Spice) or prescribed psychotropic (e.g., benzodiazepine, opiate) is allowed as long as the level of use does not meet DSM-5 criteria for any moderate or severe substance use disorder within the 12 months prior to screening and the use of alcohol or cannabis is not considered to be the precipitating factor of the current depressive episode, in the opinion of the investigator and any prescribed psychotropic is accompanied by evidence of prescription; patients are required to abstain from alcohol and cannabis use during the study.

13. The patient has used 1 of the following agents under the specified conditions:

    b. Any strong or moderate cytochrome P450 3A4 inhibitor or inducer within 7 days prior to the Visit 11 Baseline Visit.

    c. Use of any long-acting anxiolytics within 5 half-lives of the Visit 11 Baseline Visit.

d. Drugs with known psychotropic properties or any non-psychotropic drugs with known or potentially significant central nervous system effects within the last 28 days or 5 half-lives before the Visit 11 Baseline Visit, whichever is less, as reviewed by the medical monitor including, but not limited to:

   i. sedative hypnotics (with the exception of zolpidem and zolpidem CR as noted in the concomitant medication section)

   ii. central opioid agonists/antagonists including tramadol (Ultram);

   iii. anticonvulsants;

   iv. mood stabilizers, antipsychotics, antidepressants; EXCEPTION: long acting injectable antipsychotics must be washed out 1.5 cycles or 28 days, whichever is LONGER, before baseline

   v. methotrexate;

   vi. Any known 5-HT_{2A} receptor antagonist or inverse agonist including but not limited to mianserin, mirtazapine, nefazodone, cyproheptadine, pimavanserin, or fluvoxamine;

   vii. Immunosuppressants;

   viii. dietary supplements, or medical foods must be approved by the Medical Monitor. Daily multivitamin use is not excluded.

14. The patient has abnormal laboratory values or clinical findings at screening that are judged clinically significant and confirmed upon re-test (1 re-test prior to Visit 11 Baseline visit is allowed and results must be available prior to the Visit 11 Baseline Visit and must have returned to within normal range), including, but not limited to:

    a) Aspartate aminotransferase (AST) >2.0 × the upper limit of normal (ULN)

    b) Alanine aminotransferase (ALT) >2.0 × the ULN

    c) Alkaline phosphatase >2.0 × the ULN

    d) Gamma-glutamyl transpeptidase >2.0 × the ULN

    e) Total bilirubin >1.5 × the ULN

    f) Serum creatinine >1.5 × the ULN

    g) Blood urea nitrogen >1.5 × the ULN

h) Thyroid-stimulating hormone outside of the normal limits and clinically significant, as determined by the investigator. Free thyroxine levels may be measured if thyroid-stimulating hormone level is high. The patient will be excluded if the free thyroxine level is clinically significant.

i) 12-lead ECG (in a supine position at rest at the Visit 10 Screening or Visit 11 Baseline visit) corrected QT interval using the Fridericia formula (QTcF) >450 ms, and/or heart rate ≤50 beats per minute, or evidence of clinically significant bundle-branch blocks. The ECG may be repeated one time at the investigator's discretion to ensure the reproducibility of results.

j) Any other clinically significant abnormal laboratory result at the time of the Visit 10 Screening examination. Note: medical conditions that are stable with medication (e.g., hypertension, high cholesterol, and hyperthyroidism) are allowed as long as the condition has been stable for at least 3 months prior to Visit 10 Screening, the medications are documented and kept stable during the study, and the condition is not thought to affect safe participation in the study in the opinion of the investigator and confirmed by the medical monitor as part of the screening adjudication process

15. The patient has clinically significant cardiovascular (including but not limited to uncontrolled angina, or history of a myocardial infarction within 3 months prior to Visit 10 Screening, or history of a clinically significant cardiac arrhythmia including antipsychotic drug-induced corrected QT interval prolongation), endocrine (including poorly controlled diabetes defined as glycated hemoglobin A1c [HbA1c] >53 mmol/mol [7.0%] at screening with no re-test allowed for HbA1c), hepatic, renal, pulmonary, gastrointestinal, neurological, malignancy (including any malignancy and/or chemotherapy within the 2 years prior to Visit 10 Screening; malignancy more than 2 years prior to Visit 10 Screening must have been local and without metastasis and/or recurrence, and if treated with chemotherapy, without nervous system complications; some malignancies, such as basal cell carcinoma, may not preclude participation and will be individually reviewed), pheochromocytoma, metabolic, psychiatric or other condition that might be detrimental to the patient if he or she participates in the study (in the opinion of the investigator).
16. The patient has a history of human immunodeficiency virus (HIV) infection or has HIV antibodies in blood at screening.

17. The patient has a history of hepatitis B or hepatitis C infection (or demonstrated Hepatitis B surface antigen or Hepatitis C antibodies), AND evidence of active disease defined as elevated ALT, AST or bilirubin levels as specified in Exclusion 14.
18. The patient is an employee of the investigator or study center, or immediate family (i.e., spouse, parent, child, or sibling, whether biological or legally adopted) of such employees, the investigator, ITI, or contract research organizations conducting the study.
19. The patient is unable to be safely discontinued from current antidepressant medication, mood stabilizers, anticholinergics, or other psychotropic medications (in the opinion of the investigator).
20. The patient is judged by the investigator to be inappropriate for the study.

Exclusion Criteria (Part B) Direct Rollover

Patients directly enrolling into the open-label extension upon completing Part A, presenting at the Day 43 visit with any of the following characteristics, will be excluded from the study:

1. Is, in the opinion of the investigator, unable to comply with study procedures;
2. Has a significant risk for suicidal behavior during the course of their participation in the study or is considered to be an imminent danger to themselves or others, in the opinion of the investigator, and/or as assessed by the C-SSRS; or <u>> 4 on item 10 of the subject-rated MADRS</u>
3. Clinically significant (in the investigator's judgement) abnormal laboratory results at the time of the last study evaluation.

   [Note: medical conditions are allowed as long as the condition has been stable during Part A, the medications are documented and kept stable during the study, and the condition is not thought to affect safe participation in the study in the opinion of the investigator];
4. The patient is pregnant or breast-feeding; female patients of childbearing potential must have a negative pregnancy test at rescreening (if applicable) and upon entry to Part B of the study prior to treatment administration;
5. Has a positive qualitative urine drug or alcohol test (which may be confirmed with additional testing) at the last evaluation, or evidence of either withdrawal from, or acute intoxication with cocaine, opiates, amphetamines (including methamphetamine), alcohol, barbiturates, or hallucinogens or similar compounds;

[Note: Previous occasional use of alcohol or cannabis (but not synthetic marijuana/K2/Spice) or prescribed psychotropic (e.g., benzodiazepine, opiate) is allowed as long as the level of use does not meet DSM-5 criteria for any moderate or severe substance use disorder within the 12 months prior to screening and the use of alcohol or cannabis is not considered to be the precipitating factor of the current depressive episode, in the opinion of the investigator and any prescribed psychotropic is accompanied by evidence of prescription; patients are required to abstain from alcohol and cannabis use during the study.];

6. Is judged by the investigator to be inappropriate for the study.

4.2 Withdrawal of Patients from the Study

For Part A, the planned overall duration of the study for each patient is up to 10-12 weeks (9 visits): a screening phase of up to 2 weeks (exceptions may be given to allow for washout of previous medication with a long half-life, as reviewed and approved by the medical monitor, but not to exceed 28 days), a treatment phase of 6 weeks, and a follow-up phase of 2 weeks. The duration of the study is defined for each patient as the date signed written informed consent is provided through the last follow-up visit on Day 56 for patients who participate in Part A only.

In Part B, the planned overall duration of the study for each patient is up to approximately 6 months. For patients who completed Part A prior to the open-label extension becoming available, a screening phase would be up to 14 days, a treatment phase of up to 175 days ± 3 days, and a safety follow-up visit after return to standard of care. The duration of the study is defined for each patient as the date signed written informed consent is provided through the last visit on Day 189 ± 3 days.

4.2.1 Reasons for Withdrawal/Discontinuation

Patients may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Every effort should be made to keep patients in the study. The reasons for patients not completing the study will be recorded. A patient may be withdrawn from the study for any of the following reasons:

1. Does not meet the protocol inclusion criteria or meets the protocol exclusion criteria.
2. Noncompliance with the protocol.

3. A serious or intolerable AE that, in the investigator's opinion, requires withdrawal from the study.
4. Laboratory safety assessments that reveal clinically significant hematological or biochemical changes from baseline values, or baseline laboratory safety assessments that are returned after randomization in Part A or enrolling into the open-label extension in Part B, but reveal clinically significant hematological or biochemical changes from screening.
5. Symptoms or an intercurrent illness not consistent with the protocol requirements or that justify withdrawal.
6. Lost to follow-up.
7. Other (e.g., pregnancy, development of contraindications of use of study drug).
8. The investigator or sponsor decide to discontinue the patient's participation in the study.
9. The patient withdraws consent. If consent is withdrawn, the patient must be questioned by the investigator or study site staff whether the withdrawal is due to an AE, lack of efficacy, personal or family reasons, or whether the patient withdrew consent and refused all end-of-study procedures, including refusing to give a reason; these reasons must be documented in the case report form.

The investigator will also withdraw a patient if ITI terminates the study. Upon occurrence of a serious or intolerable AE, the investigator will confer with the sponsor or medical monitor as the sponsor's designee. If a patient is discontinued because of an AE, the event will be followed until it is resolved, stabilizes, is determined to be non-clinically significant, or the patient is lost to follow-up. Any patient may withdraw his or her consent at any time.

4.2.2 Handling of Withdrawals

Patients are free to withdraw from the study or study treatment at any time. Patient participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

Patients who discontinue study treatment or active participation in the study will no longer receive study drug. When a patient withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant screen of the electronic case report form

(eCRF). Whenever possible, all patients who discontinue study treatment or withdraw from the study prematurely will undergo all end-of-study assessments. Patients who fail to return for final assessments will be contacted by the study site (2 documented telephone calls followed by 1 registered letter) in an attempt to have them comply with the protocol.

It is vital to obtain follow-up data on any patient withdrawn as a result of an AE or serious AE (SAE). In every case, efforts must be made to undertake protocol-specified, safety, follow-up procedures. All data collected from all patients, including early withdrawals, will be used in the reporting and analysis of the study.

4.2.3 Replacements

In Part A, patients who have been randomly assigned to study drug and prematurely discontinue from the study will not be replaced.

A patient who fails to satisfy inclusion criteria or exhibits any of the exclusion criteria at screening may be rescreened with the permission of the medical monitor. In Part A and if applicable in Part B, any patient who is rescreened within 28 days of an initial screen may have some screening procedures waived by the medical monitor on a case by case basis; any patient who is rescreened more than 28 days following the previous screen (as defined by the date of informed consent) will need to have all screening procedures repeated. In all cases, a new informed consent must be obtained for a rescreen. A patient may not be screened more than 2 times.

5 Study Treatments

5.1 Method of Assigning Patients to Treatment Groups

In Part A, patients who continue to meet all eligibility criteria at baseline (Visit 2) will be randomly assigned to 1 of the 3 treatment arms for a 6-week, double-blind treatment period. Patients will be randomly assigned to 1 of the following groups: 40-mg ITI-007, 60-mg ITI-007, or matching placebo. The on-study treatment period will be a total of 6 weeks.

