NCT03249376

Study ID: ITI-007-404

Title: A Phase 3, Randomized, Double-blind, Placebo-Controlled, Multi-Center Study to Assess the Efficacy and Safety of Lumateperone Monotherapy in the Treatment of Patients With Major Depressive Episodes Associated With Bipolar I or II Disorder (Bipolar Depression) Conducted Globally

Protocol Amendment Version 1.3 Date: November 5, 2018

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

ITI-007-404

IND# 126,701

EUDRA CT# 2017-002317-58

Sponsor: Intra-Cellular Therapies, Inc. (ITI)

Amendment Version 1.3

November 5, 2018

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6) and the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46).

CONFIDENTIAL

Protocol Approval – Sponsor Signatory

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

Protocol Number: ITI-007-404

INVESTIGATOR SIGNATURE PAGE

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

Protocol Number: ITI-007-404

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal and/or local regulations and ICH guidelines.

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

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

Principal Investigator or Clinical Study Site Investigator:

Signed: _____ Date: _____

Name:

Title:

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

$5\text{-}HT_{2A}$	5-Hydroxytryptomine 2A Receptor
AE	Adverse Event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ARH	Heterogeneous Autoregressive
AST	Aspartate Aminotransferase
BARS	Barnes Akathisia Rating Scale
BLQ	Below the limit of quantification
BMI	Body Mass Index
CFR	Code of Federal Regulations
CGI-BP	Clinical Global Impression Scale, Bipolar version
CGI-BP-S	Clinical Global Impression Scale, Bipolar version, Severity
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CS	Compound Symmetry
CSH	Heterogeneous Compound Symmetry
C-SSRS	Columbia Suicide Severity Rating Scale
D_2	Dopamine 2 Receptor
DSM-5	Diagnostic and Statistical Manual, 5^{th} Edition
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ENR	All Patients Enrolled
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA_{1C}	Glycated Hemoglobin A_{1C}
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

IND	Investigational New Drug Application
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 Over
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 (M.I.N.I.)
MMRM	Mixed Model for Repeated Measures
NDA	New Drug Application
OHRP	Office for Human Research Protections
PET	Positron Emission Tomography
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per Protocol
QA	Quality Assurance
QC	Quality Control
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
RND	All Patients Randomized
SAE	Serious Adverse Event
SERT	Serotonin Transporter
SAP	Statistical Analysis Plan
SAS	Simpson Angus Scale
SOP	Standard Operating Procedure
TEAE	Treatment emergent adverse event
TOEP	Toeplitz Structure
TOEPH	Heterogeneous Toeplitz Structure
ULN	Upper Limit of Normal

UP	Unanticipated Problem
US	United States
YMRS	Young Mania Rating Scale

PROTOCOL SUMMARY

Title:

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

Précis:

This is a Phase 3, randomized, double-blind, placebo-controlled, multi-center study to evaluate the efficacy and safety of lumateperone monotherapy in the treatment of patients with major depressive episodes associated with Bipolar I or Bipolar II Disorder (Bipolar Depression). The study consists of the following periods: screening period, double-blind on-treatment period, and safety follow-up period.

Screening Period (2 Weeks)

Potential patients will be evaluated during a screening period lasting up to 2 weeks to ensure sufficient washout of restricted medications. Extension to the screening period may be approved by the Sponsor or representative in extenuating circumstances related to the patient or caregiver.

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

[redacted]

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

On-Treatment Period (6 Weeks)

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

treatment period. Following randomization, patients will make clinic visits 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) and will be asked to return to the clinic for a safety follow-up visit 2 weeks following their last dose of study medication.

Objectives:

Primary Objective:

The primary objective of this study is to compare the efficacy of lumateperone administered orally once daily to that of placebo as measured by mean change from baseline to Day 43 in the total score on the Montgomery-Åsberg Depression Rating Scale (MADRS) in patients with Bipolar Depression.

Secondary Objectives:

Key Secondary Objective:

The key secondary objective of this study is to compare the efficacy of lumateperone administered orally once daily to that of placebo as measured by mean change from baseline to Day 43 in the total score on the Clinical Global Impression Scale, Bipolar version – Severity (CGI-BP-S) in patients with Bipolar Depression.

[redacted]

Safety Secondary Objectives:

The safety secondary objectives of this study are to determine the safety and tolerability of lumateperone administered orally once daily for 6 weeks in patients with Bipolar Depression, compared to placebo. Safety and tolerability will be assessed in relation to:

- Incidence of adverse events (AEs);
- Mean change from baseline in the Young Mania Rating Scale (YMRS);
- Mean change from baseline in the Columbia Suicide Severity Rating Scale (C-SSRS);
- Mean change from baseline in the Abnormal Involuntary Movement Scale (AIMS);
- Mean change from baseline in the Barnes Akathisia Rating Scale (BARS);
- Mean change from baseline in the Simpson Angus Scale (SAS);
- Changes from baseline in clinical laboratory evaluations;
- Changes from baseline in electrocardiograms (ECGs);
- Changes from baseline in vital sign measurements;

- Physical and neurological examination findings.

[redacted]

Population:	Male and female patients between the ages of 18 and 75 years, inclusive, with a diagnosis of Bipolar I or Bipolar II Disorder experiencing a major depressive episode may be eligible for participation in the study. (See Inclusion and Exclusion Criteria for details.) Patients will be enrolled in multiple countries globally.
Phase:	III
Number of Sites:	Approximately 70 sites
Description of Intervention:	Patients will be assigned to receive either lumateperone or placebo. Doses in the clinical study refer to ITI-007 as the tosylate salt (lumateperone tosylate or ITI-007 tosylate). ITI-007 60 mg is equivalent to 42 mg active base (lumateperone). Patients will self-administer doses orally, once daily, at home, each evening, for the duration of the double-blind On-treatment Period. Treatments will be provided in dose cards containing over-encapsulated tablets, and patients will be instructed to take 1 tablet per dose.
Study Duration:	Approximately 18 months from first patient screened or 17 months from first patient randomized until data analysis is completed, assuming an approximate 13-month enrollment period depending on clinic and patient availability, plus two months to complete clinical conduct and an additional two months to complete data analysis.
Patient Participation Duration:	For each patient completing the study, the study will last a maximum of approximately 10-12 weeks (9 visits), including screening, the on-study treatment period, and the safety follow up.

Estimated Time to Complete Enrollment:	Approximately 13 months is anticipated from first patient randomized to last patient randomized, depending on clinic and patient availability.
Statistical Methods:	A formal and detailed statistical analysis plan (SAP) will be finalized prior to unblinding the patients' treatment assignments.

