NCT02600507

Study ID: ITI-007-402

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Assess the Efficacy and Safety of ITI-007 Adjunctive to Lithium or Valproate in the Treatment of Patients With Major Depressive Episodes Associated With Bipolar I or II Disorder (Bipolar Depression)

Protocol Amendment Version 1.5 Date: September 4, 2019

CLINICAL STUDY PROTOCOL
ITI-007-402

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

Confidential

[redacted]

Version of Amended Protocol: Version 1.5

Date of Amended Protocol: 04 September 2019

EudraCT No.: 2018-002749-12

CONFIDENTIAL

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

Protocol Approval – Sponsor Signatory

Study Title	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Assess the Efficacy and Safety of ITI-007 Adjunctive to Lithium or Valproate in the Treatment of Patients with Major Depressive Episodes Associated with Bipolar I or Bipolar II Disorder (Bipolar Depression)
Protocol Number:	ITI-007-402
Protocol Version	1.5
Amended Protocol Date	04 September 2019

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 to assess the efficacy and safety of ITI-007 adjunctive to lithium or valproate in the treatment of patients with major depressive episodes associated with bipolar I or bipolar II disorder (bipolar depression)" and the accompanying associated Investigator's Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Amended Protocol version 1.5, dated 04 September 2019, 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 (the Sponsor) 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 sub-investigator.

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 the Sponsor.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

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Protocol Synopsis

Protocol Number:	ITI-007-402
Title:	A Phase 3, randomized, double-blind, placebo-controlled, multi-center study to assess the efficacy and safety of ITI-007 adjunctive to lithium or valproate 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 93 study sites globally
Indication:	Major depressive episodes associated with bipolar I or bipolar II disorder (bipolar depression)
Rationale:	Bipolar disorder is a serious psychiatric disorder associated with shifts in mood including manic or hypomanic episodes, depressed episodes, or mixed episodes. Every year bipolar disorder affects approximately 2.6% of the United States (US) population age 18 years and older, according to the National Institute of Mental Health. Bipolar depression, the predominant presentation of bipolar disorder, remains a significantly underserved medical need, with only a few regulatory-approved treatment options available. Lithium and valproate have shown efficacy in treating the mania of bipolar disorder and are used as mood stabilizer monotherapy in first-line treatment for people with acute bipolar depression. However, monotherapy with mood stabilizers has been less effective in treating the depressive phase of the disease. Little evidence exists to guide adjunctive therapy of bipolar disorder, where drugs could be added to the mood stabilizers to treat the depressive symptoms of the disease. Antidepressants are commonly used as adjunctive therapy for patients with bipolar disorder, although concerns exist regarding their efficacy and their potential to induce manic switching or reduce cycle length. Hence, a significant need exists for an adjunctive agent that can be combined with mood stabilizers in patients with bipolar depression. 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 (D2) receptors in vivo, with mesolimbic/mesocortical selectivity. ITI-007 also increases the phosphorylation of the NR2B, or GluN2B, subunit of N-methyl-D-aspartate channels in extrastriatal dopamine-rich brain

regions (eg, nucleus accumbens), and indirectly modulates glutamatergic (NDMA and AMPA) activity downstream from dopamine 1 receptor activation.

Evidence supports the use of D2 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 D2 antagonism that appears efficacious in bipolar disorder and other pharmacological properties that may confer better safety and tolerability than other D2 antagonists. As a 5-hydroxytryptomine 2A (5-HT2A) receptor antagonist and serotonin reuptake inhibitor, ITI-007 is predicted to have antidepressant efficacy with fewer side effects than selective serotonin reuptake inhibitors. ITI-007's indirect glutamatergic modulation in combination with serotonin reuptake inhibition predicts rapid-acting antidepressant response. 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-HT2C and no measurable affinity for histamine 1 (H1) 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 study. ITI-007 rapidly penetrated the brain, showed long-lasting and dose-related occupancy, and was generally safe and well-tolerated. Cortical 5 HT2A 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 D2 occupancy (average of 29%) and up to 31% striatal serotonin transporter (SERT) occupancy (average of 22%). Together, these data confirm a central mechanism for ITI-007 at dopaminergic and serotonergic brain targets. An additional PET study in patients with schizophrenia (ITI-007-008) demonstrated an average of approximately 40% striatal D2 receptor occupancy at 60 mg, at plasma steady state, lower than that observed with most antipsychotic drugs. Relatively

low striatal D2 receptor occupancy likely contributes to a relatively low liability for extrapyramidal side effects and hyperprolactinemia compared with most antipsychotic drugs.

Clinical data from 3 well-controlled studies in patients with schizophrenia (ITI-007-005, ITI-007-301, and ITI-007-302) are consistent with respect to the pharmacological profile and prediction for antidepressant effects with favorable safety and tolerability. In these 3 studies, ITI-007 has been safely administered once daily for up to 42 days at doses ranging from 20 to 140 mg. Furthermore, the ITI-007 60 mg dose had a similar trajectory and magnitude of improvement in psychosis as demonstrated a reduction from baseline in the Positive and Negative Syndrome Scale (PANSS) total score in all 3 studies, which was statistically significant at Day 28 compared with placebo in 2 of these studies (ITI-007-005 and ITI-007-301). In addition to improving psychotic symptoms, ITI-007 also improved symptoms of depression in patients with schizophrenia and comorbid depression at baseline. Safety data from these and other trials with ITI-007 have shown that ITI-007, which has been administered to more than 1500 individuals, is well tolerated across a dose range from 1 to 140 mg and administered once daily for up to 42 days with a safety profile similar to placebo. 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:

Primary Objective

The primary objective of this study is to compare the efficacy of 2 doses of ITI-007 adjunctive to treatment with lithium or valproate, administered orally once daily, to that of placebo adjunctive to treatment with lithium or valproate as measured by mean change from baseline to Day 43 in the total score of the rater-administered Montgomery-Åsberg Depression Rating Scale (MADRS) in patients with bipolar depression.

Key Secondary Efficacy Objective

The key secondary efficacy objective of this study is to compare the efficacy of 2 doses of ITI-007 adjunctive to treatment with lithium or valproate, administered orally once daily to that of placebo adjunctive to lithium or valproate as measured by mean change from baseline to Day 43 in the Clinical Global Impression Scale-Bipolar Version-Severity (CGI-BP-S)-Depression score in patients with bipolar depression.

[redacted]

- [redacted]

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The safety objectives of this study are to determine the safety and tolerability of 2 doses of ITI-007 adjunctive to treatment with lithium or valproate via:

- Incidence of adverse events (AEs)
- Physical examination and neurological findings
- 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

[redacted]

Patient Population

Patient 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) (US sites only) or by the Mini International Neuropsychiatric Interview (MINI; non-US sites only) and meeting all of the following 6 criteria:

a. The start of the current major depressive episode (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 CGI-BP-S-Depression score and CGI-BP-S Overall score each ≥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;

f. A minimum of 28 days of treatment with either lithium (and 0.4 to 1.5 mEq/L blood level at screening) or valproate (minimum 25 µg/mL blood level at screening) and inadequate therapeutic response of depressive symptoms (confirmed by the treating health care provider or other reliable source). A re-test of

lithium or valproate levels is not permitted; any patient who does not meet either of the two requirements must be screen-failed.

4. Has a body mass index (BMI) of 18 to 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% 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.

Patient 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 negative serum and urine pregnancy tests at Screening. On Day 1, female patients of childbearing potential must have a negative urine pregnancy test 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 (US sites only) or by the Mini International Neuropsychiatric Interview (MINI; non-US sites only), 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. Eating disorder;
   d. Primary diagnosis of obsessive-compulsive disorder;
   e. Moderate or severe substance use disorder (including for cannabis, excluding for nicotine);
   f. 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 Criterion 4. The presence of these symptoms should be reviewed with the Medical Monitor and adjudication team on a case-by-case basis prior to inclusion;
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, as 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 Food and Drug Administration (FDA)-approved medications for bipolar depression (lurasidone, quetiapine, or Symbyax, depending on the region) at an adequate dose (per regulatory-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, (meth) amphetamines, alcohol, barbiturates, or hallucinogens or similar compounds;

    Note: Previous occasional use of alcohol or cannabis (but not synthetic marijuana/K2/Spice) or prescribed psychotropic (eg, 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 one of the following agents under the specified conditions:

a. Lifetime exposure to ITI-007 (ie, for US sites only, participation 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 short-acting anxiolytic medications within 1 week of the baseline visit or of 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, zolpidem CR, or lorazepam as needed, no more than 3 times per week, allowed during the screening period and the first 2 weeks of the treatment period). Note: If zolpidem, zolpidem CR, or lorazepam are not available in specific regions, another sedative hypnotic or benzodiazepine may be approved by the Medical Monitor. Medications may not be used in combination to treat insomnia.