An interactive voice response system (IVRS)/interactive web response system (IWRS) (English only) will be used to administer the randomization schedule. Unblinded biostatistics personnel not participating in the conduct of the study will generate a permuted block randomization schedule using SAS software Version 9.2 or later (SAS Institute Inc, Cary, North Carolina) for IVRS/IWRS, which will link sequential patient randomization numbers to treatment codes. In the event that the blind needs to be broken because of a medical emergency, the investigator may unblind an individual patient's treatment allocation (Section 5.6.1). The randomization schedule will be stratified by Bipolar I or Bipolar II diagnoses at screening.

Each patient will be assigned a randomization number, which will be separate from the patient identification number. Once a randomization number has been allocated to a patient, it may not be assigned to another patient.

The IVRS/IWRS will send visit notifications to the study center personnel, confirming the patient data that were entered. The IVRS/IWRS notifications should be filed securely at the study site.

In Part B, enrollment will occur on Day 43, Visit 8 which is Day 1 of Part B. If a patient is required to undergo screening (Visit 10), upon determination of his/her eligibility for Part B, the enrollment will occur on Visit 11 as indicated in the Schedule of Events. Patients will be issued treatment cards of ITI-007 (60 mg). ITI-007 will be administered orally once daily as tablet for up to approximately 6 months (175 days).

5.2 Treatments Administered

In Part A, patients will be assigned to receive either ITI-007 (40- or 60-mg doses) or placebo. Study center personnel will receive a treatment card number from the IVRS/IWRS for each patient at each clinic visit, to ensure that the correct investigational product is dispensed.

Patients will self-administer all doses orally, once daily, at home, in the evening for the duration of the on-treatment period. Treatment will be administered between 8:00 PM and 10:30 PM, at approximately the same time each day whenever possible. Treatments will be provided in dose cards containing 2 strips of over-encapsulated tablets (Section 5.4.1). Patients will be instructed to take 2 capsules (1 capsule from each strip) per dose.

In Part B, all patients will receive ITI-007 (60 mg). Patients will self-administer all doses orally, once daily, at home, in the evening for up to approximately 6 months (175 days) at approximately the same time each day whenever possible. Patients will be instructed to take 1 tablet per dose. (Section 5.3.2).

In Part B, a one-time dose reduction will be allowed for patients who (in the opinion of the investigator and as confirmed by the Medical Monitor) are not tolerating the 60 mg dosage. If the patient is not able to tolerate the 40 mg dose, they must be withdrawn from the study and undergo evaluations required in the early termination visit.

5.3 Identity of Investigational Product

5.3.1 Investigational Product for Part A

ITI-007 will be supplied as 20- and 60-mg over-encapsulated tablets (capsules) (Table 5–1). The following drug supplies will be used in the study:

Table 5–1 Table for Dosing Schedule

Study Drug	Dosing Schedule
40-mg ITI-007	2 over-encapsulated tablets of 20-mg ITI-007 Daily Dose: 40-mg ITI-007
60-mg ITI-007	2 over-encapsulated tablets: 1 over-encapsulated tablet of 60-mg ITI-007 and 1 over-encapsulated tablet of placebo Daily Dose: 60-mg ITI-007
Placebo	2 over-encapsulated tablets of placebo Daily Dose: 0-mg ITI-007

Each ITI-007 dosing container will be labeled according to local laws and regulations.

The composition of the over-encapsulated tablets is listed in Table 5–2.

Table 5–2 Dosage Composition for Part A

Ingredient	**Quantity/Tablet (mg)**		
	20-mg coated tablet	60-mg coated tablet	Placebo coated tablet
ITI-007	20	60.0	Not Applicable
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Over-encapsulated placebo tablets are identical in appearance to ITI-007 and have the same excipient ingredients as ITI-007 but do not have the active compound.

5.3.2 Investigational Product for Part B

ITI-007 will be supplied as 60-mg tablets for once-daily oral administration during Part B. The composition of the tablets is listed in Table 5-3 Dosage Composition for Part B.

ITI-007 will be supplied as 20 and 60 mg tablets. For dose reduction, two 20 mg tablets will be used for the 40mg dose.

[redacted]

[redacted]

[redacted]

[redacted]

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging and Storage

In Part A, ITI-007 and matching placebo will be prepared according to current Good Manufacturing Practice standards in carded blister strips and shipped under ambient conditions by Catalent, on behalf of ITI. Each treatment card will contain a sufficient quantity for 1 patient for each week (7 doses, plus 1 extra) of the 6-week treatment period, to be distributed at weekly visits. Each ITI-007 dosing container will be labeled according to local laws and regulations.

The dose card for each study treatment will contain two 1×8 strips of over-encapsulated tablets (final product in capsule form) as described in Table 5–3.

Table 5–3 Part A Weekly Treatment Cards

Treatment	Card Contents
Placebo	Two 1×8 strips of placebo over-encapsulated tablets (8 over-encapsulated tablets/strip)
60-mg ITI-007	One 1×8 strip of 60-mg ITI-007 over-encapsulated tablets (8 over-encapsulated tablets/strip); One 1x8 strip of placebo over-encapsulated tablets (8 over-encapsulated tablets /strip)
40-mg ITI-007	Two 1×8 strips of 20-mg ITI-007 over-encapsulated tablets (8 over-encapsulated tablets /strip)

Note: Each card will hold 16 over-encapsulated tablets in 2 strips of 8.

Study drug must be stored in a secure area (e.g., a locked cabinet) while in storage at the study site, protected from moisture, and kept at a room temperature between 15°C and 30°C (59°F-86°F). Patients will be instructed to store the weekly treatment card at room temperature at home, out of the reach of children. Patients will be instructed to take 2 capsules, 1 capsule from each strip per dose for Part A.

In Part B, ITI-007 will be provided to the study site by Catalent on behalf of ITI. Each treatment card will provide sufficient quantity for 1 patient for 4 weeks (28 doses). At the Part B, enrollment visit (Visit 8 of Part A), the patient will receive treatment cards containing sufficient quantities for 4 weeks. Each ITI-007 dosing container will be labeled according to local laws and regulations.

The treatment card for each study treatment is presented in Table 5-5.

Table 5-4 Part B Treatment Cards for 4 Weeks of Treatment

Treatment	Card Contents
60 mg ITI-007	Two 2 × 7 strips of 60 mg ITI-007 tablets (14 tablets/strip)

Note: Each treatment card will hold 28 tablets each.

Treatment	Card Contents
40 mg ITI-007 (two 20 mg tablets	Four 2 × 7 strips of 20 mg ITI-007 tablets (14 tablets/strip)

Note: Each treatment card will hold 56 tablets each.

Study drug must be stored in a secured locked area while in storage at the study site, protected from moisture, and kept at room temperature between 15 and 30°C (59 - 86 °F). Patients will be instructed to store the treatment card at room temperature, out of the reach of children. Patients will be instructed to take 1 tablet 60 mg each day per dose for Part B unless their dosage is reduced to two 20 mg tablets daily for a dose of 40 mg.

5.4.2 Test Article Accountability

The investigator will maintain accurate records of receipt of all test articles, including dates of receipt. In addition, accurate records will be kept regarding when and how much test article is dispensed and used by each patient in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled and retained or destroyed according to applicable regulations.

5.5 Overdose Management

An overdose is any dose of study treatment given to a patient or taken by a patient that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to the medical monitor. Overdoses without signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with the overdose, these should be reported on relevant AE/SAE sections in the eCRF.

5.5.1 Treatment of Overdose

Previous clinical trials have evaluated ITI-007 in healthy volunteers with single doses up to and including 40 mg, multiple doses up to and including 20 mg administered once daily for

5 days, and multiple doses up to and including 30 mg administered once daily for 7 days in healthy geriatric volunteers. Previous clinical trials have evaluated ITI-007 in schizophrenic patients with multiple doses up to and including 140 mg administered once daily for 5 days, multiple doses up to and including 120 mg administered once daily for 4 weeks, and multiple doses up to and including 60 mg administered once daily for 6 weeks. In case of an overdose that exceeds the previously studied doses, the patient should be closely monitored in a hospital setting with sufficient attention to the symptoms and the clinical course. Supportive measures may include gastric lavage and respiratory and cardiovascular support as needed.

5.5.2 Medication Errors

Dispensing study treatment to be taken by patients in an outpatient study increases risk for medication errors. All errors in medication dispensing or administration must be carefully documented. These errors may include but are not limited to providing the wrong dose (in Part A, not taking 2 capsules per dose or taking too many capsules per dose; in Part B, taking more than 1 tablet per dose), losing medication, or administration at the wrong time of day. Medication adherence will be emphasized at every visit. Written instructions will be provided to the patients with the weekly medication card in order to minimize medication error. Additional adherence procedures may be implemented.

5.5.3 Treatment of Medication Errors

The treatment of medication errors should be discussed with the medical monitor on a case-by-case basis. In the case of overdose, see Section 5.5.1.

5.6 Blinding

Part A of the study will be performed in a double-blind manner. All study drug will be supplied in identical treatment cards and packaging, and will be similar in color, smell, taste, and appearance, thereby enabling double-blind conditions.

Part B will be conducted as an open-label trial and no blinding procedures are required.

5.6.1 Breaking the Blind

In Part A, a patient's treatment assignment will not be broken until the end of the study unless medical treatment of the patient depends on knowing the study treatment the patient received. In the event that the blind needs to be broken because of a medical emergency, the

investigator may unblind an individual patient's treatment allocation. As soon as possible, the investigator should first contact the medical monitor to discuss the medical emergency and the reason for revealing the actual treatment received by that patient. The treatment assignment will be unblinded through IVRS/IWRS. Reasons for treatment unblinding must be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented.

Any patients whose treatments become unblinded will be discontinued from the study.

The overall randomization code will be broken only for study reporting purposes. This will occur once all final clinical data have been entered into the database and all data queries have been resolved.

5.7 Treatment Compliance

Patient compliance will be assessed by capsule counts of unused study medication at each visit during the double-blind treatment phase for Part A and unused study drug at each visit during Part B (Table 6–1 and Table 6-2).

In Part A, any irregularities in medication adherence should be discussed with the patient. Any patient who misses 2 doses of study medication per week in any 2 weeks of the study treatment period or who misses 3 or more doses of study medication in any single week should be considered for early discontinuation. Any exceptions due to unusual circumstances should be discussed on a case-by-case basis with the medical monitor to determine whether a patient may continue despite apparent treatment compliance issues.

In Part B, for patients missing more than approximately 20% of their doses, the investigator will be responsible to determine if patient's missed doses should result in patient termination from the study. These cases should be discussed with the medical monitor.