Analysis of the Primary and Key Secondary Efficacy Endpoints

The treatment effect on the primary efficacy endpoint will be evaluated using a mixed model repeated measures (MMRM) method. The model will include the change from baseline at each pre-specified time point in the MADRS total score as the response variable, visit, treatment group, site (or pooled site), and the Bipolar Disorder stratification variable (Bipolar I and Bipolar II) as factors, the baseline MADRS total score as a covariate and interaction terms for treatment group-by-visit, and visit-by-baseline MADRS total score.

The Key Secondary Efficacy Endpoint will be analyzed using the MMRM method, similar to the one specified for the analysis of the primary efficacy endpoint, while substituting MADRS total score related variables in the MMRM with the corresponding CGI-BP-S related ones, such as baseline score and visit-by-baseline score interaction.

[redacted]

Safety Analyses

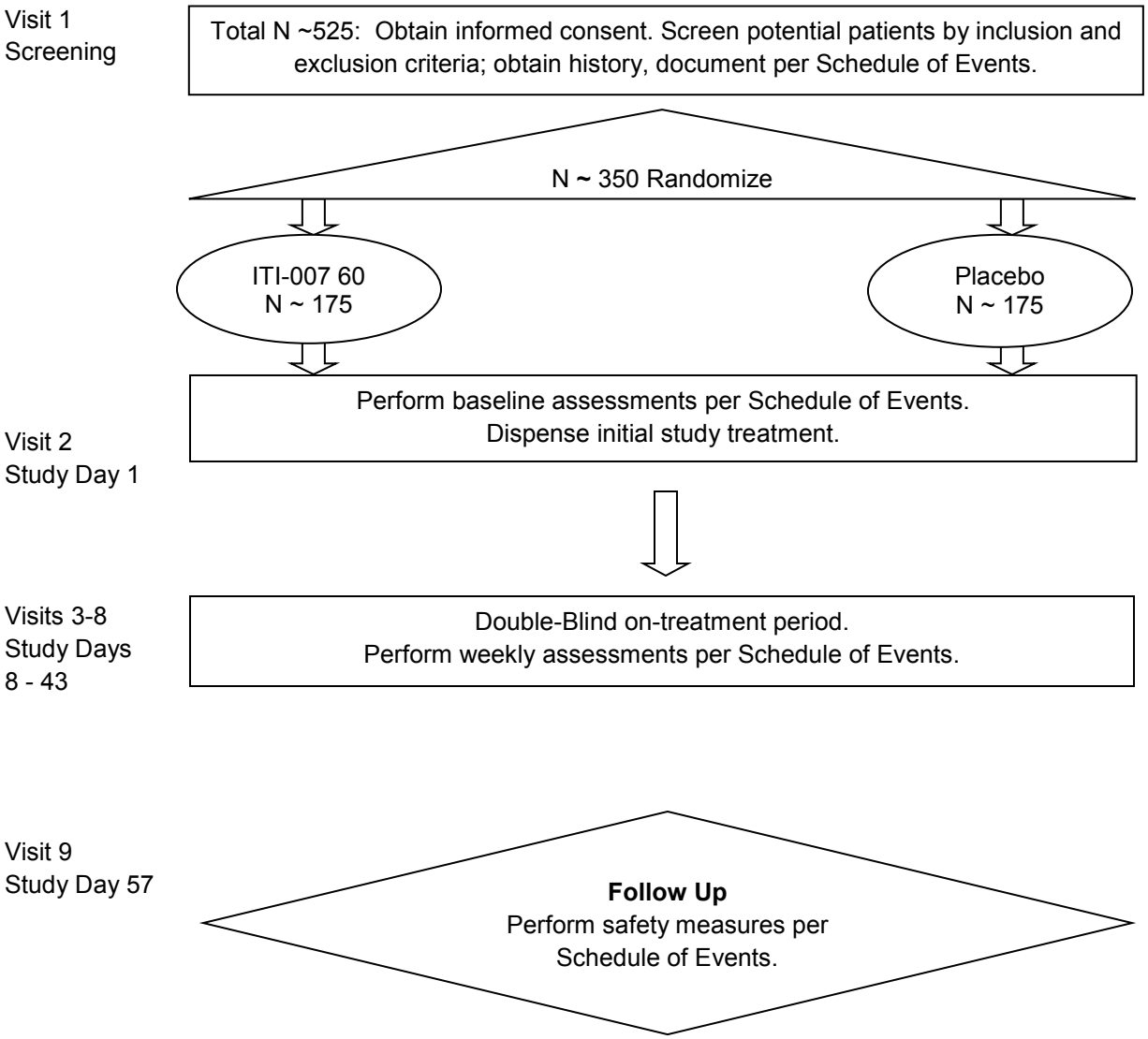
All safety parameters will be summarized using the Safety Analysis Set. Safety data such as reported and observed AEs, treatment emergent adverse events (TEAEs) and SAEs, clinical laboratory results, vital signs, physical and neurological examination findings, ECGs, and the different rating scales (YMRS, 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 laboratory parameters, ECG and weight.

[redacted]

Sample Size: Approximately 350 patients will be randomly assigned in a 1:1 ratio to 1 of the 2 treatment groups (ITI-007 60 mg or placebo). A sample size of 350 randomized patients will provide approximately 326 evaluable patients assuming a 10% early discontinuation rate before the first post-dose assessment of the primary efficacy outcome measure (MADRS). Approximately 163 patients per treatment group will provide

85% power to detect a clinically relevant treatment difference from placebo of 3 points on the MADRS total score with a common standard deviation of 9.0 at an overall 2-sided significance level of 0.05.

Schematic of Study Design:



1 KEY ROLES AND CONTACT INFORMATION

[redacted]

[redacted]

[redacted]

Clinical Study Site Investigators:	To be determined
Institutions:	To be determined

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Bipolar Disorder is a serious psychiatric disorder associated with shifts in mood including manic or hypomanic episodes, depressed episodes, or mixed episodes. Bipolar I Disorder is defined by the presence of manic or mixed episodes, whereas Bipolar II Disorder is defined by hypomania, but both are often associated with major depressive episodes. Bipolar Disorder affects approximately 5.7 million adult Americans, or about 2.6% of the U.S. population age 18 and older, every year according to the National Institute of Mental Health with similar prevalence worldwide. Depressive episodes associated with Bipolar Disorder tend to last longer, recur more often, and are associated with 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.