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

iii. Anticonvulsants except valproate;

iv. Mood stabilizers except lithium or valproate, antipsychotics, antidepressants;

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 and medical foods are excluded unless 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 × upper limit of normal (ULN);

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

    c. Alkaline phosphatase >2.0 × ULN;

    d. Gamma-glutamyl transpeptidase >2.0 × ULN

    e. Total bilirubin >1.5 × ULN;

    f. Serum creatinine >1.5 × ULN;

    g. Blood urea nitrogen >1.5 × ULN;

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

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

    j. 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 for males and females and/or heart rate ≤50 beats per minute, or evidence of clinically significant bundle-branch block. If a patient meets the QTcF and/or heart rate exclusion criteria during the screening

period, repeat ECG testing will not be permitted.
Note: If it is the opinion of the Investigator that a lower heart rate is physiological in a well-fit subject or due to stable concomitant medications, this will be reviewed and approved by the Medical Monitor on a case by case basis.

Note: Medical conditions that are stable with medication (eg, 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 A_{1c} [HbA_{1c}] >53 mmol/mol [7.0%] at screening with no re-test allowed for HbA_{1c}), 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. The patient has a history of hepatitis B or hepatitis C infection (or is tested positive for hepatitis B surface antigen or hepatitis C antibodies) *AND* at screening has evidence of active disease defined as elevated ALT, AST, or bilirubin levels as specified in Exclusion Criterion 14;
18. The patient is an employee of the Investigator or study site, or immediate family (ie, spouse, parent, child, or sibling, whether

biological or legally adopted) of such employees, the Investigator, the Sponsor, or contract research organizations (CROs) 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) or unable to safely continue on current treatment with lithium or valproate;
20. The patient is judged by the Investigator to be inappropriate for the study.

Study Design

This is a Phase 3, randomized, double-blind, parallel-group, placebo-controlled study. The study consists of the following periods: screening period, on-treatment period, and safety follow-up period.

Screening Period (2 Weeks)

Eligible patients will be evaluated during a screening period up to 2 weeks in duration to ensure sufficient washout of prior and/or restricted medications. Extension of the Screening Period may be approved by the Sponsor or its representative on a case-by-case basis.

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, including therapeutic levels of lithium or valproate, will be randomly assigned to either adjunctive ITI-007 or placebo in 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 in combination with lithium or valproate: 40-mg ITI-007, 60-mg ITI-007, or matching placebo. The random assignment will be stratified for both first-line treatment (with lithium or valproate) and diagnosis at screening (Bipolar I or Bipolar II Disorder).

Double-blind On-treatment Period (6 Weeks)

Patients will take their first dose of study medication the evening of their baseline visit. A single dose will be taken each day in the evening, with or without food, for the duration of the on-treatment period.

Following randomization, patients will attend the clinic at Days 8, 15, 22, 29, 36, and 43.

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

Safety Follow-up Period (2 Weeks)

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 withdraw prematurely will be seen for an early termination visit (within 1 week of early termination, when possible) and will be asked to return to the clinic for a safety follow-up visit 2 weeks following withdrawal.

Estimated Study Duration:	For each patient completing the study, the study will be approximately 10 weeks in duration (9 visits).
Efficacy Assessments:	The efficacy assessments will include: the MADRS, CGI-BP-S, SDS, Q-LES-Q-SF, WHO-5, and NEO-FFI.
[redacted]	[redacted]
Safety Assessments:	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 including assessment of maintenance of blood levels of lithium (0.4 to 1.5 mEq/L) and valproate (minimum 25 µg/mL); ECG evaluations; vital sign measurements; and physical and neurological examination.
Study Drug, Dosage, and Route of Administration:	Patients will be assigned to receive either ITI-007 (40 mg or 60-mg dose) or placebo in combination with lithium or valproate. 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 along with their concomitant dose of lithium or valproate.

Statistical Methods

Sample Size: Approximately 520 patients will be randomly assigned in a 1:1:1 ratio to 1 of the 3 treatment arms (ITI-007 40 mg, ITI-007 60 mg, and placebo). Assuming a common drop-out rate of 15% and a common correlation of 0.7, the sample size of 173 patients per treatment group will provide approximately 90% statistical power for the effect size of 0.4 for the primary efficacy endpoint in the ITI-007 60 mg treatment group. .

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

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

The Intent-to Treat (ITT) Set will contain all randomly assigned patients who received at least 1 dose of study medication and who had a valid baseline (pre-dose) measurement and at least 1 valid post-baseline measurement of MADRS.

The Sensitivity Set will contain all randomly assigned patients who received at least 1 dose of study medication and who had a valid baseline (pre-dose) measurement MADRS total score.

The Safety Set will be used for analysis of safety endpoints. The Safety Set will contain all patients who took at least 1 dose of study medication. All analyses using the Safety Set will classify patients according to treatment actually received.

The PK Set will contain all patients who received study medication, had a valid baseline (pre-dose) measurement, had at least 1 valid post-baseline measurement of MADRS, and had at least 1 PK sample collected and analyzed.

Patient Disposition, Demographics, and Other Baseline Data

Patient disposition will be summarized by treatment group, when applicable, and overall, and by study visit when applicable, including incidence of screening failure and incidence of treatment or study discontinuation and the corresponding reasons. Time to treatment discontinuation due to all reasons, AEs (all, AEs associated with worsening of bipolar depression, and AEs not

associated with worsening of bipolar depression), lack of efficacy, or due to any other reason of special interest will be evaluated using the Kaplan-Meier method. The Log-rank test will be used to compare the time to discontinuation between each treatment group and the placebo group.

Demographic and baseline characteristics, including bipolar disorder diagnosis and baseline efficacy measures, will be listed and summarized by treatment group and overall using descriptive statistics. 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 and treatment group using frequencies and percentages.

Additionally, the number and percent of patients receiving concomitant medications of special interest, such as lithium, valproate, zolpidem, zolpidem CR, or lorazepam, 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 with ITI-007

Study Medication Exposure and Treatment Compliance
Exposure to study medication and treatment compliance will be presented for the Safety Analysis and ITT Sets. Duration of exposure (days) and dosing compliance (%) will be calculated and summarized by treatment group. In addition, the number and percentage of patients exposed to study medication will be presented by planned study week.

Analysis of the Primary Efficacy Endpoint

The treatment effect on the primary efficacy endpoint will be evaluated using a mixed-effect 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 group, site (or pooled site), and the stratification variables (first-line treatment [lithium or valproate] and Bipolar Disorder type at Screening [I or II]), and the interaction term for treatment group-by-visit as fixed effects, the baseline MADRS total score and the interaction term of baseline MADRS-by-visit as covariates. An unstructured covariance matrix will be used to model the covariance of within-patient scores. The Kenward-Roger approximation (Kenward and

Roger, 1997) will be used to estimate denominator degrees of freedom. This analysis will be performed based on all postbaseline scores using only the observed cases without imputation of missing values.

Sensitivity analyses will be performed for the primary efficacy endpoint to assess the robustness of the MMRM results under a different assumption on the mechanism of missing data.

An estimand framework will also be employed to assess the efficacy of ITI-007.

Safety Analyses

All safety parameters will be summarized using the Safety Set.

Safety data such as clinical laboratory results, vital signs, physical and neurological examination findings, ECGs, and the different rating scales (YMRS, C-SSRS, AIMS, BARS, and SAS) will be summarized by treatment group and visit. When appropriate, out-of-range values will be flagged in data listings and tabulated. Shift tables will be prepared for pre-specified safety measures, such as selected laboratory parameters, ECG, and BMI, based on markedly abnormal criteria.

Reported AE terms will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). All treatment-emergent AEs (TEAEs), treatment-related TEAEs, and serious TEAEs will be summarized by treatment group, primary system organ class, and preferred terms and will be further broken down by severity and relationship to study medication. Additional details for analyses on safety parameters will be provided in the Statistical Analysis Plan (SAP).

[redacted]

[redacted]

Blinded Sample Size Re-estimation

A blinded sample-size re-estimation may be performed when 70% of patients either complete or discontinue from the study.

Details on the blinded sample size re-estimation will be provided in the SAP.