5.8 Prior and Concomitant Therapy

Patients are required not to use the following during the study: alcohol, cannabis, any known 5-HT_{2A} receptor antagonist or inverse agonist, any strong or moderate cytochrome P450 3A4 inhibitor or inducer. In Part A drugs with known psychotropic properties or any non-psychotropic drugs with potential central nervous system effects are prohibited, with the exceptions of zolpidem and with the following restrictions:

PART A Restrictions:

Concomitant Medication	Dose	Indication	Study period allowance	Assessment restrictions
Zolpidem	Up to 10mg/day (bedtime)	insomnia	During screening and first two weeks of the treatment period	Prohibited at least 8 hours prior to any psychiatric assessments
Zolpidem CR	Up to 12.5mg/day (bedtime)	insomnia		

In Part B, drugs with known psychotropic properties or any non-psychotropic drugs with potential central nervous system effects are prohibited, with the exception of zolpidem and lorazepam with the restrictions provided in the table below. **The table below is a guideline for use of these medications;** any use outside of these **guidelines** must be approved by the Medical Monitor:

PART B Restrictions:

Concomitant Medication	Dose	Indication	Study period allowance	Assessment restrictions
Zolpidem	Up to 10mg/day (bedtime)	insomnia	All of Part B	Prohibited at least 8 hours prior to any psychiatric assessments
Zolpidem CR	Up to 12.5 mg/day (bedtime)	insomnia		
Lorazepam	Up to 6 mg in any given week	Agitation, anxiety or insomnia		

(Section 4.1.2, Exclusion 13). Patients considered potentially eligible for participation will be required to discontinue their current antidepressant treatment and/or other psychotropic drugs for the duration of the study. Discontinuation of long-acting prohibited medications that require more than a 2-week washout should be discussed on a case-by-case basis with the medical monitor for approval of a longer screening phase to ensure washout of excluded

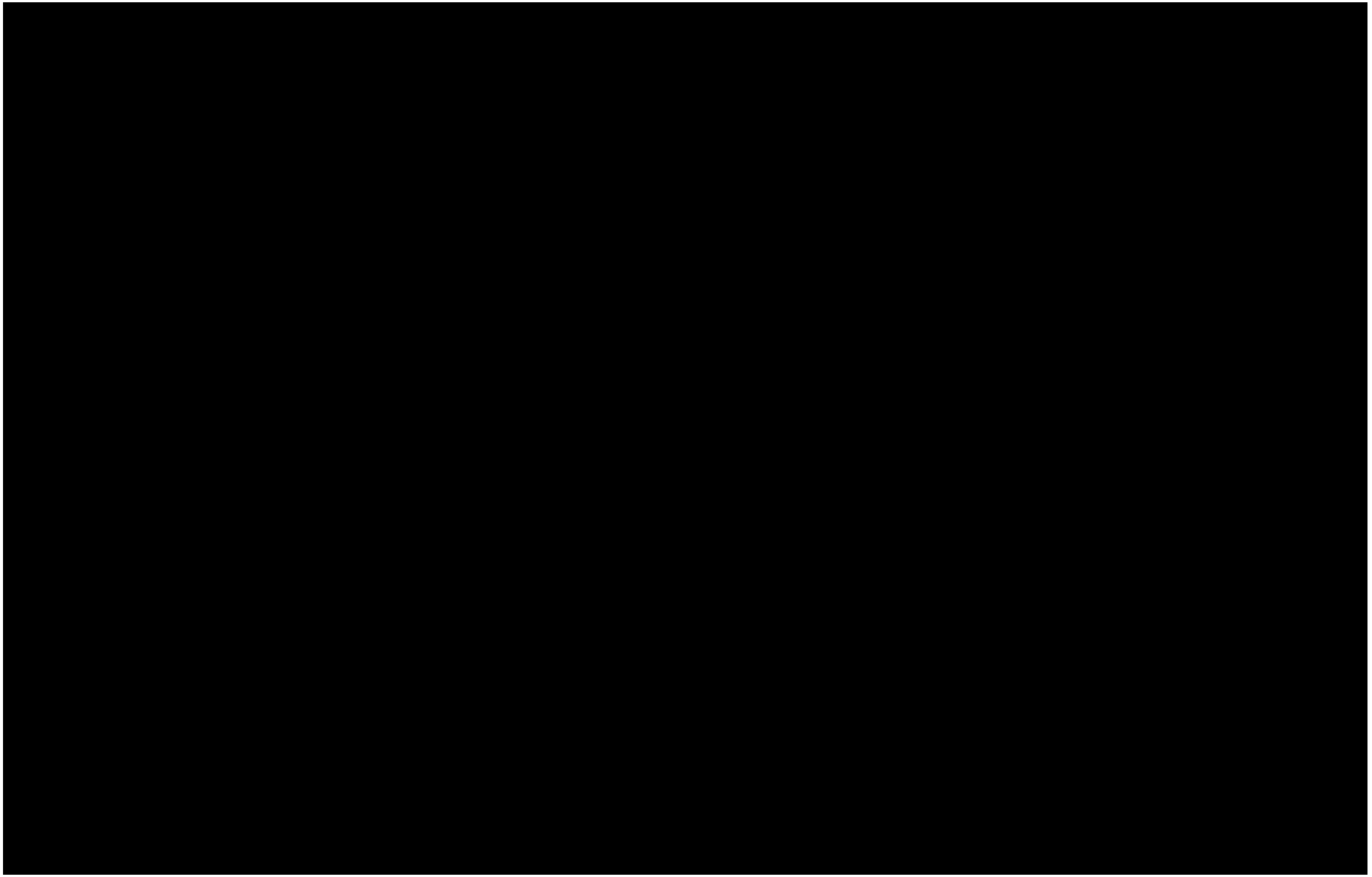
medication with longer half-life (e.g., fluoxetine) under the supervision of the investigator before baseline.

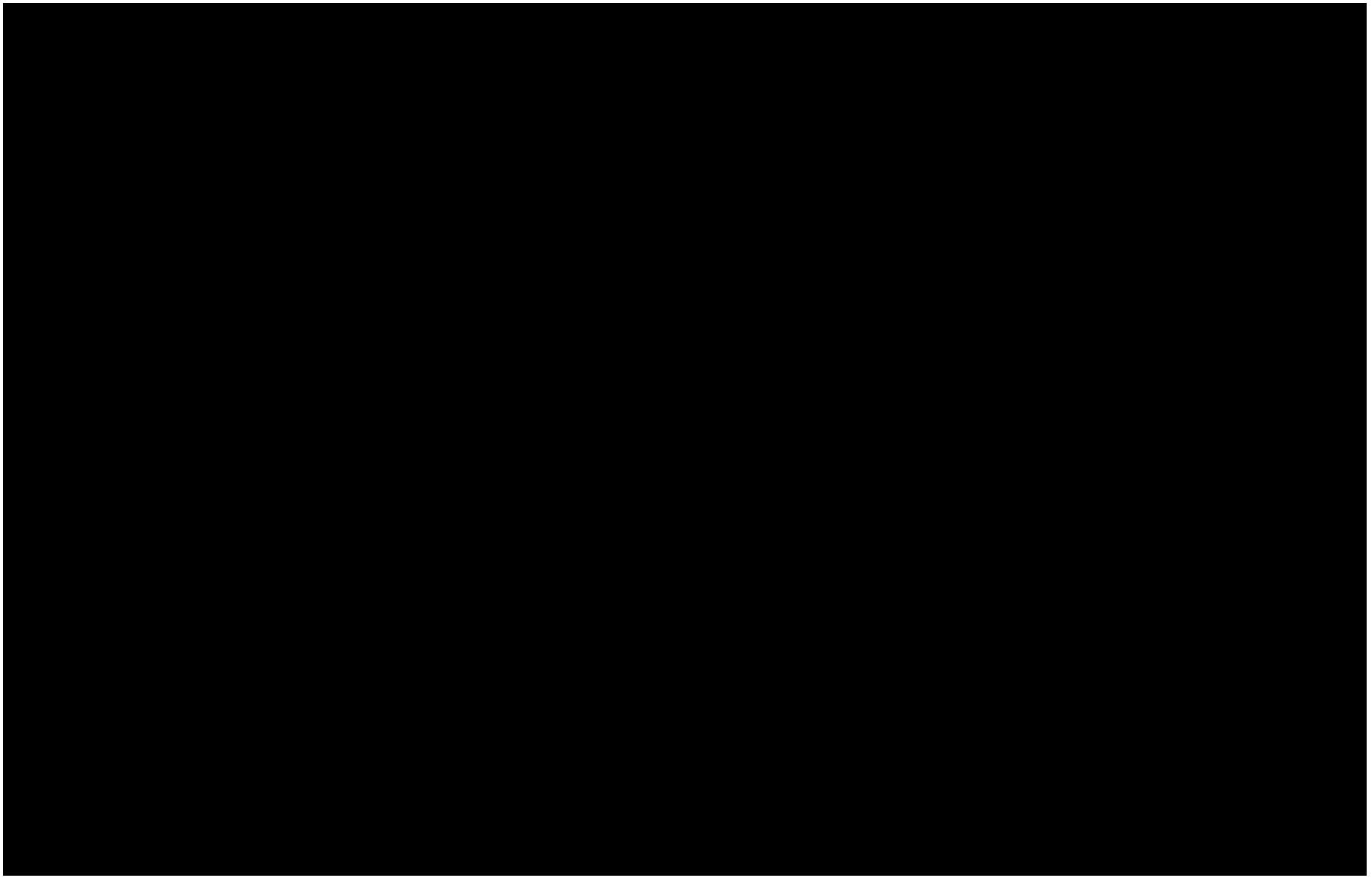
Use of all concomitant medications will be recorded in the patient's eCRF. As a minimum requirement, the drug name and dates of administration are to be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications will also be recorded in the patient's eCRF.

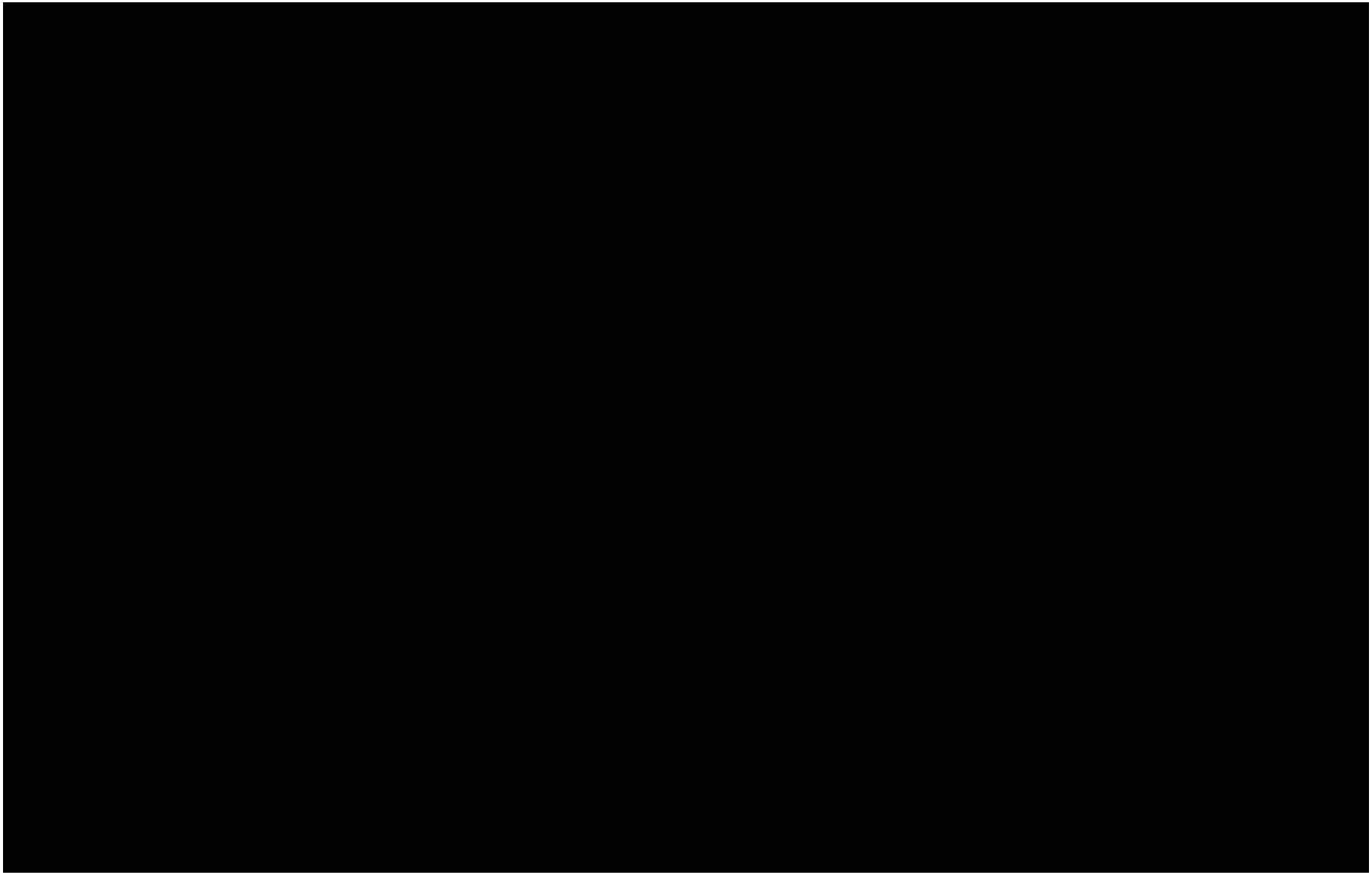
Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF.