Intra-Cellular Therapies (ITI) is developing lumateperone (ITI-007), a new chemical entity, for the treatment of patients with schizophrenia, major depressive episodes (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 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-HT_{2A} receptor antagonist with mesolimbic/mesocortical selective modulation of phosphoprotein pathways downstream of dopamine receptors, serotonin reuptake inhibition, and indirect glutamatergic modulation (Snyder et al 2015). As a dopamine receptor protein phosphorylation modulator, ITI-007 has dual properties, acting as post-synaptic antagonist and as a pre-synaptic partial agonist at dopamine 2 (D_2) receptors in vivo, with mesolimbic/mesocortical selectivity. ITI-007 also increases the phosphorylation of the NR2B, or GluN2B, subunit of N-methyl-D-aspartate channels in extrastriatal dopamine-rich brain regions (e.g., 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 et al 2013; Loebel et al 2014a, 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 (Meltzer et al 1989). 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 antipsychotics drugs approved for the treatment of Bipolar Depression. For example, ITI-007 shows relatively weak affinity for 5-HT_{2C} and no measurable affinity for H_1 or muscarinic cholinergic receptors, which predict favorable body weight and metabolic profile responses to the extent that these receptors mediate such effects. Additional details on the pharmacologic profile of ITI-007 can be found in the Investigator's Brochure.

Nonclinical data suggest that ITI-007 may have the potential to treat depression (Snyder et al 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 m/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 trial (Davis et al 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 to most antipsychotic drugs.

Clinical data from three well-controlled studies in patient 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 three studies ITI-007 has been safely administered once daily for up to 42 days at

doses ranging from 20 mg 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 three studies, which was statistically significant at Day 28 compared to placebo in two 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 mg 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.

The purpose of this study is to evaluate the efficacy and safety of ITI-007 as a monotherapy for the treatment of Bipolar Depression.

2.2 Rationale

The screening phase permits evaluation of diagnosis as well as the laboratory and ECG assessments and enables confirmation of eligibility for inclusion into the study. The screening phase will be no longer than 14 days, unless confirmed by the Medical Monitor that a longer screening phase, not to exceed 28 days, is appropriate to ensure washout of excluded medication with long half-life (e.g., fluoxetine), under the supervision of the investigator before baseline. Patients will be randomly assigned in a 1:1 ratio to 1 of 2 treatment groups at the baseline visit and will receive treatment for up to 6 weeks. In order to ensure patient safety, a mandatory 14-day follow-up visit will be performed after administration of the last dose of study medication. Any ongoing AEs at the follow-up visit must be followed until resolution, until the AE stabilizes, until it is determined to be non-clinically significant, or until the patient is lost to follow-up.

ITI-007 60 mg was selected to deliver full occupancy of the cortical 5-HT_{2A} receptors (>85% occupancy) with modest striatal D_2 receptor occupancy and SERT occupancy. Data from human PET brain receptor occupancy studies with ITI-007 indicates that a dose as low as 10 mg is associated with >85% occupancy of cortical 5-HT_{2A} receptors, while the 60-mg dose demonstrates approximately 40% striatal D_2 receptor occupancy. SERT occupancy has been demonstrated to be comparable to D_2 receptor occupancy. Moreover, once daily oral administration ITI-007 60 mg has been shown to be well tolerated with no dose titration needed and with a safety profile similar to placebo with up to 6 weeks' treatment duration in patients with schizophrenia.

Therefore, a fixed dose design will be employed in this study with once daily oral administration of ITI-007 60 mg (or placebo).

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.

The hypothesis is that ITI-007 60 mg will demonstrate efficacy for the treatment of Bipolar Depression with statistically significant superiority versus placebo on the primary outcome measure, mean change from baseline to Day 43 in the total score on the MADRS in patients with Bipolar Depression.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

There are several potential risks associated with taking part in this research study. A patient's Bipolar Depression may not improve and could even worsen by taking part in this study. Each of these risks are discussed below. Patients should ask their study doctor if they have any questions or concerns about these risks.

During this study, patients will take either 60 mg ITI-007 or placebo. Neither the patient nor the study doctor will know which drug the patient is taking.

ITI-007 is an experimental drug which is not approved by the FDA or any regulatory authority. In research studies already conducted with ITI-007, over 1500 people have received ITI-007.

The most frequent side effect observed with ITI-007 60 mg and that has been reported at a rate twice that of placebo is:

* Tiredness or sleepiness

Additional side effects that have been observed with ITI-007 include:

* Headache
* Dizziness or lightheadedness
* Low blood pressure or fast heartbeat when standing up suddenly
* Tachycardia (fast heartbeat) without standing
* Nausea and/or vomiting

* Abdominal pain/cramps
* Feeling “drunk”
* Diarrhea
* Dry mouth
* Weakness
* Anxiety
* Insomnia
* Changes in levels of liver enzymes (which could indicate liver damage)
* Hot and/or cold sensations
* Stuffy nose
* Sweating

In test tube studies, ITI-007 showed potential to be toxic to genetic material (genes or DNA). When tested in two different animal studies, ITI-007 did not cause toxicity to genes.

Only in dogs, long-term dosing of ITI-007 was associated with adverse findings that may not be relevant to humans given the striking differences in metabolism (the way the body breaks down the drug) between dogs and humans. Dogs are exposed to drug metabolites that are not detected in humans. Short-term exposure (6 weeks or less) of ITI-007 has been shown to be well-tolerated with a safety profile similar to placebo in over 1500 people. There may be other side effects of ITI-007 that have not yet been observed or reported.

ITI-007 is an experimental drug that is still being tested and may not be effective in the treatment of Bipolar Depression. The placebo is not an active drug.

Throughout the study, patients will not be taking any other medication to treat Bipolar Depression. Therefore, it is possible that patients may experience an increase in Bipolar Depression symptoms.

ECG: Some areas where the electrodes (sticky patches) will be placed may need to be shaved. The test is painless, but the electrodes may irritate skin.

Blood Draw: Drawing blood may cause discomfort, bruising and very rarely infection at the site where the skin is punctured by the needle. Patients may also experience dizziness, nausea or fainting during blood taking. Patients will have to fast for 10 hours (overnight) before blood draws.

Harm to the Unborn Child: Currently we are not fully aware of the effects of ITI-007 on unborn babies, or pregnant or breastfeeding women. In women who are pregnant, or may become pregnant, treatment with the ITI-007 may lead to new, previously

unknown, side effects and risks to the woman or her unborn baby. Because of this, women who can have children will be asked to take a pregnancy test, at the start of the study. Men and women taking study treatment must be using an effective form of birth control before starting the study treatment and while taking part in the study. Any patient who is confirmed to be pregnant during the study will be immediately discontinued from study treatment.