Date of Protocol: 04 September 2019

List of Abbreviations

Abbreviation	Definition
5-HT_{2A}	5-hydroxytryptomine 2A (receptor)
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AR	autoregressive
ARH	heterogeneous autoregressive
AST	aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
BPI	Bipolarity Index
CFR	Code of Federal Regulations
CGI-BP-S	Clinical Global Impression Scale of Bipolar Illness – Severity of Illness
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
FA0(q)	No Diagonal Factor Analytic
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H_1	histamine 1 (receptor)
HbA_{1c}	glycated hemoglobin A_{1c}
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation

IEC	Independent Ethics Committee
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
LSM	least-squares mean
MADRS	Montgomery-Åsberg Depression Rating Scale
MDE	major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed-effect model repeated measures
NEO-FFI	Neuroticism, Extraversion, and Openness to Experience-Five Factor Inventory
PET	positron emission tomography
PK	pharmacokinetic
PP	per-protocol
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form
QTcB	corrected QT interval using the Bazett formula
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
SIGMA	Structured Interview Guide for the MADRS
TEAE	treatment-emergent adverse event
TOEP	Toeplitz structure
TOEPH	heterogeneous Toeplitz structure
ULN	upper limit of normal

US	United States
WHO-5	World Health Organization-5 Well-being Index
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 (MDEs). Bipolar disorder affects approximately 5.7 million adult Americans, or about 2.6% of the United States (US) population aged 18 years and older, every year according to the National Institute of Mental Health, with a similar prevalence worldwide. 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 regulatory-approved treatment options available.

Lithium and valproate have shown efficacy in treating the mania of bipolar disorder and are used as mood stabilizer monotherapy in first-line treatment for people with acute bipolar depression. However, monotherapy with mood stabilizers has been less effective in treating the depressive phase of the disease (Van Lieshout, 2010). Little evidence exists to guide adjunctive therapy of bipolar disorder, where drugs could be added to the mood stabilizers to treat the depressive symptoms of the disease (Loebel, 2014a). Antidepressants are commonly used as adjunctive therapy for patients with bipolar disorder, although concerns exist regarding their efficacy and potential to induce manic switching or reduce cycle length (Sidor, 2011; Vázquez, 2013). Hence, a significant need exists for an adjunctive agent that can be combined with mood stabilizers in patients with bipolar depression (Loebel, 2014a).

Intra-Cellular Therapies (ITI), the Sponsor, is developing ITI-007, a new chemical entity, for the treatment of patients with MDEs associated with bipolar I or bipolar II disorder (bipolar depression) and for the treatment of agitation associated with dementia, including Alzheimer's disease. ITI-007 is currently in Phase 3 clinical development in the US for the treatment of schizophrenia.

ITI-007 is a novel small molecule therapeutic agent designed specifically to combine serotonergic, dopaminergic, and glutamatergic modulation in a dose-dependent manner. ITI-007 is a potent serotonin 5-hydroxytryptomine 2A (5-HT_{2A}) receptor antagonist with mesolimbic/mesocortical selective modulation of phosphoprotein pathways downstream of dopamine receptors, serotonin reuptake inhibition, and indirect glutamatergic modulation

(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 D_2 receptors in vivo, with mesolimbic/mesocortical selectivity. ITI-007 also increases the phosphorylation of the NR2B, or GluN2B, subunit of N-methyl-D-aspartate channels in extrastriatal dopamine-rich brain regions (eg, nucleus accumbens), and indirectly modulates glutamatergic (NDMA and AMPA) activity downstream from dopamine 1 receptor activation.

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. ITI-007's indirect glutamatergic modulation in combination with serotonin reuptake inhibition predicts rapid-acting antidepressant response. 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 histamine 1 (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 Investigator's Brochure (June 2018).

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.

Brain receptor target engagement was confirmed in healthy male volunteers in the ITI-007-003 positron emission tomography (PET) Phase 1 clinical study (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. An additional PET study in patients with schizophrenia (ITI-007-008) demonstrated an average of approximately 40% striatal D_2 receptor occupancy at 60 mg, at plasma steady state, lower than that observed with most antipsychotic drugs. Relatively low striatal D_2 receptor occupancy likely contributes to a relatively low liability for extrapyramidal side effects and hyperprolactinemia compared with most antipsychotic drugs.

Clinical data from 3 well-controlled studies in patients with schizophrenia (ITI-007-005, ITI-007-301, and ITI-007-302) are consistent with respect to the pharmacological profile and prediction for antidepressant effects with favorable safety and tolerability. In these 3 studies, ITI-007 has been safely administered once daily for up to 42 days at doses ranging from 20 to 140 mg. Furthermore, the ITI-007 60 mg dose had a similar trajectory and magnitude of improvement in psychosis as demonstrated a reduction from baseline in the Positive and Negative Syndrome Scale (PANSS) Total Score in all 3 studies, which was statistically significant at Day 28 compared with placebo in 2 of these studies (ITI-007-005 and ITI-007-301). In addition to improving psychotic symptoms, ITI-007 also improved symptoms of depression in patients with schizophrenia and comorbid depression at baseline. Safety data from these and other trials with ITI-007 have shown that ITI-007, which has been administered to more than 1500 individuals, is well tolerated across a dose range from 1 to 140 mg and administered once daily for up to 42 days with a safety profile similar to placebo. These clinical data together with the nonclinical data and the pharmacological profile support the development of ITI-007 for the treatment of bipolar depression. Details on the profile of ITI-007 can be found in the ITI-007 Investigator's Brochure.

2 Study Objectives

2.1 Primary Efficacy Objective

The primary objective of this study is to compare the efficacy of 2 doses of ITI-007 adjunctive to treatment with lithium or valproate, administered orally once daily, to that of placebo adjunctive to treatment with lithium or valproate as measured by mean change from baseline to Day 43 in the total score on the rater-administered Montgomery-Åsberg Depression Rating Scale (MADRS) in patients with bipolar depression.

2.2 Key Secondary Efficacy Objective

The key secondary efficacy objective of this study is to compare the efficacy of 2 doses of ITI-007 adjunctive to treatment with lithium or valproate, administered orally once daily to that of placebo adjunctive to lithium or valproate as measured by mean change from baseline to Day 43 in the Clinical Global Impression Scale-Bipolar Version-Severity (CGI-BP-S)-Depression score in patients with bipolar depression.

2.4 Safety Objectives

The safety objectives of this study are to determine the safety and tolerability of 2 doses of ITI-007 adjunctive to treatment with lithium or valproate via:

- Incidence of adverse events (AEs);
- Physical examination and neurological findings;

As well as change from baseline in the following safety assessments:

- 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.

[redacted]

[redacted]

3 Investigational Plan

3.1 Study Design

This is a Phase 3, randomized, double-blind, parallel-group, placebo-controlled study comparing the efficacy and safety of ITI-007 versus placebo administered orally once daily in patients with bipolar depression who have had inadequate response to their depression symptoms and are currently taking one of the mood stabilizers, lithium or valproate.

The study consists of the following periods: screening period, on-treatment period, and safety follow-up period.

Screening Period (2 Weeks)

Eligible patients will be evaluated during a Screening Period up to 2 weeks in duration to ensure sufficient washout of prior and/or restricted medications. Extension of the Screening Period may be approved by the Sponsor or its representative on a case-by-case basis.

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 and must remain on-treatment with lithium or valproate for the duration of the study.

[redacted]

At Baseline (Visit 2), patients who continue to meet all eligibility criteria, including therapeutic levels of lithium or valproate, will be randomly assigned to either adjunctive ITI-007 or placebo in 1 of the 3 treatment arms for a 6-week, double-blind treatment period. Patients will be randomly assigned to one of the following groups in combination with lithium or valproate: 40-mg ITI-007, 60-mg ITI-007, or matching placebo. The random assignment will be stratified for both the first-line treatment (with lithium or valproate) and diagnosis at screening (Bipolar I or Bipolar II Disorder).

Double-blind On-treatment Period (6 Weeks)

Patients will take their first dose of study medication the evening of their baseline 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 Days 8, 15, 22, 29, 36, and 43.

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

Safety Follow-up Period (2 Weeks)

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 withdraw prematurely will be seen for an early termination visit (within 1 week of early termination, when possible) and will be asked to return to the clinic for a safety follow-up visit 2 weeks following withdrawal.

3.1.1 Rationale of Study Design

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 either to ensure washout of excluded medication with long half-life (eg, fluoxetine), under the supervision of the Investigator before baseline or to ensure minimum exposure of at least 28 days to mood stabilizer (lithium or valproate) that is required to have been started by the patients of their own will, under standard of care, before the start of screening. 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. The stratified randomization will ensure that all treatment groups are balanced with regards to first-line treatment (lithium or valproate) and with regards to bipolar disorder diagnosis at study entry. 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.