6 Study Assessments and Procedures

Before participating in any study procedures, all potential study patients must sign an informed consent form (ICF). Patients will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the patient. The investigator will also sign the ICF and a signed copy will be provided to the patient. Separate written informed consent must be provided for each part of the study.







6.1 Screening Assessments and Procedures

After obtaining written informed consent, the following assessments are to be performed within 2 weeks prior to Day 1 (unless the medical monitor has approved an extended screening period to allow washout of prior long-acting psychotropic medication), according to the schedules of events in Table 6–1 and Table 6-2 for Parts A and B, respectively; assessments can be conducted on different days within the screening period.

6.1.1 Informed Consent

For both study parts, before any study-related activities the patient must sign and date an ICF approved by the responsible institutional review board (IRB). The format and content of the ICF must have been agreed upon by the investigator, the appropriate IRB, and ITI.

For Part A only, A separate ICF will be provided for the collection of samples to be used in the determination of genetic biomarkers. Patients may withhold consent to provide such samples and still participate in the study without prejudice.

6.1.2 Medical History and Other Information

Medical history information will be collected at screening and should include (but not be limited to) demographic information, current and past medical conditions, and current and past medications. The medical history must be documented in the patient's study chart prior to study treatment administration and also recorded in the appropriate eCRF. In addition to conventional medical history, information pertaining to the patient's average alcohol and caffeine consumption and average tobacco usage should be recorded in the eCRF. Demographic information will also be collected.

Patients will be checked for previous participation in an ITI-007 clinical study and for duplicate enrollment by study site staff using the DupCheck.org website and other methods for identifying duplicate patients.

6.1.3 Modified Physical Examination

A modified physical examination, including neurological and excluding genital/rectal examinations, will be performed. The examination should include evaluation of height (at screening only [m]); body weight (kg); waist circumference (cm); appearance and skin; head and neck; eyes, ears, nose, and throat; chest and lungs; heart; abdomen; and extremities. All physical examination findings must be documented in the patient's study chart and also recorded in the eCRF.

6.1.4 Electrocardiogram Assessments

In Part A, each ECG assessment will be comprised of a10-second epoch from a 12-lead ECG. Electrocardiogram parameters to be measured include heart rate, QRS, PR, QT, QTcF, and RR intervals.

The ECG recordings will be made on ECG machines supplied by a central ECG laboratory. Electrocardiogram data will be transferred to the central ECG laboratory on the same day as collected and interpretation will be provided to the study site within approximately 48 hours. If any 12-lead ECG recording shows an arrhythmia other than a sinus arrhythmia, sinus tachycardia, or sinus bradycardia, an additional 12-lead ECG will be recorded to confirm the original tracing. Any other clinically significant treatment-emergent cardiac conduction abnormalities will be followed until no longer deemed necessary by the investigator.

Central interpretations of ECG recordings obtained at screening will be the basis for determination that a patient is eligible for inclusion in the study. Similarly, central interpretations of ECG recordings at baseline and other visits will be included in the final study data. However, given that interpretations of recordings will not be available for up to 48 hours, investigators are to use machine generated parameters and clinical judgment to assess cardiac function for the purposes of immediate safety concerns.

In Part B, a standard single 12-lead ECG will be performed at the visits indicated in Table 6-2. Electrocardiograms will be performed after patients have been supine for at least

10 minutes. Electrocardiogram parameters to be measured include heart rate, QRS, PR, QT, QTcF, and RR intervals.

The ECG results will be centrally read and evaluated by the investigator for clinical significance. The investigator will assess whether any findings should be considered as AEs, and, if so, will be recorded as such.

6.1.5 Vital Sign Measurements

In Part A, vital sign assessments will include supine blood pressure and pulse rate, respiratory rate, and oral temperature. Blood pressure and pulse rate will be measured after 10 minutes in the supine position. Height will be measured only at screening. Body weight and waist circumference will be measured at all scheduled visits through Visit 9 (Day 57). Each patient's BMI will be calculated before Day 1 to ensure that the patient meets the BMI inclusion criterion.

In Part B, vital sign assessments will be performed at the visits indicated in Table 6-2, and will include blood pressure and pulse rate, respiratory rate, and oral temperature. The blood pressure and pulse rate will be measured after 10 minutes in the supine position. Height will be measured only at screening. Body weight will be measured at all scheduled visits.

Vitals sign measurements should also be collected, if feasible, at the time of an AE such as vertigo, dizziness, fall, or any sign or symptom that might indicate a fall in blood pressure.

6.1.6 Hepatitis Screening

Blood samples will be collected at screening from all patients in order to perform hepatitis B surface antigen and hepatitis C antibody (immunoglobulin G) testing. Test results will be sent to the screening site and must be reviewed before the Day 1 visit. Any patient who tests positive for hepatitis B or C, AND shows evidence of active disease will be excluded from participating in the study. Details regarding sample collection, processing, and shipping can be found in the study reference manual.

6.1.7 HIV Screening

Patients are required to provide blood samples for HIV virus types 1 and 2 testing. Test results will be sent to the screening site and must be reviewed before the Day 1 visit. Any patient who tests positive for HIV will be excluded from participating in the study. Patients will be informed of positive HIV results and referred for follow-up testing and counseling, and health authorities will be notified of positive HIV results consistent with federal, state, and local laws. Details regarding sample collection, processing, and shipping can be found in the study reference manual.

6.1.8 Urine Drug and Alcohol Screening

Qualitative urine drug (amphetamines, barbiturates, benzodiazepines, cannabinoids [THC], cocaine metabolites, methadone, opiates, phencyclidine, propoxyphene) and alcohol tests will be performed. Any patient who tests positive for any drug or alcohol at screening will be excluded from participating in the study except as noted in Exclusion #12. Further information regarding sample collection, processing, and shipping can be found in the study reference manual.

6.1.9 Laboratory Assessments

Laboratory assessments performed at screening are described in Section 6.5.

6.1.10 Urine Pregnancy Test

Female patients who are of childbearing potential will undergo urine pregnancy tests at the study clinic using a urine dipstick. If the pregnancy test at screening or Day 1 is positive, the patient will not be eligible to participate in the study. If a urine pregnancy test performed after initiation of study treatment is positive, it should be confirmed by a serum pregnancy test. Further details regarding sample collection and processing can be found in the study reference manual.

6.1.11 Structured Clinical Interview

The major clinical criterion for inclusion in the study is that the patient be diagnosed with Bipolar I or Bipolar II Disorder, meeting the DSM-5 criteria. The methodology for confirming this diagnosis is the SCID-5-CT, which is a semi-structured interview for making the major DSM-5 diagnoses (First, 2014). It will be used in this study at screening in Part A only to confirm the diagnosis of bipolar depression in patients evaluated for inclusion in the study. It will be completed by the investigator or an expert site-based rater approved by the sponsor.

6.1.12 Bipolarity Index (BPI)

The Bipolarity Index was designed to provide a measure of quantitative measure of diagnostic confidence by mapping the known information about an individual patient on five dimensions of illness (signs and symptoms, age of onset, course of illness, response to treatment and family history) onto a scoring hierarchy based on the presence of elements considered most characteristics of bipolar disorder. The information necessary to score the Bipolarity Index can be extracted from clinical interviews, either administered by clinicians or as a self-report questionnaire. The BPI will be completed by a qualified site-based rater at the screening visit in Part A only. The patient's responses to the BPI and the Bipolarity Index score generated by the BPI may be reviewed by an independent expert as a component of the systematic patient adjudication process in Part A.

The Bipolarity Index was developed by a group of Bipolar Disorder experts including Gary Sachs (Sachs, 2004). The scoring system is divided into five dimensions including episode characteristics, age of onset (1st affective episode), course of illness/associated features, response to treatment, and family history. Each dimension is given a score of 0-20 based on its correlation with BD characteristics, and the scores are added to derive the Bipolarity index score. The maximum score is 100. The score represents how close the patient is to having bipolar disorder. The Bipolarity Index has been used to evaluate diagnostic confidence for patients entering global clinical trials.

6.1.13 Columbia Suicide Severity Rating Scale

The C-SSRS is a questionnaire developed and validated by Kelly Posner and colleagues (2011) for the assessment of suicidal ideation and behavior. Several versions have been developed including the "Baseline" and "Screening" versions and a combined "Baseline/Screening" version of the scale which assesses suicidal ideation and behavior in a patient's lifetime and during a predefined time period. This version can assess a patient's lifetime suicidality as well as eligibility based on inclusion/exclusion criteria. A separate "Since Last Visit" version of the scale has been developed which is used to assess suicidality since the patient's last visit. This version is meant to assess patients who have completed at least 1 initial C-SSRS assessment, and should be used in every subsequent visit. The "Since Last Visit" version of the C-SSRS addresses any suicidal thoughts or behaviors the patient/participant may have had since the last time the C-SSRS was administered.

In Part A, the C-SSRS will be administered by the investigator or an expert site-based rater, as indicated in the Schedules of Events (Table 6–1 and Table 6-2 for Parts A and B, respectively). In Part B, on Days 75, 125, and 150, the C-SSRS will be administered via telephone by a qualified site-based rater. Concerns for participant safety after phone interviews should be addressed immediately by the investigator.

At screening a potential study participant will not be eligible if he or she reports suicidal ideation of type 4 or 5 on the C-SSRS within 6 months prior to screening or any suicidal behavior in the last 2 years prior to screening, as indicated by any "yes" answers on the suicidal behavior section of the C-SSRS.

[Note: For Part B, all C-SSRS assessments used should be the "Since Last Visit" version, since the patient has had an initial assessment at the Part A Screening Visit.]