2.3.2 Potential Benefits

Patients will be monitored carefully for their mental health status and general health. Symptoms of Bipolar Disorder (Bipolar Depression) may improve during participation in this study, although half the people in the study will receive placebo and may not improve. However, the information obtained from this study may help to treat people with Bipolar Depression better in the future.

3 OBJECTIVES

3.1 Study Objectives

3.1.1. Primary Objective:

The primary objective of this study is to compare the efficacy of lumateperone administered orally once daily to that of placebo as measured by mean change from baseline to Day 43 in the total score on the Montgomery-Åsberg Depression Rating Scale (MADRS) in patients with Bipolar Depression.

3.1.2. Secondary Objectives:

3.1.2.1. Key Secondary Objective:

The key secondary objective of this study is to compare the efficacy of lumateperone administered orally once daily to that of placebo as measured by mean change from baseline to Day 43 in the total score on the Clinical Global Impression Scale of Bipolar - Severity of Illness (CGI-BP-S) in patients with Bipolar Depression.

[redacted]

3.1.2.3. Safety Secondary Objectives:

The safety secondary objectives of this study are to determine the safety and tolerability of lumateperone administered orally once daily for 6 weeks in patients with Bipolar Depression, compared to placebo. Safety and tolerability will be assessed in relation to:

- Incidence of adverse events (AEs);
- Mean change from baseline in the Young Mania Rating Scale (YMRS);
- Mean change from baseline in the Columbia Suicide Severity Rating Scale (C-SSRS);
- Mean change from baseline in the Abnormal Involuntary Movement Scale (AIMS);
- Mean change from baseline in the Barnes Akathisia Rating Scale (BARS);
- Mean change from baseline in the Simpson Angus Scale (SAS);
- Changes from baseline in clinical laboratory evaluations;

- Changes from baseline in electrocardiograms (ECGs);
- Changes from baseline in vital sign measurements;
- Physical and neurological examination findings.

[redacted]

3.2 Study Outcome Measures

3.2.1 Primary

The change from baseline to Day 43 in MADRS total score is the primary outcome measure for the study. The MADRS is defined in Section 8.2.1 and will be assessed according to the Schedule of Events.

3.2.2 Secondary

The key secondary outcome measure is change from baseline to Day 43 in CGI-BP-S total score. CGI-BP-S is defined in section 8.1.9 and will be assessed according to the Schedule of Events.

Other secondary efficacy outcome measures include change from baseline in the MADRS, CGI-BP-S, and the Q-LES-Q-SF. These are described in Section 8 and will be assessed according to the Schedule of Events.

The secondary safety outcome measures include AEs, YMRS, C-SSRS, AIMS, BARS, SAS, clinical laboratory evaluations, ECGs, vital signs, and physical exams and neurological findings. These are described in Section 8 and will be conducted according to the Schedule of Events.

[redacted]

4 STUDY DESIGN

This is a Phase 3, randomized, double-blind, placebo-controlled, multi-center study to evaluate the efficacy and safety of lumateperone monotherapy in the treatment of patients with major depressive episodes associated with Bipolar I or Bipolar II Disorder (Bipolar Depression). The study consists of the following periods: Screening Period, double-blind On-treatment Period, and Safety Follow-up Period.

Screening Period (2 Weeks)

Potential patients will be evaluated during a Screening Period lasting up to 2 weeks, to ensure sufficient washout of restricted medications. Extension to the screening period may be approved by the Sponsor or representative in extenuating circumstances related to the patient or caregiver.

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

[redacted]

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

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 6-week On-treatment Period.

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

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) and will be asked to return to the clinic for a safety follow-up visit 2 weeks following withdrawal.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 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 M.I.N.I. International Neuropsychiatric Interview and meeting all of the following 5 criteria:
    a. The start of the current MDE is at least 2 weeks but no more than 6 months prior to the screening visit;
    b. Appropriate severity of illness, at least moderately ill, as measured by a rater-administered MADRS total score ≥20 and corresponding to a CGI-BP-S score of ≥4 at the screening and baseline visits;
    c. Sufficient history and/or independent report (such as family member or outside practitioner) verifying that the current MDE is causing clinically significant distress or impairment in social, occupational, or other important areas of functioning;
    d. A lifetime history of at least 1 Bipolar manic episode or mixed episode (for Bipolar I) or hypomanic episode (for Bipolar II);
    e. A rater-administered YMRS total score of ≤12 at the screening and baseline visits.
4. Has a body mass index (BMI) of 19 – 35 kg/m^2, inclusive.
5. Either must agree to use highly effective methods of birth control (defined as those, alone or in combination, that result in a failure rate less than 1 percent per year when used consistently and correctly) for at least 2 weeks prior to randomization (starting with signing informed consent) through to the end-of-study follow-up visit or must be of non-childbearing potential (defined as either permanently sterilized or, if female, post-menopausal; the latter is defined as at least 1 year with no menses without an alternative medical explanation).

6. In the opinion of the investigator, the patient is willing and able to comply with study requirements, study visits, and to return to the clinic for follow-up evaluations as specified by the protocol.

5.2 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 urine and serum pregnancy tests at screening and a negative urine pregnancy test on Day 1 prior to study treatment administration.
4. The patient has a history within 12 months of screening, based on previous psychiatric evaluation or a confirmed diagnosis upon screening based on the DSM-5, of a psychiatric diagnosis other than Bipolar Disorder, including:
    a. Schizophrenia or other psychotic disorder;
    b. Anxiety disorders such as panic disorder, general anxiety disorder, or post-traumatic stress disorder as a primary diagnosis (however, anxiety symptoms may be allowed, if secondary to Bipolar Disorder, provided these symptoms do not require current treatment);
    c. Feeding or eating disorder;
    d. Primary diagnosis of obsessive compulsive disorder;
    e. Personality disorder;

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

g. Any other psychiatric condition (other than Bipolar Disorder) that has been the main focus of treatment within 12 months of screening.

5. Patients who have experienced hallucinations, delusions, or any other psychotic symptomatology in the current depressive episode may be allowed as long as these symptoms are not attributable to a primary DSM-5 diagnosis other than Bipolar Disorder as described in exclusion number 4. The presence of these symptoms should be reviewed with the Medical Monitor and the adjudication team on a case by case basis prior to inclusion. Patients with YMRS of >12 will be reviewed on a case by case basis to rule out possible impending mania/hypomania.