Two ITI-007 doses, as adjunctive therapy with the mood stabilizers, lithium or valproate, 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 the present study, ITI-007 40 mg and ITI-007 60 mg, 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.

The placebo control group is needed to establish the efficacy of a new compound.

The treatment duration of 6 weeks has been chosen because this is considered an acceptable period to demonstrate efficacy in this patient population.

4 Patient Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 520 patients (173 patients/arm) will be enrolled at approximately 93 study sites globally. Patients will be randomly assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

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.

Appropriateness of patient eligibility will be adjudicated as described in Section 3.1. Once a final decision is made, no waivers for exceptions will be provided.

4.1.1 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) (US sites only) or by the Mini International Neuropsychiatric Interview (MINI; non-US sites only) and meeting all of the following 6 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 CGI-BP-S Depression and Overall scores each ≥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;

f. A minimum of 28 days of treatment with either lithium (and 0.4 to 1.5 mEq/L blood level at screening) valproate (minimum 25 µg/mL blood level at screening) and inadequate therapeutic response of depressive symptoms (confirmed by the treating health care provider or other reliable source). A re-test of lithium or valproate levels is not permitted; any patient who does not meet either of the two requirements must be screen failed.

4. Has a body mass index (BMI) of 18 to 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% 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 nonchildbearing 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 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 negative serum and urine pregnancy tests at screening. On Day 1, female patients of childbearing potential must have a negative urine pregnancy test 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, (US sites only) or by the Mini International Neuropsychiatric Interview (MINI; non-US sites only), 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. Eating disorder;

d. Primary diagnosis of obsessive-compulsive disorder;

e. Moderate or severe substance use disorder (including for cannabis, excluding for nicotine);

f. 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 Criterion 4. The presence of these symptoms should be reviewed with the Medical Monitor and adjudication team on a case-by-case basis prior to inclusion;

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 Food and Drug Administration (FDA)-approved medications for bipolar depression (lurasidone, quetiapine, or Symbyax, depending on the region) at an adequate dose (per regulatory-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;

    Note: Previous occasional use of alcohol or cannabis (but not synthetic marijuana/K2/Spice) or prescribed psychotropic (eg, 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 one of the following agents under the specified conditions:
    a. Lifetime exposure to ITI-007 (ie, for US sites only, participation 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 short-acting anxiolytic medications within 1 week of the baseline visit or of 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, zolpidem CR, or lorazepam as needed, no more than 3 times per week, allowed during the screening period and the first 2 weeks of the treatment period); Note: If zolpidem, zolpidem CR, or lorazepam are not available in specific regions, another sedative hypnotic or benzodiazepine may be approved by the Medical Monitor. Medications may not be used in combination to treat insomnia;

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

iii. Anticonvulsants except valproate;

iv. Mood stabilizers except lithium or valproate, antipsychotics, antidepressants;

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 and medical foods are excluded unless 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 the 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 × upper limit of normal (ULN);

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

    c. Alkaline phosphatase >2.0 × ULN;

    d. Gamma-glutamyl transpeptidase >2.0 × ULN;

    e. Total bilirubin >1.5 × ULN;

    f. Serum creatinine >1.5 × ULN;

    g. Blood urea nitrogen >1.5 × ULN;

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

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

j. 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 for males or females and/or heart rate ≤50 beats per minute, or evidence of clinically significant bundle-branch blocks. If a patient meets the QTcF and/or heart rate exclusion criteria during the screening period, repeat ECG testing will not be permitted.
Note: If it is the opinion of the Investigator that a lower heart rate is physiological in a well-fit subject or due to stable concomitant medications, this will be reviewed and approved by the Medical Monitor on a case-by-case basis.

Note: medical conditions that are stable with medication (eg, 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 A_{1c} [HbA_{1c}] >53 mmol/mol [7.0%] at screening with no re-test allowed for HbA_{1c}), 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. The patient has a history of hepatitis B or hepatitis C infection (or is tested positive for hepatitis B surface antigen or hepatitis C antibodies) *AND* at screening has evidence of active disease defined as elevated ALT, AST, or bilirubin levels as specified in Exclusion Criterion 14;
18. The patient is an employee of the Investigator or study site, or immediate family (ie, spouse, parent, child, or sibling, whether biological or legally adopted) of such employees, the Investigator, the Sponsor, or contract research organizations (CROs) 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) or unable to safely continue on current treatment with lithium or valproate;
20. The patient is judged by the Investigator to be inappropriate for the study.

4.2 Withdrawal of Patients from the Study

The planned overall duration of the study for each patient is up to approximately 10 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.

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 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 (eg, pregnancy, development of contraindications of use of study medication);
8. The Investigator or Sponsor decides 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 Sponsor 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 Patient Withdrawals or Patient Discontinuation of Study Intervention

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 medication. 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 adverse event (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

Patients who have been randomly assigned to study medication and prematurely discontinue from the study will not be replaced.

A patient who fails to satisfy inclusion criteria and exhibits any of the exclusion criteria at screening may be rescreened with the permission of the Medical Monitor. 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 screening (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

At Baseline (Visit 2), patients who continue to meet all eligibility criteria, including therapeutic levels of lithium or valproate, will be randomly assigned to one of the following groups in combination with lithium or valproate: 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 based on both treatment with either lithium or valproate and Bipolar I or Bipolar II diagnosis at screening.

The dose of mood stabilizer will be adjusted to maintain a serum level in the range of 0.4 to 1.5 mEq/L for lithium or minimum 25 µg/mL for valproate throughout the study as clinically appropriate per Investigator judgment.

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

5.2 Treatments Administered

Patients will be assigned to receive either ITI-007 (40- or 60-mg doses) or placebo in combination with their standard of care lithium or valproate. Study site personnel will receive a treatment card number from the IVRS/IWRS for each patient at each treatment dispensing 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 with or without food in the evening, and 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 along with their concomitant dose of lithium or valproate.

5.3 Identity of Investigational Product

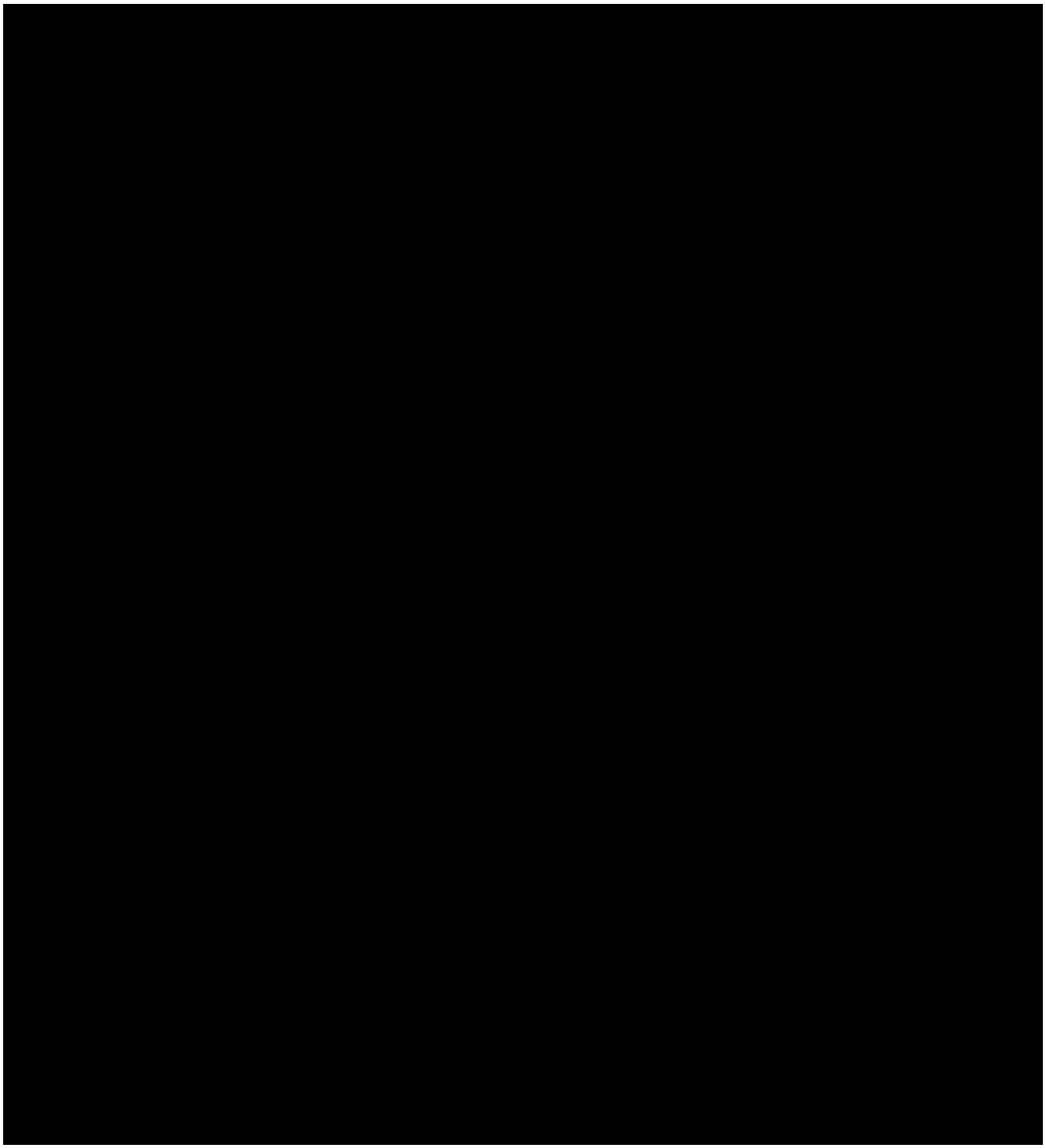
ITI-007 will be supplied as 20- and 60-mg over-encapsulated tablets (capsules) (see Table 5-1). [redacted]

Table 5-1 Study Medication and Dosing Schedule

Study Medication	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.