6.1.14 Young Mania Rating Scale

The YMRS is an 11-item, clinician-administered mania rating scale with established reliability, validity, and sensitivity that was designed to assess the severity of manic symptoms (Young, 1978). Four of the YMRS items are rated on a 0 to 8 scale, with the

remaining 7 items rated on a 0 to 4 scale. The total score is appropriate both for assessing baseline severity of manic symptoms and for assessing treatment-emergent manic symptoms in patients with Bipolar I or Bipolar II Disorder with depression. In Part A, it will be completed by the investigator or an expert site-based rater.

At each visit with a YMRS assessment, the rater-administered YMRS interview will be audio recorded; at each visit after the screening visit, a computer-administered YMRS interview will also be completed by patients. The computer-administered interview will involve a series of probe and follow up questions with multiple-choice response options. At all visits (except screening) the rater-administered YMRS will be conducted before the computer-administered YMRS.

In Part B, YMRS administration will be done by each patient who will complete an interactive, computer-administrated YMRS interview on the dedicated study device.

6.1.15 Clinical Global Impressions of Severity

The Clinical Global Impressions Scale (CGI) has been modified specifically for use in assessing global illness severity and change in patients with bipolar disorder (Spearing, 1997). The CGI-BP-S is a standardized assessment tool that a clinician can use to rate the severity of illness, change over time, and efficacy of medication, taking into account the patient's clinical condition and the severity of side effects. The CGI-BP-S is used to document the clinician's impression of the patient's current illness state; it will be used in this study at screening (as a criterion for inclusion or exclusion) and throughout the study as a measure of efficacy (Section 6.2.2). Scores on the CGI-BP-S range from 1 (not ill at all) to 7 (among the most extremely ill). A CGI-BP-S assessment will be completed at screening in Part A by the investigator or another ITI-approved expert site-based rater.

In Part B, the CGI-BP-S will be administered after review of the patient-completed computerized MADRS and YMRS assessments.

[redacted]

6.2 Efficacy Assessments and Procedures

6.2.1 MADRS

The MADRS is a 10-item checklist designed to measure the overall severity of depressive symptoms. Individual items are rated by the investigator (or another ITI-approved expert site-based rater) on a scale of 0 to 6 in which a score of 6 represents the most severe symptoms for each item assessed. The total score ranges from 0 to 60.

Remission of depression based on the MADRS is generally defined as a patient with a MADRS total score of ≤12 at endpoint. A "responder" on the MADRS is defined as a ≥50% reduction from baseline in total MADRS score at endpoint.

The total score on the MADRS at screening is a major criterion for inclusion in the study, as well as the primary outcome measure for the study.

In Part A, at each visit with a MADRS assessment, the rater-administered MADRS interview will be audio recorded; at each visit after the screening visit, a computer-administered MADRS interview will also be completed by patients. The computer-administered interview will involve a series of probe and follow up questions with multiple-choice response options. At all visits (except screening) the rater-administered MADRS will be conducted before the computer-administered MADRS.

In Part B, MADRS administration will be done by each patient, who will complete an interactive, computer-administered MADRS interview on the dedicated study device.

6.2.2 Clinical Global Impression of Severity

The CGI-BP-S (Section 6.1.15) will be a clinical efficacy assessment by the investigator of each patient's severity of illness. The CGI-BP-S score at Part A screening will be considered in the adjudication process for enrollment (Section 6.1.16). The Clinical Global Impression Scale is a widely accepted measure of illness severity in a variety of psychiatric disorders. These items have been extensively used in psychopharmacologic trials since their introduction into the Early Clinical Drug Evaluation Unit Assessment Manual for Psychopharmacologic Trials published by the US National Institute of Mental Health. The Clinical Global Impression Scale is rated by the clinician based on all information available at the time of rating. The bipolar version has been validated for use as a global clinical assessment of symptoms specific to bipolar disorder.

The severity of illness is rated on a 1 to 7 scale. The clinician indicates his or her assessment of the patient's severity of illness relative to the clinician's experience with the population experiencing bipolar depression.

6.2.3 SDS (Part A Only)

The SDS is a validated patient self-reported measure of psychosocial disability. It is widely used in many chronic mental illnesses because of its generic design. The SDS consists of 3 subscales for the items "Work/School," "Social Life," and "Family Life/Home Responsibilities." Each subscale consists of a visual analog scale on which the patient scores each item from 0 ("not at all") to 10 ("extremely") in response to each question of how much each subscale aspect is impaired. Changes in the score for each item are evaluated to assess the change in severity of each domain. The scores may also be summed across the 3 subscales to assess overall change in disability.

6.2.4 Q-LES-Q-SF

The Q-LES-Q-SF is a patient self-reported questionnaire that assesses how satisfied a patient is, using a 5-point rating scale from very poor to very good, with 14 items. The items assessed include physical health, mood, work, household activities, social relationships, family relationships, leisure time activities, ability to function in daily life, sexual drive/interest/performance, economic status, living/housing situation, ability to get around physically without feeling dizzy or unsteady or falling, vision in terms of ability to do work or hobbies, and overall sense of well-being that are summed to provide a raw total score ranging from 14 to 70. There are an additional 2 stand-alone items (1 for medication satisfaction and the other for overall life satisfaction). The total raw score is converted to a percent score.

6.2.5 WHO-5 Well-Being Index (Part A Only)

The WHO-5 is a patient-reported outcome measure developed by the World Health Organization. This self-reported questionnaire consists of 5 questions regarding subjective quality of life based on positive mood, vitality, and general interest, each rated on a 6-point Likert scale from 0 (at no time) to 5 (all the time). The sum of scores represents the raw scores with 0 representing the worst possible quality of life and 25 representing the best possible quality of life. A score below 13 represents poor well-being. To calculate the percentage score, the raw score is multiplied by 4, with 100% representing the best possible quality of life. A 10% difference over time indicates a meaningful change. The WHO-5 has been found to have adequate validity as an outcome measure in clinical trials (Topp, 2015).

6.2.6 NEO-FFI (Part A Only)

The NEO-FFI is a 60-item self-report scale (Costa, 1992). Each item is ranted on a 5-point scale. Twelve items assess each of five dimensions of personality: neuroticism (N), extraversion (E), conscientiousness (C), openness (O), and agreeableness (A).

6.3 Safety and Tolerability Assessments

All patients who receive study drug will be evaluated for safety. Safety assessments will include incidence of AEs, suicidality assessment by the C-SSRS, mania assessment by the YMRS, movement disorder assessment by the AIMS, BARS and SAS, clinical laboratory evaluations, ECG evaluations, vital sign measurements, and physical examination and neurological findings.

6.3.1 Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

6.3.1.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a study patient administered a study drug, whether or not considered drug related. This can be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, without any judgment of causality.

The AE may be:

- A new illness;
- A worsening sign or symptom of the condition under treatment, or of a concomitant illness;
- An effect of the study medication, including comparator; or
- A combination of 2 or more of these factors.

No causal relationship with the study medication or with the clinical study itself is implied by the use of the term AE.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures, if permitted by the clinical study protocol and the conditions leading to those measures are not AEs.

All AEs fall into the categories of "nonserious" or "serious (Sections 6.3.1.2 and 6.3.1.3).

6.3.1.2 Definition of Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death;
- Is life threatening;
- Requires hospitalization or prolongation in existing hospitalization;
- Results in persistent or significant disability or incapacity; or
- Is a congenital anomaly or birth defect.

The term "life threatening" refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether an AE is serious. Some important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when they may jeopardize the patient such that medical or surgical intervention is needed to prevent 1 of the outcomes previously listed. Examples of such medical events include intensive emergency treatment for an allergic reaction, blood dyscrasias or convulsions that do not result in inpatient hospitalization, and the development of drug dependency or drug abuse.

If either the sponsor or principal investigator believes that any event is serious, the event must be considered and evaluated by the sponsor for possible expedited reporting.

Clarification of the difference between "serious" and "severe":

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as “serious,” which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

6.3.1.3 Nonserious Adverse Event

A nonserious AE is any AE not meeting the SAE criteria.

6.3.1.4 Definition of Relationship to Study Drug

By definition, any AE that starts before the first dose of study drug administration is considered to be “unrelated.”

The investigator will assess the causality/relationship between the study drug and the AE (Table 6–3). One of the following categories should be selected based on medical judgment, considering the following definitions and all contributing factors.

Table 6–3 Causality Categories

Category	Definition
Definitely related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration, and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment (dechallenge[1]) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge[2] procedure if necessary.
Probably related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
Possibly related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, but which could also be explained by concurrent disease or other drugs or chemicals. Information on treatment withdrawal may be lacking or unclear.
Unlikely to be related	A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Unrelated	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically, explained by extraneous factors (e.g., concomitant disease, environmental factors, or other drugs or chemicals).

[1] Dechallenge is when a drug suspected of causing an adverse event (AE) is discontinued. If the symptoms of the AE disappear partially or completely, within a reasonable time from drug discontinuation, this is termed a positive dechallenge. If the symptoms continue despite withdrawal of the drug, this is termed a negative dechallenge. Note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (e.g., bone marrow suppression, fixed drug eruptions, tardive dyskinesia).

[2] Rechallenge is when a drug suspected of causing an AE in a specific patient in the past is readministered to that patient. If the AE recurs upon exposure, this is termed a positive rechallenge. If the AE does not recur, this is termed a negative rechallenge.

6.3.1.5 Definition of Intensity

The principal investigator will assess all AEs for intensity (severity) in accordance with the following standard ratings (Table 6-4):

Table 6-4 Intensity Categories

Category	Definition
Mild	Ordinarily transient symptoms, does not influence performance of patient's daily activities. Treatment is not ordinarily indicated.
Moderate	Marked symptoms, sufficient to make the patient uncomfortable. Moderate influence on performance of patient's daily activities. Treatment may be necessary.
Severe	Symptoms cause considerable discomfort. Substantial influence on patient's daily activities. May be unable to continue in the study and treatment may be necessary.
Life threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted for that day. Any change in intensity of signs and symptoms over a number of days will be captured by recording a new AE, with the amended intensity grade and the date (and time, if known) of the change.

6.3.1.6 Period of Observation for Adverse Events

For the purposes of this study, the period of observation extends from the time the patient gives his study-specific informed consent until the end of study procedures are completed.

Serious AEs occurring after completion or discontinuation of the study should be reported if they occur within 30 days after the last dose of study treatment. If the Investigator detects an SAE in a study patient after the end of the period of observation and considers the event possibly related to prior study treatment, he or she should contact the Sponsor to determine how the AE should be documented and reported.

6.3.1.7 Documenting, Reporting, and Eliciting Adverse Events

All AEs reported or observed during the study will be collected and recorded on the AE page of the eCRF for each patient from the date the ICF was signed until the end of their participation in the study, i.e., the patient has discontinued or completed the study.

Adverse events may be volunteered spontaneously by the patient, or discovered by the study staff during physical examinations or by asking an open, non-leading question such as, "How have you been feeling since you were last asked?" All AEs and any required remedial action will be recorded. The nature of the AE, date (and time, if known) of the AE onset, date (and time, if known) of the AE outcome to date, severity, and action taken for the AE will be documented together with the investigator's assessment of the seriousness of the AE and causal relationship to study drug and/or study procedure.

All AEs should be recorded individually in the study patient's own words (verbatim) unless, in the opinion of the investigator, the AEs constitute components of a recognized condition, disease or syndrome. In the latter case, the condition, disease or syndrome should be named rather than each individual symptom. The AEs will subsequently be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

6.3.1.8 Notification About Serious or Unexpected Adverse Events

The investigator will review each SAE (Section 6.3.1.2) and evaluate the intensity and the causal relationship of the event to study drug. All SAEs will be recorded from signing of informed consent until follow-up.