6. The patient has been hospitalized for mania associated with Bipolar I Disorder within 30 days of screening.
   Note: This criterion is included to ensure that any manic phase has completely resolved before enrollment in the study.

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

8. The patient is considered a rapid cycler, defined by the occurrence of at least 6 major depressive, manic, hypomanic, or mixed episodes during the previous year. These episodes must be demarcated either by a partial or full remission of at least 2 months' duration or by a switch to an episode of opposite polarity. (Each MDE must have lasted at least 2 weeks, each manic or mixed episode must have lasted at least 1 week, and each hypomanic episode must have lasted at least 4 days, as validated by a reliable informant).
   Note: This criterion is included to avoid spontaneous remission during participation in the study that might confound treatment results.

9. The patient is considered treatment-resistant, defined as having a lifetime history of treatment resistance (no remission) to ≥2 treatments with medications approved by the regional regulatory authority for Bipolar Depression [which may include, for example, lurasidone, quetiapine or Symbyax (olanzapine/fluoxetine combination), 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 at the screening visit, or presents evidence of either withdrawal from or acute intoxication with cocaine, opiates, amphetamines (including methamphetamine), alcohol, barbiturates, or hallucinogens or similar compounds. The urine drug screen may be repeated once based on investigator judgment and reviewed for medical appropriateness by the Medical Monitor as part of the screening adjudication process.

    Note: Previous occasional use of alcohol or cannabis (but not synthetic marijuana/K2/Spice) or prescribed psychotropic (e.g., benzodiazepine, opiate) is allowed as long as the level of use does not meet DSM-5 criteria for any moderate or severe substance use disorder within the 12 months prior to screening and the use of alcohol or cannabis is not considered to be the precipitating factor of the current depressive episode, in the opinion of the investigator and any prescribed psychotropic is accompanied by evidence of prescription; patients are required to abstain from alcohol and drug use during the study.
13. The patient has used 1 of the following agents under the specified conditions:
    a. Lifetime exposure to ITI-007 (i.e., participated in previous clinical study with ITI-007) 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 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 is not available in specific regions, another sedative hypnotic may be approved by the Medical Monitor.

ii. central opioid agonists/antagonists including tramadol;

iii. anticonvulsants;

iv. mood stabilizers, 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, medical foods, or pharmaceuticals containing Omega-3 fatty acids, melatonin, St. John's Wort, kava kava, Vitamin B12, folate (no L-methylfolate in current episode), or valerian root. Daily multivitamin use is not excluded.

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

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

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

    c. Alkaline phosphatase >2.0 × the ULN

    d. Gamma-glutamyl transpeptidase >2.0 × the ULN

    e. Total bilirubin >1.5 × the ULN

    f. Serum creatinine >1.5 × the ULN

    g. Blood urea nitrogen >1.5 × the ULN

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

i. 12-lead ECG (in a supine position after a rest of approximately 10 minutes at the screening visit) mean of triplicate corrected QT interval using the Fridericia formula (QTcF) >450 ms for males or females, corrected QT interval using the Bazett formula (QTcB) >450 ms for males or >470 ms for females, and/or heart rate ≤50 beats per minute, or evidence of clinically significant bundle-branch blocks.

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

15. The patient has clinically significant cardiovascular (including but not limited to uncontrolled angina, or history of a myocardial infarction within 3 months prior to screening, or history of a clinically significant cardiac arrhythmia including antipsychotic drug-induced corrected QT interval prolongation), endocrine (including poorly controlled diabetes defined as glycated hemoglobin A1c [HbA1c] >53 mmol/mol [7.0%] at screening with no re-test allowed for HbA1c), hepatic, renal, pulmonary, gastrointestinal, neurological, malignancy (including any malignancy and/or chemotherapy within the 2 years prior to screening; malignancy more than 2 years prior to screening must have been local and without metastasis and/or recurrence, and if treated with chemotherapy, without nervous system complications; some malignancies, such as basal cell carcinoma, may not preclude participation and will be individually reviewed), pheochromocytoma, metabolic, psychiatric or other condition that might be detrimental to the patient if he or she participates in the study (in the opinion of the investigator).
16. The patient has a history of human immunodeficiency virus (HIV) infection or has HIV antibodies in blood at screening.
17. The patient has a history of hepatitis B or hepatitis C infection or shows evidence of active hepatitis B or hepatitis C infection at screening.
18. 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).
19. The patient is judged by the investigator to be inappropriate for the study.

5.3 Strategies for Recruitment and Retention

Strategies for recruitment and retention will be determined by individual participating clinical study sites using Institutional Review Board (IRB) / Independent Ethics Committee (IEC) approved recruitment/retention materials consistent with ICH guidelines. Patients may be compensated for study participation as reviewed and approved by the IRB/IEC and consistent with customary regional practices and ICH guidelines. Patient compensation (if regionally allowed) will be described in the informed consent form.

5.4 Treatment Assignment Procedures

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

5.4.1 Randomization Procedures

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 [redacted] 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 5.4.3). The randomization schedule will be stratified by Bipolar I or Bipolar II diagnoses at screening.

Each patient will be assigned a randomization number, at the time of randomization, 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.

5.4.2 Masking Procedures

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

5.4.3 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 treatments become unblinded will continue in the study as planned, but will be excluded from the per-protocol set (Section 12).

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.

5.5 Patient Withdrawal

The planned overall duration of the study for each patient is up to 10-12 weeks (9 visits): i.e. a screening phase of up to 2 weeks (to ensure sufficient washout of restricted medication), a double-blind on-treatment period 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 obtained through the last follow-up visit on Day 57. Patients may withdraw voluntarily from the study or the investigator or sponsor may terminate a patient's participation.

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

A patient who fails to satisfy inclusion 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 screen (as defined by the date of

informed consent) will need to have all screening procedures repeated. In all cases, a new informed consent must be obtained for a rescreen. A patient may not be screened more than 2 times.

5.5.1 Reasons for Withdrawal

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 (e.g., pregnancy, development of contraindications of use of study drug).
8. The investigator or sponsor decide to discontinue the patient's participation in the study.
9. The patient withdraws consent. If consent is withdrawn, the patient must be questioned by the investigator or study site staff whether the withdrawal is due to an AE, lack of efficacy, personal or family reasons, or whether the patient withdrew consent and refused all end-of-study procedures, including refusing to give a reason; these reasons must be documented in the case report form.