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

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging and Storage

ITI-007 and matching placebo will be prepared according to current Good Manufacturing Practice standards in carded blister strips and shipped under ambient conditions [redacted] 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 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 1×8 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 medication must be stored in a secure area (eg, 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 to 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. Patients will be instructed to bring the weekly treatment card to the study site at the next visit to assess compliance.

5.4.2 Accountability Procedures for the Study Product

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 medication 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 studies 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 studies 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 (not taking 2 capsules per dose, taking too many capsules 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

The study will be performed in a double-blind manner. All study medication will be supplied in identical treatment cards and packaging, and will be similar in color, smell, taste, and appearance, thereby enabling double-blind conditions.

5.6.1 Breaking the Blind

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 treatment assignment is unblinded will discontinue 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 (Table 6-1). 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.

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 (not taking 1 capsule per dose or taking too many capsules 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.

5.8 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, any short-acting anxiolytic, or any drugs with known psychotropic properties, or any non-psychotropic drugs with potential central nervous system effects. The only exceptions are zolpidem, zolpidem CR, and lorazepam, which may be taken no more than 3 times per week, allowed only during the Screening Period and taken within the first 2 weeks of the Treatment Period (Section 4.1.2, Exclusion Criterion 13). Table 5-4 presents the permitted use of zolpidem, zolpidem CR, and lorazepam. If zolpidem, zolpidem CR, or lorazepam are not available in specific regions, another sedative hypnotic or benzodiazepine may be approved by the Medical Monitor.

Medications may not be used in combination to treat insomnia. If a patient is not able to discontinue use of zolpidem, zolpidem CR, or lorazepam (or equivalent) by the end of the first 2 weeks of the treatment period, the Investigator must contact the Sponsor or Sponsor's representative to discuss the patient's appropriateness to continue in the study.

Table 5-4 Permitted Zolpidem and Lorazepam Use

Concomitant Medication	Dose	Indication	Study Period Allowance	Assessment Restrictions
Zolpidem	Up to 10 mg/day (bedtime)	Insomnia	During screening and first 2 weeks of the treatment period	Prohibited at least 8 hours prior to any psychiatric assessments
Zolpidem CR	Up to 12.5 mg/day (bedtime)	Insomnia		
Lorazepam	Up to 2mg/day	Insomnia, agitation, anxiety		

Note: Zolpidem, zolpidem CR, and lorazepam should be used sparingly and for symptoms severe enough to require treatment as per the Investigator's judgment. Prophylactic use is not allowed. If zolpidem, zolpidem CR, or lorazepam are not available regionally, then an alternative sedative hypnotic or benzodiazepine up to an equivalent maximum dose may be approved for use by the Medical Monitor.

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 (eg, fluoxetine) under the supervision of the Investigator before baseline.

Use of all concomitant medications, including lithium and valproate, 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 Schedule

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.

The schedule of events for the study is presented in Table 6-1. Detailed instructions for the conduct of study assessments and procedures will be provided in the study reference manual.

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 schedule of events in Table 6-1; assessments can be conducted on different days within the Screening Period.

6.1.1 Informed Consent

Before any study-related activities the patient must sign and date an ICF approved by the responsible institutional review board (IRB)/Independent Ethics Committee (IEC). The format and content of the ICF must have been agreed upon by the Investigator, the appropriate IRB/IEC, and the Sponsor.

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. Note: Use of DupCheck applies to US patients only.

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: 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

Each ECG assessment will be a single 10-second epoch from 12-lead ECGs. Electrocardiogram parameters to be measured include heart rate and QRS, PR, QT, QTcB, 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.

6.1.5 Vital Sign, Waist, Weight, and Height Measurements

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 56). It is recommended that vital signs, waist circumference, and weight are always measured after conducting the ECGs, as applicable, and prior to any other assessments, including needle sticks for laboratory or PK samples scheduled for the same visit. Each patient's BMI will be calculated before Day 1 to ensure that the patient meets the BMI inclusion criterion.

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. 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

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, excluding prescription benzodiazepines, prescription opiates, and cannabinoids, or alcohol at screening will be excluded from participating in the study. 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 6.4.2.9.

6.1.10 Serum and Urine Pregnancy Tests

Female patients who are of childbearing potential will undergo serum and urine pregnancy tests at the study clinic at Screening, at the Baseline Visit (Day 1), and, at the discretion of the Investigator, at an Unscheduled Visit. Serum pregnancy testing will be performed using blood collected as part of protocol-specified sample; urine pregnancy testing will use a urine dipstick.

If the urine and serum pregnancy tests at screening are positive, the patient will not be eligible to participate in the study. If a urine pregnancy test is negative and the associated serum pregnancy test is positive, the patient will be discontinued from the study. 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 either the SCID-5-CT, a semi-structured interview for making the major DSM-5 Axis I diagnosis (First, 2014) to be used by US sites only, or by the MINI 7.0.2 (08 August 2016 version) by Dr. David V. Sheehan (Sheehan et al, 1998), to be used by non-US sites. These assessments will be used in this study at screening only to confirm the diagnosis of bipolar depression in patients evaluated for inclusion in the study. The diagnostic assessment will be completed by the Investigator or an expert site-based rater approved by the Sponsor.

6.1.12 Bipolarity Index

The Bipolarity Index (BPI) was designed to provide a measure of quantitative measure of diagnostic confidence by mapping the known information about an individual patient on 5 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 BPI 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. The patient's responses to the BPI and the BPI score generated by the BPI may be reviewed by an independent expert as a component of the systematic patient adjudication process.

The BPI was developed by a group of bipolar disorder experts including Gary Sachs (Sachs, 2004). The scoring system is divided into 5 dimensions including episode characteristics, age of onset (first affective episode), course of illness/associated features, response to treatment, and family history. Each dimension is given a score of 0 to 20 based on its correlation with bipolar disorder characteristics, and the scores are added to derive the BPI score. The

maximum score is 100. The score represents how close the patient is to having bipolar disorder.

The BPI has been used to evaluate diagnostic confidence for patients entering global clinical studies. This assessment will be used by US sites only in conjunction with the SCID-5-CT.

[redacted]

6.1.14 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.

The C-SSRS will be administered by the Investigator or an expert site-based rater, as indicated in the schedule of events (Table 6-1).

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.

6.1.15 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. It will be completed by the Investigator or an expert site-based rater.

Note: Computer-based assessments will be utilized at sites that initiated under Version 1.3 of this protocol or prior versions. Assessments completed at sites initiated with Version 1.4 and any future versions of the protocol will be paper-based.

At each visit with a YMRS assessment, the rater-administered YMRS interviews will be audio recorded (this applies to computer-administered assessment only); at each visit after the screening visit, a computer-administered interview will also be completed by patients. Where computer-administered assessments are not being used, the assessment completed by the patient will be paper-based.

6.1.16 Clinical Global Impression Scale of Bipolar Illness–Severity of Illness

The Clinical Global Impressions Scale has been modified specifically for use in assessing global illness severity and change in patients with bipolar disorder (CGI-BP-S) (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 by the Investigator or another Sponsor-approved expert site-based rater. The Depression score is based on the clinician's assessment of depression symptom severity; the Mania score is based on the clinician's assessment of mania symptom severity; and the Overall score is based on the clinician's overall impression of illness severity.