The investigator is responsible for providing notification to the sponsor or designee of any SAE, whether deemed related to study drug or not, that a patient experiences during their participation in study within 24 hours of becoming aware of the event.

As a minimum requirement, the initial notification should provide the following information:

- Study number
- Patient number
- Gender
- Date of birth
- Name of investigator and full study site address
- Details of SAE
- Criterion for classification as "serious"
- Study drug code, or name if unblinded, and treatment start date and stop date, if applicable
- Date of SAE onset
- Causality assessment (if sufficient information is available to make this classification)

The sponsor will request clarification of omitted or discrepant information from the initial notification. The investigator or an authorized delegate is responsible for faxing the requested information to the sponsor within 24 hours of the sponsor's request.

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (e.g., hospital reports, consultant reports, autopsy reports), with the study patient's personal identifiers removed. All relevant information obtained by the investigator through review of these documents will be recorded and faxed to the sponsor within 24 hours of receipt of the information. If a new SAE Report Form is faxed, then the investigator must sign and date the form. The sponsor may also request additional information on the SAE, which the investigator or an authorized delegate must fax to the sponsor within 24 hours of the request.

The SAE reporting contact information will be provided to all participating study sites by the contract research organization (CRO) before study initiation.

6.3.1.9 Exceptions

Visits to urgent care or emergency room facilities may not warrant reporting as SAEs unless the patient is admitted to the hospital or the event meets other "serious" criteria. As discussed in Section 6.3.1.2, medical and scientific judgment should be exercised in deciding whether an AE is serious. Events that are not clearly meeting "serious" criteria can be discussed on a case-by-case basis with the medical monitor to help the investigator determine whether the event meets "serious" criteria.

6.3.1.10 Follow-Up of Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, or until the patient is considered to be stable.

A follow-up telephone call will be performed for those patients with an ongoing AE which the investigator believes to be not related to study drug administration. A follow-up visit to

the study site may occur for those patients with an ongoing AE which the investigator believes to be possibly related to study drug administration.

All AEs must be reported in detail on the appropriate page in the eCRF and followed until they are resolved or stable, or judged by the investigator to be not clinically significant.

6.3.2 Safety Assessments

Safety assessments scheduled through the course of the study (Table 6–1 and Table 6-2 for Parts A and B, respectively) will include suicidality assessment by the C-SSRS, mania assessment by the YMRS, movement disorder assessment by the AIMS, BARS and SAS, vital sign measurements, ECG evaluations, and physical and neurological examination.

6.3.2.1 C-SSRS

The C-SSRS will be completed at screening, baseline, and at every subsequent scheduled clinic visit (Table 6–1 and Table 6-2 for Parts A and B, respectively). Details of the C-SSRS are presented in Section 6.1.13.

6.3.2.2 YMRS

The YMRS will be completed at screening, baseline, and at every subsequent scheduled clinic visit (Table 6–1 and Table 6-2 for Parts A and B, respectively). Details of the YMRS are presented in Section 6.1.14.

6.3.2.3 Abnormal Involuntary Movement Scale

The AIMS (Guy, 1976) measures facial and oral movements, extremity movements, and trunk movements. Seven items are rated on a scale from none (0) to severe (4). A score of "mild" (2) in 2 or more categories or a score of "moderate" or "severe" in any 1 category results in a positive AIMS score (i.e., the scores are not averaged). Additionally, overall severity is scored on the basis of severity of abnormal movements and incapacitation due to abnormal movements. The patient's awareness of and distress caused by the abnormal movements are also noted. The AIMS is to be completed at baseline and periodically

throughout the study as specified in the schedule of events (Table 6–1 and Table 6-2 for Parts A and B, respectively).

6.3.2.4 Barnes Akathisia Rating Scale

The BARS is a rating scale for drug-induced akathisia developed by Barnes (1989). It includes the rating of observable restless movements, the subjective awareness of restlessness, and the distress associated with the akathisia. There is also a global rating for severity. The scale is completed by the investigator or an expert site-based rater after a standard examination. Objective akathisia, subjective awareness and subjective distress are rated on a 4-point scale from 0 to 3, yielding a total score from 0 to 9. The Global Clinical Assessment of Akathisia is rated separately, on a 5-point scale from 0 to 4. The BARS is to be completed at baseline and periodically throughout the study as specified in the schedule of events (Table 6–1 and Table 6-2 for Parts A and B, respectively).

6.3.2.5 Simpson-Angus Scale

The SAS is a measure of extrapyramidal side effects (Simpson, 1970). Ten items including rating gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head rotation, glabella tap, tremor, and salivation are rated on a scale from 0 (normal) to 4 (extreme in severity). The SAS should be conducted by the investigator or an expert site-based rater in a room where the patient can walk a sufficient distance to allow a natural pace (e.g., 15 paces). Each side of the body should be examined. The SAS is to be completed at baseline and periodically throughout the study as specified in the schedule of events (Table 6–1 and Table 6-2 for Parts A and B, respectively).

6.3.2.6 Vital Sign Measurements

Vital signs will be measured at screening and at every subsequent scheduled clinic visit (Table 6–1 and Table 6-2 for Parts A and B, respectively). Details of the vital sign measurements are presented in Section 6.1.5.

6.3.2.7 ECG Assessments

The ECG assessments will be performed at screening and periodically throughout the study, as scheduled (Table 6–1 and Table 6-2 for Parts A and B, respectively). Details of the ECG assessments are presented in Section 6.1.4.

6.3.2.8 Physical and Neurological Examination

The physical and neurological examinations will be conducted at screening and periodically throughout the study, as scheduled (Table 6–1 and Table 6-2 for Parts A and B, respectively). Details of the physical and neurological examinations are presented in Section 6.1.3.

6.4 Safety Monitoring Committee

No safety monitoring committee will be used for the study.

6.5 Laboratory Analyses

Blood and urine samples collected from patients will be forwarded to a central laboratory for analysis. Further details regarding sample collections, processing and specific testing can be found in the study reference manual.

All samples for clinical laboratory analysis will be collected after an overnight fast (≥10 hours), for all visits subsequent to screening, prior to dosing with study drug. Samples for clinical laboratory analysis will be used only for the evaluation of safety and tolerability.

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, vital sign measurements), including those that worsen from baseline, felt to be clinically significant, in the medical and scientific judgment of the investigator, are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition, are not to be reported as AEs or SAEs.

The following clinical analytes will be determined:

Hematology: hematocrit; hemoglobin; HbA_{1c}; red blood cell count with indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration); reticulocytes; white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) reported as percent (%) and absolute values; and platelets (platelet count, prothrombin time and partial thromboplastin time, international normalization ratio).

Clinical chemistry: albumin; alkaline phosphatase; blood urea nitrogen; gamma-glutamyl transferase; calcium; creatinine; glucose; insulin; cholesterol (high-density lipoprotein and low-density lipoprotein [LDL] [calculated] and homogenous LDL will be reported, and homogenous LDL will be reflexed if a patient's triglycerides are >400); triglycerides; phosphate; potassium; prolactin, ALT; AST; lactate dehydrogenase; sodium; chloride; bilirubin (total, direct); total protein; uric acid; creatine phosphokinase; and thyroid panel (at screening only, thyroid-stimulating hormone will be assayed and if the result is abnormal, the free thyroxine and free triiodothyronine will be assayed).

Urinalysis: macroscopic (pH, specific gravity, glucose, protein, ketones, nitrates, blood) and microscopic – report only if present (red blood cells/high-power field, white blood cells/high-power field, casts, epithelial cells, crystals, granulation).

Serology: anti-HIV antibodies, hepatitis B surface antigen, and hepatitis C antibody (only during screening).

[redacted]

[redacted]

6.7 Sample Collections

[redacted]

6.7.3 Frequency and Volume of Blood Collection

Blood samples will be collected for laboratory assessments, hepatitis and HIV screening, determination of plasma concentrations of ITI-007 and metabolites, and also for the assessment of protein and genetic biomarkers. The sampling times for all blood sample

collections are given in Table 6–1 and Table 6-2 for Parts A and B, respectively (Schedules of Events).

The estimates of blood sample volume and sample numbers are presented in Table 6–5.

Table 6–5 Number and Volume of Blood Samples for Part A

	Number of Blood Samples					
Study Day/Visit	**PK**	**Protein Biomarker**	**Genetic Biomarker**	**Laboratory Assessment**	**Hepatitis Screening**	**HIV Screening**
Screening				X	X	X
Day 1		X	X	X		
Day 8	X	X		X		
Day 22	X	X		X		
Day 43	X	X		X		
Day 57				X		
Total number of samples	4 samples	4 samples	1 sample	6 samples	1 sample	1 sample
Total maximum volume[1]	40 mL	40 mL	10 mL	60 mL	10 mL	10 mL
Total blood volume per patient: up to 170 mL						

[1] Each sample will have a volume of up to 10 mL.

Note: Additional blood samples may be collected for repeat safety follow up.

Table 6-6 Number and Volume of Blood Samples for Part B

Study Day	**Laboratory Assessment**	**Hepatitis Screening**	**HIV Screening**
Screening	X	X	X
Days 25, 75, 125, 175, 189	X		
Days 75, 175, 189			
Total number of samples	6 samples	1 sample	1 sample
Total maximum volume[1]	60 mL	10 mL	10 mL

[1] Each sample will have a volume of up to 10 mL.

Note: Additional blood samples may be collected for repeat safety follow up.

6.8 Pregnancy

Pregnancy is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported using a clinical study pregnancy form. The patient must stop study drug immediately after pregnancy is discovered and have an Early Termination visit as soon as possible. Additionally, each pregnancy must be reported to ITI within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the patient was discontinued from the study. Pregnancy complications and elective terminations for medical reasons should not be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the patient has completed the study, and considered by the investigator as possibly related to the study treatment, must be promptly reported to ITI.

7 Statistical and Analytical Plan

A formal and detailed statistical analysis plan (SAP) for Part A will be finalized prior to the planned IA, and will provide further details regarding the definition of analysis endpoints, analysis methodology, and the IA to address all study objectives. Similarly, a SAP for Part B will be finalized prior to database lock. Changes made to the data analysis methods as described in the protocol will be documented in the SAP and will not necessitate a protocol amendment. All departures from the statistical analyses described in the approved protocol, whether made before or after database lock, will be documented, and justified in the final clinical study report.

Blinded (Part A) and unblinded (Part B) data review will be conducted prior to unblinding the patients' treatment assignments (Part A) or finalizing the outputs (Part B) for assessing the accuracy and completeness of the study database and defining analysis datasets. An unblinded review of Part A interim data will be conducted by an independent external unblinded Data Monitoring Committee (DMC) in accordance with the IA plan.

7.1 Analysis Endpoints

7.1.1 Primary Efficacy Endpoints (Part A)

The primary efficacy endpoint of Part A is the change from baseline in the rater-administered MADRS total score at Week 6.

7.1.2 Secondary Efficacy Endpoints (Part A)

7.1.2.1 Key Secondary Efficacy Endpoint (Part A)

The key secondary objective of Part A of this study is to compare the efficacy of 2 doses of ITI-007 administered orally once daily to that of placebo in time to first response, defined as the number of days from first dose of study drug to the earliest date the patient experiences a sustained ≥50% reduction from baseline in the rater-administered MADRS total score.