The investigator will also withdraw a patient if ITI terminates the study. Upon occurrence of a serious or intolerable AE, the investigator will confer with the sponsor or Medical Monitor as the sponsor's designee. If a patient is discontinued because of an AE, the event will be followed until it is resolved, stabilizes, is determined to be non-

clinically significant, or the patient is lost to follow-up. Any patient may withdraw his or her consent at any time.

5.5.2 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 treatment. 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 or similar procedures depending on regional differences) in an attempt to have them comply with the protocol.

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

5.6 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 principal 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.

6 STUDY INTERVENTION

6.1 Study Product Description

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

Table 6-1 Table for Dosing Schedule

Study Treatment	Dosing Schedule
60-mg ITI-007	1 over-encapsulated tablet of 60-mg ITI-007 Daily Dose: 60-mg ITI-007
Placebo	1 over-encapsulated tablet of placebo Daily Dose: 0-mg ITI-007

ITI-007 60 mg refers to the tosylate salt (ITI-007 tosylate or lumateperone tosylate) and is equivalent to 42 mg of the active base (lumateperone).

[redacted]

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 6-2.

[redacted]

[redacted]	[redacted]	
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.1.1 Acquisition

Adequate supplies of ITI-007 and matched placebo will be provided to each study site.

6.1.2 Formulation, Packaging, and Labeling

ITI-007 and matching placebo will be prepared according to current Good Manufacturing Practice standards in carded blister strips and shipped under ambient conditions. Each treatment card will contain a sufficient quantity of capsules for 1 patient for two weeks (14 doses, plus 2 extras), to be dispensed every other visit of the 6-week treatment period. 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 6-.

Table 6-3 Bi-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	Two 1×8 strips of 60-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.

6.1.3 Product Storage and Stability

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

6.2 Dosage, Preparation and Administration of Study Product

Patients will be assigned to receive either ITI-007 (60-mg dose) or placebo. Study site personnel will receive a treatment card number from the IVRS/IWRS for each patient at every second clinic visit (e.g. at baseline and Study Days 15 and 29), 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, between approximately 8:00 PM and 10:30 PM, and at approximately the same time each day whenever possible. Treatments will be provided in dose cards containing 2 strips of over-encapsulated tablets. Patients will be instructed to take 1 capsule per dose. Patients will be instructed to bring the bi-weekly treatment card to the study site at the next visit to assess compliance.

6.3 Modification of Study Product Administration for a Patient

Patients who do not tolerate the study treatment should be withdrawn from the study treatment. There are no modifications of dosing allowed except withdrawal. See Section 5.5 for details regarding patient withdrawal.

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.

Previous clinical trials have evaluated ITI-007 in healthy volunteers with single doses up to and including 40 mg, multiple doses up to and including 20 mg administered once daily for 5 days, and multiple doses up to and including 30 mg administered once daily for 7 days in healthy geriatric volunteers. Previous clinical trials have evaluated ITI-007 in patients with schizophrenia 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 as needed) with sufficient attention to the symptoms and the clinical course. Supportive measures may include gastric lavage and respiratory and cardiovascular support as needed.

6.4 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 treatment will be reconciled and retained or destroyed according to applicable regulations.

6.5 Assessment of Patient Compliance with Study Product Administration

Patient compliance will be assessed by capsule counts of unused study medication at each visit during the double-blind treatment phase. 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.

6.6 Concomitant Medications/Treatments

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 exception is zolpidem, 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 5.2, Exclusion 13). Patients considered potentially eligible for participation will be required to discontinue their current antidepressant treatment and/or other psychotropic drugs for the duration of the study.

Discontinuation of long-acting prohibited medications that require more than a 2-week washout should be discussed on a case-by-case basis with the Medical Monitor for approval of a longer screening phase to ensure washout of excluded medication with longer half-life (e.g., fluoxetine) under the supervision of the investigator before baseline.

Acetaminophen (Paracetamol) use is prohibited, but ibuprofen is allowed.

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

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

7 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 Appendix A. Detailed instructions for the conduct of study assessments and procedures will be provided in the study reference manual.

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8 STUDY PROCEDURES /EVALUATIONS

8.1 Study Procedures/Evaluations

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 Appendix A; assessments can be conducted on different days within the screening period.

8.1.1 Informed Consent

Before any study-related activities the patient must sign and date an ICF approved by the responsible IRB/IEC. The format and content of the ICF must have been agreed upon by the investigator, the appropriate IRB/IEC, and ITI.

8.1.2 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 and cannabis 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 any methods available for identifying duplicate patients.

8.1.3 Modified Physical Examination

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

8.1.4 Electrocardiogram Assessments

Each ECG assessment at screening will comprise of triplicate 10-second epochs from 12-lead ECGs recorded 5 minutes apart. Subsequent ECGs will be single 10-second epochs from 12-lead ECGs. Electrocardiogram parameters to be measured include heart rate, 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.

8.1.5 Vital Sign Measurements

Vital signs include: respiratory rate, oral temperature, 60-second pulse readings, blood pressure, body weight and height (height only at V1, screening), waist circumference and BMI. Vital signs are always taken after conducting the ECGs, as applicable, and prior to any other assessments, including needle sticks for laboratory or pharmacokinetic samples, scheduled for the same visit. At V1, V2, V8, and V9 vital signs include 3-positional blood pressure readings (after at least 10 minutes in the supine position, after approximately 1 minute sitting, immediately upon standing, and after approximately 3 minutes standing). Pulse will be measured by counting pulse over 60 seconds. Height will be measured only at screening. Body weight will be measured at all scheduled visits through Visit 9 (Day 57). Each patient's BMI will be calculated before Day 1 to ensure that the patient meets the BMI inclusion criterion.

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.

8.1.6 Mini International Neuropsychiatric Interview

The major clinical criterion for inclusion in the study is that the patient be diagnosed with Bipolar I or Bipolar II Disorder, meeting the DSM-5 criteria. The methodology for confirming this diagnosis is the M.I.N.I. International Neuropsychiatric Interview 7.0.2 (8/8/16 version) by Dr. David V. Sheehan. The M.I.N.I. is a well-validated clinical tool (Sheehan et al., 1998). It will be used in this study at screening only to confirm the diagnosis of Bipolar Depression in patients evaluated for inclusion in the study. It will be completed by the investigator or an expert site-based rater approved by the sponsor.

8.1.7 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 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 (Appendix A).

At screening, a patient 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.

8.1.8 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 et al 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 according to Appendix A (Schedule of Events).