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 Sponsor-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. The MADRS is administered using a structured interview to ensure reliability and completeness. The format of the interview varies by region based on use of either Structured Interview Guide for the MADRS (SIGMA; when paper forms are used) or a similar interview structure when electronic tablets are used for scoring.

Note: Computer-based assessments will be utilized at sites that initiated under Version 1.3 of this protocol or prior versions. Assessments completed at sites initiated with Version 1.4 and any future versions of the protocol will be paper-based.

Remission of depression based on the MADRS is generally defined as a patient with a MADRS total score of ≤12 at endpoint. A response based 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.

At each visit with a MADRS assessment, the rater-administered MADRS interview will be audio recorded (note: audio-recording applies to computer-based assessments only). At each

visit after screening, 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. Where paper scales are used, the SIGMA will be used to collect data for scoring MADRS.

6.2.2 Clinical Global Impression of Bipolar Illness–Severity

The CGI-BP-S, described in Section 6.1.16, will be a clinical efficacy assessment by the Investigator of each patient's severity of illness. The Clinical Global Impression Scale is a widely accepted measure of illness severity in a variety of psychiatric disorders. The CGI-BP-S will be assessed at Baseline/Visit 2, Visits 3-8, and Visit 9/ET. Details related to the statistical analysis of the CGI-BP-S scores are provided in Sections 7.5.5 and 7.5.6.

6.2.3 Sheehan Disability Scale

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. Note: This scale is to be administered to US patients only.

6.2.4 Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form

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. here 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 World Health Organization-5 Well-Being Index

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 studies (Topp, 2015). Note: This scale is to be administered to US patients only.

6.2.6 Neuroticism, Extraversion, and Openness to Experience-Five Factor Inventory

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 5 dimensions of personality: neuroticism (N), extraversion (E), conscientiousness (C), openness (O), and agreeableness (A). Note: This scale is to be administered to US patients only.

6.3 Patient Placebo-Response Training

A brief training explaining the use of placebo in this study will be provided to all patients at Baseline (Visit 2). In addition, site staff will receive a brief training defining the placebo response in clinical drug trials. Completion of placebo-response training will be documented for both patient and site staff.

6.4 Safety and Tolerability Assessments

All patients who receive study medication 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 and neurological examinations.

6.4.1 Adverse Events

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

6.4.1.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a study patient administered a study medication, 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 medication, 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 6.4.1.2 and 6.4.1.3).

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, 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.

6.4.1.2 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 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.

6.4.1.3 Nonserious Adverse Event

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

6.4.1.4 Definition of Relationship to Study Medication

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

The Investigator will assess the causality/relationship between the study medication and the AE (Table 6-2). One of the following categories should be selected based on medical judgment, considering the following definitions and all contributing factors.

Table 6-2 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 (eg, 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 (eg, 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.

6.4.1.5 Definition of Intensity

The Investigator will assess all AEs for intensity (severity) in accordance with the following standard ratings (Table 6-3):

Table 6-3 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.

6.4.1.6 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.

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.

6.4.1.7 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, ie, 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 medication 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).

6.4.1.8 Notification About Serious or Unexpected Adverse Events

The Investigator will review each SAE (Section 6.4.1.2) and evaluate the intensity and the causal relationship of the event to study medication. 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 medication 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 medication 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 (eg, 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 CRO before study initiation.

6.4.1.9 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 6.4.1.2, 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.

6.4.1.10 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 medication 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 medication 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.

6.4.2 Other Safety Assessments

6.4.2.1 C-SSRS

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

6.4.2.2 YMRS

The YMRS will be completed at screening, baseline, and at every subsequent scheduled clinic visit (Table 6-1). Details of the YMRS are presented in Section 6.1.15.

6.4.2.3 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 (ie, 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).

6.4.2.4 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).

6.4.2.5 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 (eg, 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).

6.4.2.6 Vital Sign Measurements

Vital signs will be measured at screening and at every subsequent scheduled clinic visit (Table 6-1). Details of the vital sign measurements are presented in Section 6.1.5.

6.4.2.7 ECG Assessments

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

6.4.2.8 Physical and Neurological Examination

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

6.4.2.9 Laboratory Analyses

Blood and urine samples collected from patients will be forwarded to a central laboratory for analysis. The Investigator must review all laboratory results for all patients. If a laboratory value is reported as deleted, cancelled, unable to perform, or otherwise missing, the test must be repeated as soon as possible. If the Investigator determines that the missing value does not require an immediate repeat, he/she must provide clinical reasoning to the Sponsor or its representative.

Additional 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), after any scheduled ECG or vital signs have been recorded, and prior to dosing with study medication. Samples for clinical laboratory analysis will be used only for the evaluation of safety and tolerability.

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. Thyroid panel (thyroid-stimulating hormone) will be assayed at Screening (Visit 1) and at Visit 8 (end of Treatment Period) or at Visit 9 (Early Discontinuation). 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).

Drug Assays: Lithium and valproate blood levels will be assessed at screening and at each specified visit to assess maintenance within the respective therapeutic ranges.

6.5 Safety Monitoring Committee

No safety monitoring committee will be used for the study.

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. To ensure patient safety, each pregnancy must be reported to the Sponsor 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.

Completion of the pregnancy form is not required for screen-failed patients who have had positive pregnancy test(s).

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 the Sponsor.

7 Statistical and Analytical Plan

A formal and detailed statistical analysis plan (SAP) will be finalized prior to the planned interim analysis and will provide further details regarding the definition of analysis endpoints, analysis methodology, and the interim analysis to address all study objectives. Changes made to the data analysis methods as described in this 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 unblinding, will be documented, and justified in the final clinical study report.

A blinded data review will be conducted prior to unblinding the patients' treatment assignments for assessing the accuracy and completeness of the study database and defining analysis sets.

7.1 Analysis Endpoints

7.1.1 Primary Efficacy Endpoints

The primary efficacy endpoint is the change from baseline to Day 43 in the rater-administered MADRS total score.

7.1.2 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the mean change from baseline to Day 43 in the CGI-BP-S-Depression score.

7.1.4 Safety Endpoints

- AEs;
- YMRS total score;
- C-SSRS scores;
- AIMS scores;

- BARS scores;
- SAS score;
- Physical examination and neurological findings;
- Vital signs (blood pressure, heart rate), weight, and waist circumference;
- ECGs;
- Clinical laboratory evaluations.

7.2 Sample Size Calculations

The sample size calculation of the study is based on the primary efficacy endpoint, the change from baseline to Day 43 in MADRS total score. Adjusting for multiple comparisons of two ITI-007 treatment groups with placebo by using the fixed sequence procedure (test the 60 mg vs placebo first, and if statistically significant then proceed to test the 40 mg placebo vs placebo), a sample size of approximately 520 patients (173 per group) will provide approximately 90% power to detect an effect size of 0.4. This sample size estimation also assumes a common dropout rate of 15% at Day 43, and a common within-patient correlation of 0.7 for the change from baseline in MADRS total scores at Days 8, 15, 22, 29, 36, and 43.

7.3 Analysis Sets

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

All Enrolled (ENR) Set: The ENR Set will contain all patients who signed the 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 medication. Patients will be classified according to randomized treatment;

Intent-to-treat (ITT) Set: The ITT Set will contain all randomly assigned patients who received at least 1 dose of study medication and who had a valid baseline (pre-dose) measurement and at least 1 valid post-baseline measurement of MADRS. All analyses using the ITT Set will classify patients according to randomized treatment, regardless of the treatment actually received during the course of the study;

Sensitivity Set: The Sensitivity Set will contain all randomly assigned patients who received at least 1 dose of study medication and who had a valid baseline (pre-dose) measurement MADRS total score. All analyses using the Sensitivity Set will classify patients according to randomized treatment, regardless of the treatment actually received during the course of the study.

Safety Set: The Safety Set will contain all patients who received at least 1 dose of study medication. All analyses using the Safety Set will classify patients according to treatment actually received;

PK Set: The PK Set will contain all patients who received study medication, a baseline as well as at least 1 valid post-baseline MADRS measurement and had at least 1 PK sample collected and analyzed. Protocol deviations (eg, dosing errors) and AEs (eg, emesis) will be considered when assigning patients to the PK Set; patients who experience such events may be excluded from the PK Set on a case-by-case basis.

Unless otherwise specified, the ITT Set will be used for analysis of efficacy endpoints and the Safety Set will be used for analysis of safety endpoints.

7.4 Description of Subgroups to be Analyzed

In addition to the ITT Set, efficacy measures will be analyzed by a subgroup defined by the concomitant treatment (lithium or valproate). Other subgroup analyses of efficacy and safety variables may be conducted as deemed appropriate and will be detailed in the SAP.