7.1.2.2 Other Secondary Efficacy Endpoints (Part A)

- MADRS:
    - Time course of improvement, as measured by mean change from baseline in the MADRS total score at each assessment time point;
    - The proportion of treatment responders, where response is defined as a ≥50% decrease in the MADRS total score from baseline at Weeks 1, 2, 3, 4, 5, and 6. Patients who discontinue treatment early will be imputed as non-responders in the responder analysis.
    - The proportion of remitters, where remission is defined as a MADRS total score ≤12 at Weeks 1, 2, 3, 4, 5, and 6. Patients who discontinue treatment early will be imputed as non-remitters in the remitter analysis.
    - Change from baseline in MADRS Item 4 "reduced sleep" score for patients with baseline MADRS Item 4 score ≥4 (patients with mild sleep disturbance) at Weeks 1, 2, 3, 4, 5, and 6.
    - Change from baseline in MADRS individual item scores at Weeks 1, 2, 3, 4, 5, and 6.
- CGI-BP:
    - Change from baseline in the CGI-BP-S score at Weeks 1, 2, 3, 4, 5, and 6;
- SDS:
    - Change from baseline in the score for each item and total score at Weeks 3 and 6;
- Q-LES-Q-SF:
    - Change from baseline in the percent score at Weeks 3 and 6.

- WHO-5 Well-Being Index
    - Change from baseline in the percent score at Weeks 3 and 6.
- NEO-FFI
    - Change from baseline in the percent score at Week 6.

[redacted]

7.1.3 Secondary Effectiveness Endpoints (Part B)

Secondary effectiveness objectives of Part B of this study are to determine whether 60 mg ITI-007, administered once daily for up to approximately 6 months to patients with bipolar disorder who have responded to treatment with ITI-007, improves and/or maintains symptoms, function, and quality of life as measured by change from baseline on the following measures:

- MADRS total score;
- CGI-BP-S;
- Q-LES-Q-SF

[redacted]

[redacted]

7.1.5 Safety Endpoints (Parts A and B)

- AEs;
- YMRS total score;
- MADRS score (safety endpoint for Part B only);
- C-SSRS scores;
- AIMS scores;
- BARS scores;
- SAS score;
- Physical examination and neurological findings;
- Vital signs (blood pressure, heart rate), weight, and height (height, only at screening);
- ECGs;
- Clinical laboratory evaluations.

7.2 Sample Size Calculations

In Part A, approximately 549 patients will be randomly assigned in a 1:1:1 ratio to 1 of the 3 treatment arms, which will provide approximately 471 evaluable patients, assuming an approximate 14% early discontinuation rate before a post-dose assessment in the primary efficacy endpoint (MADRS). A sample size of 471 patients (157/arm) will provide at least 90% power to detect a clinically relevant treatment difference from placebo of 3 points on the MADRS total score within each ITI-007 dose level, with a common standard deviation of 7.5

at an overall 2-sided significance level of 0.05. It was not possible to apply the proposed Hommel procedure for multiplicity adjustments (for comparing 2 doses of ITI-007 to placebo) to the sample size calculation; therefore, the sample size calculation used a more conservative Bonferroni adjustment. The study therefore has at least 90% power to detect the previously mentioned clinically relevant treatment difference within each ITI-007 dose. The sample size calculation was performed using PASS software version 12.

In Part B, up to approximately 549 patients will be enrolled. The sample size is not based on statistical considerations, rather on the number of patients who may be eligible based on participation in Part A of the study. It is estimated that the majority of patients will continue treatment for the full 6 months.

7.3 Analysis Sets

The following analysis sets will be used in the statistical analyses.

All Patients Enrolled (ENR) Set: The ENR Set will contain all patients who signed informed consent for the study.

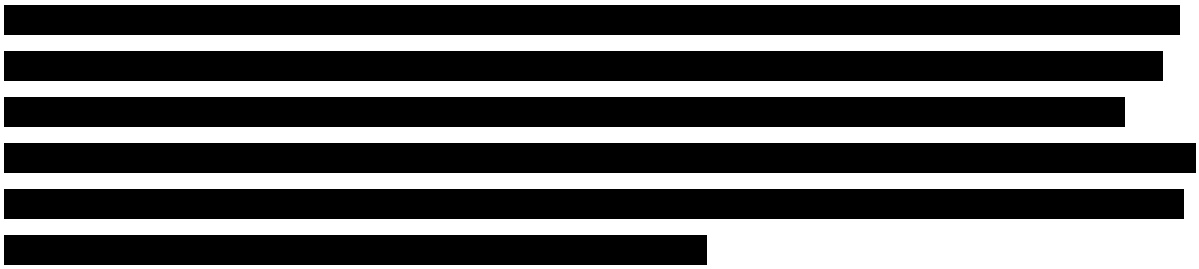
All Patients Randomized (RND) Set: The RND Set will contain all patients who signed the informed consent and were randomized to study drug.

Intent-to-treat (ITT) Set: The ITT Set will contain all randomly assigned patients who received at least 1 dose of study drug and who have a valid (pre-dose) baseline measurement and at least 1 valid post-baseline measurement of MADRS. Primary, secondary, and exploratory efficacy analyses of Part A data will be performed using the ITT Set. All analyses using the ITT will group patients according to randomized treatment, regardless of the treatment received during the course of the study.

Per-protocol (PP) Set: For Part A, the PP Set will contain all ITT patients who did not have any major protocol deviations. For Part B, the PP Set will contain all patients in the Safety Analysis Set who did not have any major protocol deviations. The major protocol deviation criteria will be finalized prior to any analysis. For Part A, all analyses using the PP Set will

group patients according to the treatment actually received. The classification of patients according to study drug does not apply to Part B.

Safety Analysis Set: The Safety Analysis Set will contain all patients who took at least 1 dose of study drug. All analyses using the Safety Set will group patients according to treatment actually received. In case of incorrect dosing, the treatment most often received will be taken as the actual treatment.



The following analysis sets will be used for the analyses of Part B data: ENR Set, Safety Analysis Set, and PP Sets. The classification of patients according to study drug does not apply to Part B.

Unless otherwise specified, the ITT and PP Sets will be used for analysis of efficacy endpoints in Part A and the Safety Set will be used for analysis of safety endpoints in Part A and safety and effectiveness endpoints in Part B.

7.4 Description of Subgroups to be Analyzed

Subgroup analyses of efficacy and safety variables may be conducted as deemed appropriate. For subgroup analyses using either MMRM or ANCOVA with LOCF, the corresponding subgroup terms will be added to the model: subgroup, subgroup-by-treatment, subgroup-by-visit, and subgroup-by-treatment-by-visit interactions. Subgroup analyses will be detailed in the SAP.

7.5 Statistical Analysis Methodology

Categorical variables (e.g., race and gender) will be summarized using the number and percentage of patients in specified categories will be presented. Unless otherwise specified, descriptive statistics of continuous variables (e.g., age, height, weight) will consist of the number of patients (n), mean, standard deviation, median, minimum, and maximum. Source data for summary tables and statistical analyses will be presented as patient data listings.

Unless stated otherwise, statistical tests will be 2-sided and use a 5% significance level, leading to 95% (2-sided) confidence intervals (CIs). All statistical analyses will be performed using SAS software Version 9.2 or higher. Adjustments for multiplicity due to the comparison of 2 doses of ITI-007 versus placebo for primary efficacy variables will be made using the Hommel procedure. No adjustment for multiplicity will be made for secondary efficacy (Part A) or safety variables (Part A), or any analysis of Part B data, unless otherwise stated in the SAP.

All investigative sites with fewer than 5 patients per treatment group with non-missing values of the response variable will be pooled together and considered a single site for analysis. If this results in a site still having fewer than 5 patients per treatment group, this site will be pooled together with the next smallest investigative site, if one exists; otherwise, no further pooling is needed. These pooled investigative sites will be used for any analysis that has investigative site as a fixed effect in the model. The actual investigative site numbers will be included in the listings.

Additional details regarding the statistical analysis methodology will be provided in the SAP.

7.5.1 Patient Disposition, Analysis of Demographics and Other Baseline Characteristics

Patient disposition will be summarized for each Part by treatment group, when applicable, and overall, including incidence of screen failure, and treatment or study discontinuation and the corresponding reasons. The number and percentage of randomized patients who discontinued due to an adverse event associated with worsening of bipolar depression will be

summarized. Similarly, the number and percentage of randomized patients who discontinued due to an adverse event not associated with worsening of bipolar depression will also be presented. Time to treatment discontinuation due to all reasons, adverse events, lack of efficacy, or due to any other reason of special interest will be evaluated separately using the Kaplan-Meier method, where patients who complete the On-Treatment Period or who discontinue for a reason other than the one being evaluated will be censored. The Log-rank test will be used to compare the time to discontinuation between each treatment group and the placebo group (Part A).

Demographic and baseline characteristics, including bipolar disorder diagnosis and bipolar disorder baseline efficacy measures, will be summarized for each part by treatment group for Part A only using descriptive statistics. No inferential statistics will be presented.

7.5.2 Prior and Concomitant Medications

Prior, prior concomitant, concomitant, and post-treatment medications, defined by start and stop dates relative to study medication administration, will be summarized by preferred term for each Part and by treatment group for Part A only, using the Safety Analysis Set. Patients with multiple occurrences of a medication in the same preferred term and study period will only be counted once within the preferred term and study period.

During the study, a patient may be treated with zolpidem as described in Section 5.8. For Part A, the number and percent of patients in the ITT Set receiving zolpidem and the total number of days on zolpidem will be summarized by treatment group for the Screening Period, for each week during the On-Treatment Period and for post treatment. Other medications will be summarized for Part A by treatment group and study period or overall for Part B if deemed necessary.

7.5.3 Study Medication Exposure and Treatment Compliance

Exposure to study medication and treatment compliance will be presented for each Part using the Safety Analysis Set and, additionally for Part A, using the ITT Set. Duration of exposure (days) and dosing compliance (%) will be calculated and summarized for each Part and by

treatment group for Part A only. In addition, the number and percentage of patients exposed to study medication will be presented.

7.5.4 Analysis of Part A Primary and Key Secondary Efficacy Endpoints

Part A of the study is designed to evaluate the efficacy of two doses of ITI-007, 60 mg and 40 mg, based on the primary and key secondary endpoints. The primary efficacy endpoint, mean change from baseline to Week 6 in the rater-administered MADRS total score, will be evaluated using a mixed model repeated measures (MMRM) method. The model will include the change from baseline at each pre-specified time point in the rater-administered MADRS total score as the response variable and visit, treatment, site, and the bipolar disorder at screening (I or II) stratification variable as factors, the baseline MADRS total score as a covariate, and interaction terms for treatment-by-visit, visit-by-baseline MADRS total score, and treatment-by-site. An unstructured covariance matrix will be used to model the correlation among repeated measurements within patient. If convergence cannot be attained with the unstructured correlation matrix, alternative structures will be evaluated in the order specified in the SAP. Model parameters will be estimated using restricted maximum likelihood. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

Estimates for change from baseline in MADRS total score, standard errors and 95% confidence intervals (CIs) will be presented by treatment group and time point. The least-squares mean difference between treatment groups will be presented along with the corresponding 95% CIs, effect sizes, and p-values will be presented for each visit.