8.1.9 Clinical Global Impressions of Severity

The Clinical Global Impressions Scale (CGI) has been modified specifically for use in assessing global illness severity and change in patients with Bipolar Disorder (Spearing et al 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. Scores on the CGI-BP-S range from 1 (not ill at all) to 7 (among the most extremely ill). A CGI-BP-S assessment will be completed at screening by the investigator or another ITI-approved expert site-based rater according to Appendix A (Schedule of Events).

[redacted]

8.2 Efficacy Assessments and Procedures

8.2.1 MADRS

The MADRS is a 10-item checklist designed to measure the overall severity of depressive symptoms (Montgomery and Åsberg, 1979). Individual items are rated by the investigator (or another ITI-approved expert site-based rater) according to Appendix A (Schedule of Events) on a scale of 0 to 6 in which a score of 6 represents the most severe symptoms for each item assessed. The total score ranges from 0 to 60.

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

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

8.2.2 Clinical Global Impression of Severity

The CGI-BP-S will be a clinical efficacy assessment by the investigator of each patient's severity of illness, as described in Section 8.1.9.

8.2.3 Q-LES-Q-SF

The Q-LES-Q-SF is a patient self-reported questionnaire that assesses how satisfied a patient is, using a 5-point rating scale from very poor to very good, with 14 items (Endicott et al., 1993). The items assessed include physical health, mood, work, household activities, social relationships, family relationships, leisure time activities, ability to function in daily life, sexual drive/interest/performance, economic status, living/housing situation, ability to get around physically without feeling dizzy or unsteady or falling, vision in terms of ability to do work or hobbies, and overall sense of well-being that are summed to provide a raw total score ranging from 14 to 70. There are an additional 2 stand-alone items (1 for medication satisfaction and the other for overall life satisfaction). The total raw score is converted to a percent score. The Q-LES-Q-SF will be administered according to Appendix A (Schedule of Events).

8.3 Patient Placebo Questionnaire and Training:

A brief placebo response questionnaire will be administered to assess the patient's perception of likelihood their symptoms will improve as well as their perception at the end of the study whether they received placebo or active investigational drug. A brief training module will be provided describing placebo response at baseline.

8.4 Safety and Tolerability Assessments

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

8.5 Laboratory Procedures/Evaluations

8.5.1 Clinical Laboratory Evaluations

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

All samples for clinical laboratory analysis will be collected after an overnight fast (≥10 hours), after any scheduled ECG or vital signs have been recorded, and prior to dosing with study treatment. Samples for clinical laboratory analysis will be used only for the evaluation of safety and tolerability.

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

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

The following clinical analytes will be determined:

Hematology: hematocrit; hemoglobin; HbA_{1c} (only at screening V1 and end of study treatment V8); 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).

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

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

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

8.5.2 Hepatitis Screening

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

8.5.3 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.

8.5.4 Urine Drug and Alcohol Screening

Qualitative urine drug (amphetamines, barbiturates, benzodiazepines, cannabinoids [THC], cocaine metabolites, methadone, opiates, phencyclidine, propoxyphene) and alcohol tests will be performed. Any patient who tests positive for drugs of abuse or alcohol test at the screening visit, or presents evidence of either withdrawal from or acute intoxication with cocaine, opiates, amphetamines (including methamphetamine), alcohol, barbiturates, or hallucinogens or similar compounds will be excluded. The urine drug screen may be repeated once based on investigator judgment and reviewed for medical appropriateness by the Medical Monitor as part of the screening adjudication process.

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

Further information regarding sample collection, processing, and shipping can be found in the study reference manual.

[redacted]

[redacted] [redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted].

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

9.1.1 C-SSRS

The C-SSRS will be completed at screening, baseline, and at every subsequent scheduled clinic visit according to Appendix A (Schedule of Events). Details of the C-SSRS are presented in Section 8.1.7.

9.1.2 YMRS

The YMRS will be completed at screening, baseline, and at every subsequent scheduled clinic visit according to Appendix A (Schedule of Events). Details of the YMRS are presented in Section 8.1.8.

9.1.3 Abnormal Involuntary Movement Scale

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

9.1.4 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 according to Appendix A (Schedule of Events).

9.1.5 Simpson-Angus Scale

The SAS is a measure of extrapyramidal side effects (Simpson and Angus 1970). Ten items including rating gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head rotation, glabella tap, tremor, and salivation are rated on a scale from 0 (normal) to 4 (extreme in severity). The SAS should be conducted by the

investigator or an expert site-based rater in a room where the patient can walk a sufficient distance to allow a natural pace (e.g., 15 paces). Each side of the body should be examined. The SAS is to be completed at baseline and periodically throughout the study according to Appendix A (Schedule of Events).

9.1.6 Vital Sign Measurements

Vital signs will be measured at screening and at subsequent scheduled clinic visits according to Appendix A (Schedule of Events). Details of the vital sign measurements are presented in Section 8.1.5.

9.1.7 ECG Assessments

The ECG assessments will be performed at screening and periodically throughout the study, according to Appendix A (Schedule of Events). Details of the ECG assessments are presented in Section 8.1.4.

9.1.8 Physical and Neurological Examination

The physical and neurological examinations will be conducted at screening and periodically throughout the study, according to Appendix A (Schedule of Events). Details of the physical and neurological examinations are presented in Section 8.1.3.

9.1.9 Unanticipated Problems

The investigator will review each SAE (Section 9.1.4) and evaluate the intensity and the causal relationship of the event to study treatment. 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 treatment 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 treatment 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 transmitting (via fax or email) the requested information to the sponsor within 24 hours of the sponsor’s request.

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (e.g., hospital reports, consultant reports, autopsy reports), with the study patient’s personal identifiers removed. All relevant information obtained by the investigator through review of these documents will be recorded and transmitted to the sponsor within 24 hours of receipt of the information. If a new SAE Report Form is transmitted, 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 transmit to the sponsor within 24 hours of the request.

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

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to patients or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB/IEC-approved research protocol and informed consent document; and (b) the characteristics of the patient population being studied;
- related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- suggests that the research places patients or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.1.10 Adverse Events

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

9.1.10.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a study patient administered a study treatment, 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 treatment, 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” (Section 9.1.4).

9.1.11 Serious Adverse Events

9.1.11.1 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.

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. 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.

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

Clarification of the difference between "serious" and "severe":
The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as “serious,” which is based on patient/event outcome or action criteria usually

associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

9.2 Time Period and Frequency for Event Assessment and Follow-Up

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.

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 treatment 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 treatment 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.