7.5 Statistical Analysis Methodology

Categorical variables (eg, AEs) will be summarized using the number and percentage of patients in specified categories. Unless otherwise specified, the calculation of percentages will be based on the number of patients in the analysis set of interest. Continuous variables (eg, MADRS scores) will be summarized using descriptive statistics, including number of patients, mean, standard deviation, median, minimum, and maximum.

First treatment with study medication and baseline assessments are scheduled for Visit 2 on Day 1. For analysis purposes, baseline is defined as the last non-missing assessment before the first treatment with study medication. Assessments on Day 1 for which the time is recorded will be considered baseline if the assessment time is before the time of the first treatment. Assessments on Day 1 for which the time is missing, and are, according to the study schedule of events, supposed to be collected prior to treatment, will be considered baseline.

Safety, efficacy, and quality of life data will be listed for all treated patients and summarized by treatment group and visit, unless stated otherwise in the SAP. All total and subscale scores will be derived from available individual items. In case of missing items, the total and subscale scores will be considered missing. Plasma concentrations below the limit of quantification will be flagged in the data listings and will be set to 0 in the calculation of summary statistics of concentration values and derivations of PK parameters.

Unless stated otherwise, statistical tests will be 2-sided significant level of 0.05, leading to 95% (2-sided) confidence intervals (CIs).

All investigative sites with fewer than 6 ITI-007 patients will be pooled as follows: the largest site with fewer than 2 patients per treatment group will be pooled with the smallest site with fewer than 2 patients per treatment group within the same country or geographic region. If this results in a pooled site still having fewer than 2 patients per treatment group, this site will be pooled together with the next smallest investigative site within the same

country or geographic region, if one exists; otherwise, no further pooling is needed. If the primary efficacy analysis model presents convergence issues due to the too small number of patients per site, including pooled sites, the same site pooling algorithm will be applied again, but this time pooling sites with fewer than a pre-specified larger number of ITI-007 patients per site within each country or geographic region, as described in the SAP. The pooled investigative sites, as determined based on the primary efficacy variable, will be used for any analysis model that includes site as a fixed effect. The actual investigative site numbers will be included in the listings.

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

All statistical analysis will be performed using SAS® software Version 9.4 or higher.

7.5.1 Patient Disposition, Analysis of Demographics and Other Baseline Characteristics

Patient disposition will be summarized by treatment group, when applicable, and overall, and by study visit when applicable, including incidence of screening failure and incidence of treatment or study discontinuation and the corresponding reasons. The number and percentage of randomized patients who discontinued due to an AE associated with worsening of bipolar depression will be summarized. Similarly, the number and percentage of randomized patients who discontinued due to an AE not associated with worsening of bipolar depression will also be presented. Time to treatment discontinuation due to all reasons, AEs (all, AEs associated with worsening of bipolar depression, and AEs not associated with worsening of bipolar depression), lack of efficacy, or due to any other reason of special interest will be evaluated separately using the Kaplan-Meier method. The Log-rank test will be used to compare the time to discontinuation between each treatment group and the placebo group.

Demographic and baseline characteristics, including bipolar disorder diagnosis and baseline efficacy measures, will be listed and summarized by treatment group and overall. 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

and treatment group. 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 lithium, valproate, zolpidem, zolpidem CR, or lorazepam, as described in Section 5.8 and detailed in Table 5-4. The number and percent of patients in the ITT Set receiving any of these medications 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 with ITI-007.

7.5.3 Study Medication Exposure and Treatment Compliance

Exposure to study medication and treatment compliance will be presented for the ITT and Safety Sets. Duration of exposure (days) and dosing compliance (%) will be calculated and summarized by treatment group. In addition, the number and percentage of patients exposed to study medication will be presented by study week, defined by the planned visits.

7.5.4 Analysis of Primary Efficacy Endpoint

The study is designed to evaluate the efficacy profile of ITI-007 40 mg and 60 mg based on the change from baseline to Day 43 in the MADRS total score.

The treatment effect on the primary efficacy endpoint will be evaluated using a mixed-effect 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 group, site (or pooled site), and the stratification variables, first-line treatment (lithium or valproate) and Bipolar Disorder type at screening (I or II), and interaction term for treatment group-by-visit interaction as fixed effects, and the baseline MADRS total score and baseline MADRS total score-by-visit interaction as covariates. The patient term will be included in the model as a random effect and other terms as fixed effects. The treatment group-by-site (or pooled site) interaction term will not be included in the MMRM model for the primary efficacy analysis. Rather, it will be examined as part of the exploratory analysis. An unstructured covariance matrix will be used to model the correlation among repeated measurements within patient. In the event the convergence cannot be attained with the unstructured correlation matrix, the following alternative structures will be attempted in the specified order: heterogeneous Toeplitz structure (TOEPH), heterogeneous autoregressive (1) (ARH[1]), heterogeneous compound symmetry,

No Diagonal Factor Analytic (FA0(q), with q equal to the number of time points), Toeplitz structure (TOEP), autoregressive (1) (AR[1]), and compound symmetry. Model parameters will be estimated using restricted maximum likelihood. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The treatment group and treatment group-by-visit interaction terms allow for comparisons of the treatment groups at each of the following: Days 8, 15, 22, 29, 36, and 43. Treatment differences will be evaluated via contrasts for the treatment group-by-visit factor. This methodology will be used to compare each of the ITI-007 doses, 40 mg and 60 mg, to placebo for change from baseline at each day. Estimates of model parameters will be presented, as well as LSM estimates for change from baseline in MADRS total score, standard errors and 95% CIs for LSMs will be presented by treatment group and day. Contrast estimates (LSMs) for between-group comparisons, the corresponding standard errors, 95% CIs, effect sizes, and p-values will be presented for day.

A number of sensitivity analyses of the primary efficacy endpoint will be performed to explore the robustness of the MMRM results under a different assumption on the mechanism of missing data. All sensitivity analyses will be performed based on the Sensitivity Set. The MMRM method assumes a missing-at-random mechanism for missing data. That is, the probability that measurements are missing depends on the set of observed measurements but is unrelated to the specific unobserved missing values that, in principle, should have been obtained. Sensitivity analyses will be conducted to assess the impact of missing data under different assumptions on the mechanism of missing data and will be detailed in the SAP.

Additionally, as a supportive analysis of the primary efficacy variable, the change from baseline to Day 43 in MADRS total score will be evaluated using analysis of covariance (ANCOVA) model with last observation carried forward (LOCF) based on the ITT Set. The model will contain the main effects of treatment group, site (or pooled site), the baseline value of MADRS total score, and the stratification variables (first-line treatment - lithium or valproate) and the bipolar disorder at screening [I or II]). Analysis of the LOCF Day 43 endpoint will provide an estimate of efficacy attributable to ITI-007 compared with 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. LSMs for each treatment, the LSM difference between treatment groups, the associated standard errors and 2-sided 95% CIs for the differences between the treatment groups, and p-values for between-treatment tests of differences will be presented.

7.5.5 Analysis of Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint of the study is the change from baseline to Day 43 in the CGI-BP-S-Depression score. The key secondary efficacy endpoint will be analyzed using the similar MMRM model as for the primary efficacy endpoint. Details will be provided in the SAP.

A fixed sequence procedure will be employed to control the overall type I error rate for multiple comparisons across the primary and the key secondary efficacy endpoints for the 60-mg and 40 mg treatment groups. Specifically, the primary and the key secondary efficacy endpoints will be tested in the following specified order:

#1: ITI-007 60 mg vs placebo comparison for change from baseline in MADRS total score at Day 43;