Sensitivity analyses will be conducted to assess the impact of missing data and the robustness of the MMRM results for the primary efficacy analysis, such as a pattern-mixture model using a placebo-based multiple imputation method and delta-adjusted tipping point analysis, and will be detailed in the SAP.

As a supportive analysis of the primary efficacy variable, the change from baseline in MADRS total score will be evaluated using analysis of covariance (ANCOVA) with last observation carried forward (LOCF), defined as the last post-baseline measurement collected

within the study On-Treatment Period. Analysis of the LOCF Week 6 endpoint will provide an estimate of efficacy attributable to ITI-007 compared to placebo at the end of period of adherence to treatment without taking into account the ability of patients to adhere to treatment for the full planned period of 6 weeks. Least square means for each treatment, the least squares mean difference between treatment groups, the associated standard errors and two-sided 95% CIs for the differences between the treatment groups, and p-values for between-treatment tests of differences will be presented. This analysis will be conducted for the ITT set and PP set.

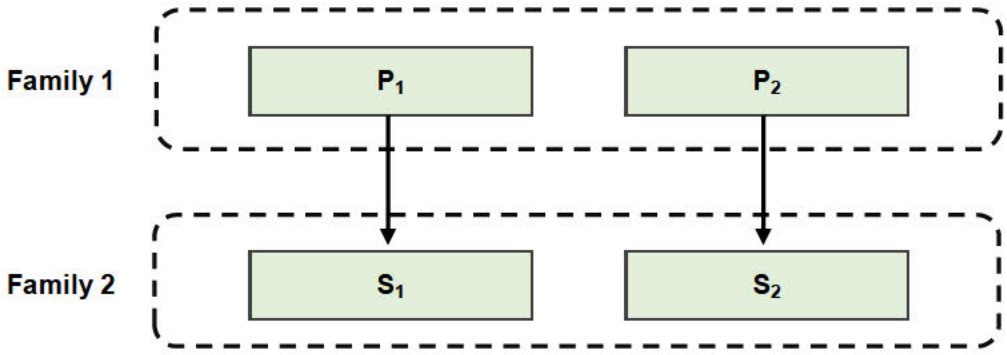
The key secondary efficacy endpoint, time to first response, defined as ≥50% reduction from baseline in rater-administered MADRS total score and maintaining it through the end of the 6-week treatment, will be analyzed using time-to-event methods. Time to the first response will be analyzed using the Cox's Proportional Hazards model with terms for treatment, site, baseline MADRS total score, the bipolar disorder stratification variable and treatment-by-site interaction. Patients who do not experience at least 50% reduction from baseline in the rater-administered MADRS total score, or do not maintain it through the end of the 6-week treatment, and patients who discontinue treatment, will be considered non-responders and will be censored.

Time to first response will be compared between treatment groups using the Kaplan-Meier product limit method.

Evaluating the efficacy of two doses of ITI-007 vs. placebo based on the primary and key secondary efficacy endpoints requires multiple comparisons defined by four hypotheses which are grouped into two families corresponding to the two endpoints:

- Family 1 – Primary Efficacy Endpoint:
    - Let P_1 represents the hypothesis associated with the primary efficacy endpoint for 60 mg ITI-007 vs. Placebo;
    - Let P_2 represents the hypothesis associated with the primary efficacy endpoint for 40 mg ITI-007 vs. Placebo;
- Family 2 – Key Secondary Efficacy Endpoint:

- Let S_1 represents the hypothesis associated with the key secondary efficacy endpoint for 60 mg ITI-007 vs. Placebo;
- Let S_2 represents the hypothesis associated with the key secondary efficacy endpoint for 40 mg ITI-007 vs. Placebo



In this study there are two sources of multiplicity: the comparison of two doses of ITI-007 (40 mg and 60 mg) to placebo, and the evaluation of two families of efficacy endpoints, corresponding to the primary and key secondary objectives. Testing multiple hypotheses may result in an inflation of the familywise error rate (FWER), defined as the probability of making at least one Type I error, and, therefore, requires an adjustment. A gatekeeping procedure will be used to control the overall Type I error rate in the strong sense across the primary and key secondary efficacy endpoints at a two-sided alpha=0.05. The primary endpoint will serve as a gatekeeper for the key secondary endpoint in the sense that a key secondary endpoint will be tested only if at least one primary test is significant, and the ITI-007 dose or doses to be compared to placebo for the key secondary endpoint will be determined based on the results for the primary one. Additionally, a multiplicity adjustment will be applied within family 1, and, possibly, within family 2, if the two doses are evaluated, depending on the results for family 1.

Details on the gatekeeping procedure will be provided in the SAP.

[redacted]

7.5.7 Analyses of Part B Secondary Endpoints - Effectiveness

Secondary effectiveness objectives of Part B of this study are to determine whether 60 mg ITI-007, administered once daily for up to approximately 6 months to patients with bipolar disorder and who have responded to treatment with ITI-007, improves and/or maintains symptoms, function, and quality of life as measured by change from baseline on the following measures:

- MADRS total score;
- CGI BP-S;
- Q-LES-Q-SF

Unless otherwise stated, analyses of Part B effectiveness endpoints will primarily consist of change from baseline summaries for the single treatment group of ITI-007 60 mg and will be conducted on the Safety Set.

7.5.8 Safety Analyses (Parts A and B)

All safety parameters will be summarized using the Safety Analysis Set.

Medical history, prior medications, concomitant medications, and compliance/exposure will be summarized by treatment group using descriptive statistics. Safety data such as reported and observed AEs, TEAEs, SAEs, clinical laboratory results, vital signs, physical examinations and neurological findings, ECGs, and the different rating scales (YMRS, C-SSRS, AIMS, BARS, and SAS) will be summarized by visit (Part A and Part B) and treatment group (Part A). Parameters planned to be collected more than once at pre-specified timepoints will be analyzed as an average of the measures for the relevant time point, including screening and baseline.

Observed and reported AE terms will be coded using the latest version of MedDRA. TEAEs will be defined as any AEs, regardless of the relationship to study drug, that occur or worsen in intensity after the first dose of study drug and within 14 days after the last dose of study drug. Study-drug-related TEAEs will be defined as any AEs that are considered by the investigator to be either possibly, probably, or definitely related to study drug. If relationship to study drug is missing, the TEAE will be considered as treatment-related. TEAEs, and SAEs will be listed summarized by SOC, PT, relationship to study drug, intensity (Part A and Part B) and treatment group (Part A). Patients who discontinue study or study drug due to an AE will be listed and summarized by SOC and PT (Parts A and B) and by treatment group (Part A).

Laboratory assessments, including hematology and chemistry, vital signs, and ECGs, will be listed and summarized by visit and time point (Parts A and B and by treatment group (Part A). Summaries will include actual and change from baseline values, incidence of abnormal values according to normal range criteria, shifts from baseline to each visit and

time point according to markedly abnormal criteria, and listings of patients meeting markedly abnormal criteria.

The observed and change from baseline in YMRS, AIMS, BARS, SAS and C-SSRS scores will be summarized by visits (Part A and B) and by treatment group (Part A).

Additional details for analyses on safety parameters will be provided in the statistical analysis plan.

[redacted]

7.5.10 Interim Analysis

One IA is planned during Part A of the study, after 375 patients have completed the 6-week treatment period or confirmed to have discontinued treatment or study. The IA will be conducted such that the ongoing study integrity is maintained, and the interim data will be reviewed by an independent external unblinded DMC.

The IA will be used to review interim safety and efficacy data and reassess the assumptions on variability and effect size. It may be used for a decision to terminate the study due to superior efficacy or to adjust the sample size. Additional details regarding the statistical analysis methodology will be provided in the SAP.

7.6 Data Quality Assurance

To ensure compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements, ITI or its designee may conduct a quality assurance audit of the study site records and regulatory agencies may conduct a regulatory inspection at any time during or after the study. In the event of an audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues. Responsibility for the accuracy, completeness, and reliability of the study data presented to the sponsor lies with the investigator generating the data.

7.6.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include records of screening assessments such as the SCID-5-CT (Table 6–1), laboratory reports, and ECG strips.

Investigative site personnel will enter patient data into electronic data capture (EDC). All eCRF fields are to be filled in. If an item is not available or is not applicable, this fact should be indicated. Blank fields should not be present unless otherwise directed. The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

Clinical data management will be performed in accordance with applicable ITI standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medication terms will be coded using MedDRA, an internal validated medication dictionary.

After database lock, each study site will receive a CD-ROM containing all of their study site-specific eCRF data as entered into the EDC, including full discrepancy and audit history. Additionally, a CD-ROM copy of all of the study site's data will be created and sent to the

sponsor for storage. The CRO will maintain a duplicate CD-ROM copy for their records. In all cases, patient initials will not be collected or transmitted to the sponsor.

8 Ethics

8.1 Independent Ethics Committee or Institutional Review Board

Federal regulations and the International Council for Harmonisation (ICH) guidelines require that approval be obtained from an IRB before participation of human patients in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with ICH harmonised tripartite guideline E6(R1): GCP will be maintained by the study site and will be available for review by the sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address; the clinical protocol by title, protocol number, or both; and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB. The investigator must promptly supply the sponsor or its designee, the IRB, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to patients.

8.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

8.3 Patient Information and Consent

A written informed consent in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50 shall be obtained from each patient before entering the study or performing any unusual or nonroutine procedure that involves risk to the patient. An informed consent template may be provided by the sponsor to investigative sites. If any institution-specific

modifications to study-related procedures are proposed or made by the study site, the consent should be reviewed by the sponsor, its designee, or both before IRB submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form.

Before recruitment and enrollment, each prospective patient or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study by signing the ICF.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient or legal guardian.

9 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB and will not result in protocol amendments.

9.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the US FDA, or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor the CRO is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor the CRO is financially responsible for further treatment of the patient's disease.

9.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R1) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB approval
- Original investigator-signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae for the investigator and each subinvestigator listed on Form FDA 1572
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after study completion.
- IRB-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardian, and
- Laboratory certifications and normal ranges for any local laboratories used by the study site, in accordance with 42 CFR 493

9.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R1). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins.

9.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R1) and all applicable guidelines and regulations.

9.6 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the time line and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB, as appropriate.

9.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any required reports.

9.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

9.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

10 Study Management

10.1 Monitoring

10.1.1 External Data Monitoring Committee

There will be an external DMC for this study which will review the unblinded interim efficacy and safety data. Additional details regarding the DMC will be provided in the SAP the DMC Charter.

10.1.2 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation to closely follow the study. In doing so, the monitor will visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact with the investigator and study site. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

10.1.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (e.g., FDA or other regulatory agency) access to all study records.

The investigator should promptly notify the sponsor and the CRO of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

10.2 Management of Protocol Amendments and Deviations

10.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB for approval before patients can be enrolled into an amended protocol.

10.2.2 Protocol Deviations

The investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study patients without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the patient or investigator that results in a significant, additional risk to the patient. Significant deviations can include nonadherence to inclusion or exclusion criteria, enrollment of the patient without prior sponsor approval, or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the patient being withdrawn from the study (Section 4.1.3).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB should be notified of all protocol deviations in a timely manner.

10.3 Study Termination

Although ITI has every intention of completing the study, ITI reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last patient completes the last visit (includes follow-up visit).

10.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Upon completion of the clinical study report, the study results will be posted on publicly available clinical trial registers.

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