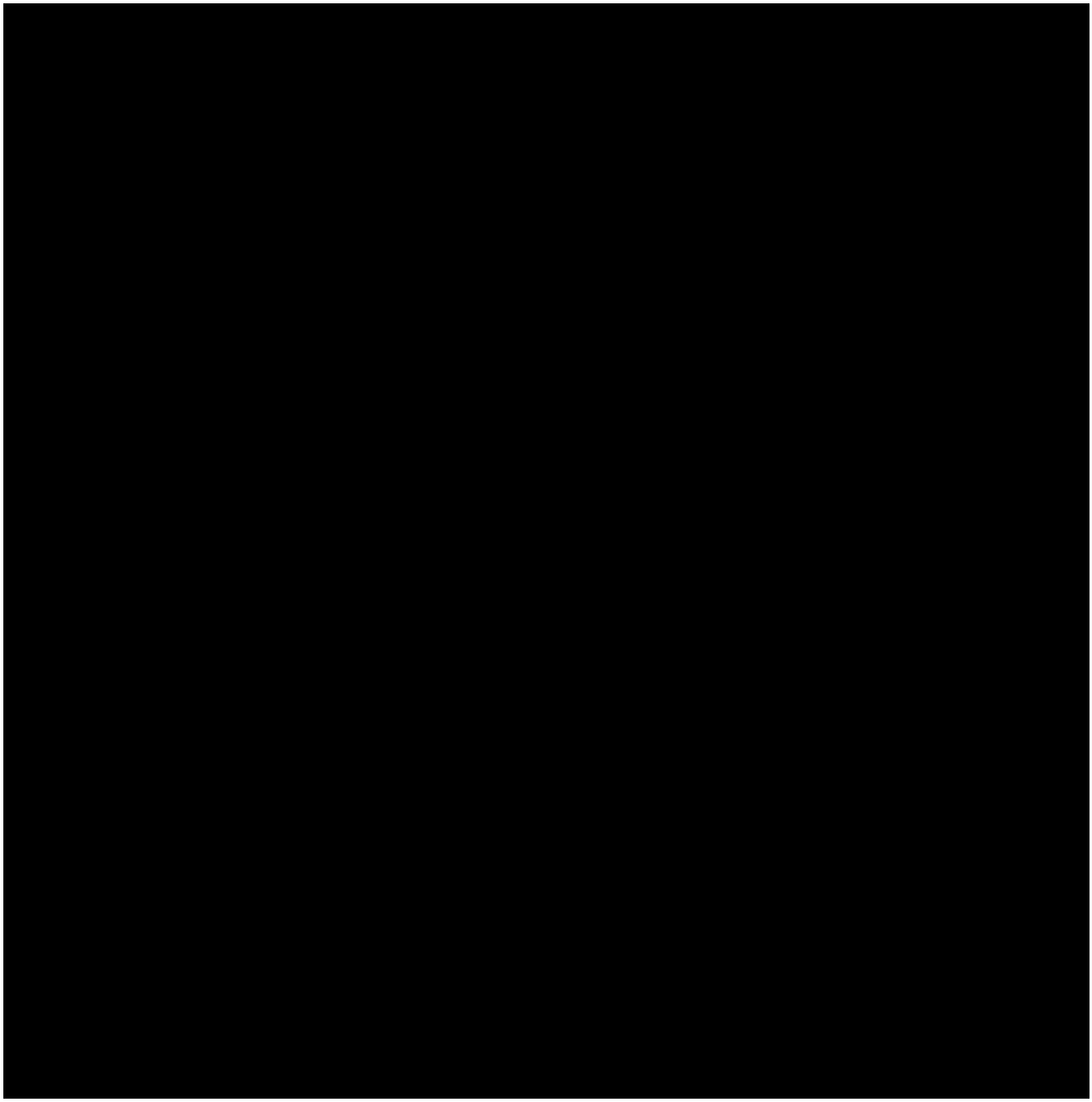
#2: ITI-007 40 mg vs placebo comparison for change from baseline in MADRS total score at Day 43;

#3: ITI-007 60 mg vs placebo comparison for change from baseline in CGI-BP-S score at Day 43;

#4: ITI-007 40 mg vs placebo comparison for change from baseline in CGI-BP-S score at Day 43.

All tests will be performed at the 0.05 level. Once one hypothesis fails to achieve statistical significance, all subsequent tests will not have p-values reported as nominal and will not be used to suggest statistical significance.

[redacted]



7.5.7 Safety Analyses

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 treatment group and visit. When appropriate, out-of-range values will be flagged in data listings and

tabulated. Shift tables will be prepared for pre-specified safety measures, such as selected laboratory parameters, ECG, and BMI, based on markedly abnormal criteria.

Reported AE terms will be coded using the latest version of MedDRA. Treatment-emergent AEs will be defined as any AEs, regardless of the relationship to study medication, that occur or worsen in severity after the first dose of study medication and before the last dose of study medication. Treatment-related TEAEs will be defined as any TEAEs that are considered by the Investigator to be either possibly, probably, or definitely related to study medication. If relationship to study medication is missing, the TEAE will be considered as treatment-related. Severity of TEAEs will also be determined by the Investigator. All TEAEs, treatment-related TEAEs, and serious TEAEs will be summarized by treatment group, primary system organ class, and preferred terms and will be further broken down by severity and relationship to study medication. If a patient reports the same TEAE more than once within the same system organ class and preferred term, the event with the worst-case relationship to study medication will be used in the corresponding relationship summaries. Similarly, if a patient reports a TEAE more than once within the same system organ class and preferred term, the event with the worst-case severity will be used in the corresponding severity summaries. The TEAEs occurring in at least 5% of patients in any treatment group will be summarized. Additional summaries of TEAEs will be presented as deemed necessary and will be specified in the SAP.

Patients who discontinue study or study medication due to AEs will be listed and summarized by system organ class and preferred term.

Treatment-emergent AEs will be categorized to monitor signals of potential abuse of ITI-007 and the number and percentage of patients with at least 1 abuse-related TEAE will be summarized by the pre-specified categories.

Laboratory assessments, including hematology and chemistry, vital signs, and ECGs, will be listed and summarized by treatment group and visit. Summaries may include actual and change from baseline, incidence of abnormal values according to normal range criteria, shift from baseline to each visit according to markedly abnormal criteria, and listing of patients meeting markedly abnormal criteria. Certain chemistry results, including but not limited to blood levels of fasting glucose, total cholesterol, triglycerides, and insulin will be evaluated for whether there is a difference between ITI-007 and placebo, using ANCOVA with LOCF. Any comparison between the treatment groups will be considered exploratory.

The observed values and changes from baseline in the scores of the rating scales (YMRS, C-SSRS, AIMS, BARS, and SAS) will be summarized by treatment group and study visit.

[redacted]

7.5.9 Blinded Sample Size Re-estimation

A blinded sample size re-estimation may be performed when 70% of randomized patients have either completed the study or discontinued to obtain an estimate of the pooled standard deviation on change from baseline to Day 43 in the MADRS total score. If the estimated pooled standard deviation is larger than the assumed pooled standard deviation in the sample size calculation , sample sizes may be increased to ensure an adequate power. The number of patients in each treatment arm will be capped at 200.

Details on the blinded sample size re-estimation will be provided in the SAP.

7.6 Estimand Framework

An estimand framework will also be employed to assess the efficacy of ITI-007 and its detail will be presented in the SAP of this study.

7.7 Data Quality Assurance

To ensure compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements, ITI (the Sponsor) 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.

7.7.1 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 or MINI (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 (eg, laboratory data).

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

After database lock, each study site will receive an electronic data storage device containing all of their study site- specific eCRF data as entered into the EDC, including full discrepancy and audit history. Additionally, an electronic 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 electronic 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/IEC 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/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC 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/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address; the clinical protocol by title, or 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/IEC. The Investigator must promptly supply the Sponsor or its designee, the IRB/IEC, 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/IEC submission. Once reviewed, the consent will be submitted by the Investigator to his or her IRB/IEC 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/IEC 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/IEC.

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/IEC 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 sub-investigator 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/IEC-approved informed consent, samples of study 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 registries 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 timeline and method outlined in the protocol. In addition, the Investigator agrees to submit annual reports to the study site IRB/IEC, 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/IEC 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 not be an external DMC for this study.

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/IEC 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 (eg, 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/IEC 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/IEC 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/IEC 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/IEC 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 4.2).

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/IEC should be notified of all protocol deviations in a timely manner.

10.3 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated by the Sponsor. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the Investigator, and regulatory authorities. If the study is prematurely terminated or suspended, the Investigator will promptly inform the IRB/IEC and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients;
- Insufficient adherence to protocol requirements;

- Data that are not sufficiently complete and/or evaluable;
- Determination of futility.

10.4 Halting Rules

Individual patient participation in the study may be stopped at any time at the discretion of the Investigator (see Section 4.2). Individual patient participation may also be stopped at any time at the request of the Sponsor. Additionally, the Sponsor may place a temporary or permanent suspension of enrollment at any site or for the entire study. Reasons for stopping or suspending patient participation and/or enrollment include, but are not limited to, violation of inclusion/exclusion criteria, major protocol deviation(s), or safety concerns.

Review of serious, unexpected, and related AEs by the IRB/IEC, the Sponsor, or the FDA or relevant local regulatory authorities may also result in suspension of further study interventions/administration of study product at a site. The FDA or other local regulatory authorities and study Sponsor retain the authority to suspend additional enrollment and study interventions/administration of study product for a site or the entire study, as applicable.

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

10.5 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 agencies as required by the applicable regulatory requirements. 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 registries.

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