9.3 Characteristics of an Adverse Event

9.3.1 Relationship to Study Intervention

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

The investigator will assess the causality/relationship between the study treatment and the AE according to Appendix A (Schedule of Events). One of the following categories should be selected based on medical judgment, considering the following definitions and all contributing factors.

Table 9-1 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 possibility that the adverse event may have been caused by the treatment. Information on treatment withdrawal may be lacking or unclear.
Unlikely to be related	A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Unrelated	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically, explained by extraneous factors (e.g., concomitant disease, environmental factors, or other drugs or chemicals).

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

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

9.3.2 Expectedness of SAEs

The sponsor or designee will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature,

severity, or frequency of the event is not consistent with the risk information previously described for the intervention as documented in the Investigator's Brochure.

9.3.3 Severity of Event

The investigator will assess all AEs for intensity (severity) in accordance with the following standard ratings (Table 9-2):

Table 9-2 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.

9.4 Reporting Procedures

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

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

9.4.1 Unanticipated Problem Reporting to IRB/IEC

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB/IEC:

- appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB/IEC project number;
- a detailed description of the adverse event, incident, experience, or outcome;
- an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported to the IRB/IEC according to institutional policy. Unanticipated problems that are not adverse events will be reported to the sponsor within 2 weeks of the investigator becoming aware of the problem. Unanticipated problems that are serious adverse events will be reported to the sponsor according to Section 9.4.2.

Additional information will be provided in the study reference manual.

9.4.2 Serious Adverse Event Reporting to the Sponsor

Any AE meeting the specified Serious Adverse Event criteria will be submitted on an SAE form to the sponsor's centralized safety reporting system. This process applies to both initial and follow-up SAE reports.

For any initial SAE, whether deemed related to the study treatment or not, the investigator will complete a Serious Adverse Event Form and submit via fax or email within 24 hours of becoming aware of the event.

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

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

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

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (e.g., hospital reports, consultant reports, autopsy reports), with the study patient’s personal identifiers removed. All relevant information obtained by the investigator through review of these documents will be recorded and provided to the sponsor within 24 hours of receipt of the information. If a new SAE Report Form is provided, 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 provide to the sponsor within 24 hours of the request.

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

9.4.3 Reporting of SAEs and AEs to FDA and Other Regulatory Authorities

The sponsor or designee will be responsible for complying with mandatory reporting of safety events to the Food and Drug Administration (FDA) and other regulatory authorities.

9.4.4 Reporting of 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 in a patient or a partner of a patient 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. Pregnancy will result in immediate discontinuation from the study. . Pregnancy complications and elective terminations for medical reasons should not be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the patient has completed the study, and considered by the investigator as possibly related to the study treatment, must be promptly reported to ITI according to Section 9.4.2.

9.5 Halting Rules

Individual patient participation in the study may be stopped at any time at the discretion of the investigator. 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 concern.

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

10 STUDY OVERSIGHT

10.1 External Data Monitoring Committee

In addition to the investigator's responsibility for oversight, study oversight will be under the direction of the sponsor and the Medical Monitor(s). The Medical Monitor(s) will be available in real time to review and recommend appropriate action regarding adverse events and other safety issues. Blinded safety data across sites will be monitored throughout the study. Blinded data regarding enrollment and retention, adverse events, outlier safety parameters (e.g. clinical laboratory results, ECG parameters) and other relevant parameters will be reviewed regularly. If necessary, additional steps may be taken to ensure data integrity and protocol compliance.

11 CLINICAL SITE MONITORING

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.

12 STATISTICAL CONSIDERATIONS

A formal and detailed statistical analysis plan (SAP) will be finalized prior to unblinding the patients' treatment assignments and will provide further details regarding the definition of analysis endpoints and analysis methodology to address all study objectives. Changes made to the data analysis methods as described in the protocol will be documented in the SAP and will not necessitate a protocol amendment. All departures from the statistical analyses described in the approved protocol, whether made before or after 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, patient evaluability, and appropriateness of the planned statistical methods.

12.1 Sample Size Considerations

Approximately 350 patients will be randomly assigned in a 1:1 ratio to 1 of the 2 treatment arms (60 mg ITI-07 or placebo). A sample size of 350 patients randomized, which will provide approximately 326 evaluable patients (approximately 163/treatment group) assuming a 10% early discontinuation rate before the first post-dose assessment in the primary efficacy outcome measure (MADRS), will provide 85% power to detect a clinically relevant treatment difference from placebo of 3 points on the MADRS total score with ITI-007, with a common standard deviation of 9.0at an overall 2-sided significance level of 0.05.

12.2 Planned Interim Analyses (if applicable)

No interim analysis is currently planned. If an interim analysis is conducted, it will be described in the SAP which will be finalized before any unblinding of treatment groups occurs.

12.3 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 or 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 randomized patients who received at least 1 dose of study drug and who had a valid (pre-dose) baseline assessment and at least 1 valid post-baseline assessment of MADRS. Patients will be classified according to randomized treatment, regardless of the treatment received during the course of the study.

Per-protocol (PP) Set: The PP Set will contain all ITT patients who do not have any major protocol deviations. The major protocol deviation criteria will be specified in the SAP and finalized as part of the blinded data review prior to the final database lock. Patients will be classified according to treatment actually received.

Safety Analysis Set: The Safety Analysis Set will contain all patients who received at least 1 dose of study drug. Patients will be classified according to treatment actually received.

Pharmacokinetic (PK) Set: The PK Set will contain all patients who received at least one dose of study medication and had at least 1 PK sample collected and analyzed and for whom at least one valid assay result (according to laboratory guidelines) has been obtained. Protocol deviations (e.g., dosing errors) and certain AEs (e.g., emesis) will be considered when assigning patients to the PK set. Patients with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for meaningful analyses.

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

12.4 Statistical Analysis Methodology

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

Source data for summary tables and statistical analyses will be presented as patient data listings.

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 measurement before the first treatment with study medication. Assessments on Day 1 for which time are recorded will be considered baseline if the assessment time is before the time of the first treatment with study medication. 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 (pre-dose), will be considered baseline.

Safety, efficacy, and quality of life data will be listed for all treated patients and summarized by treatment group and time point (visit and relative study day), 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 (BLQ) will be flagged in the data listings and will be set to zero in the calculation of summary statistics of concentration values and derivations of PK parameters.

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

All investigative sites with fewer than a prespecified number of patients who received ITI-007, as detailed in the SAP, will be pooled together and considered a single site for analysis as follows: the largest site with fewer than the prespecified number of ITI-007 patients will be pooled with the smallest site with fewer than the prespecified number of ITI-007 patients within the same country or geographic region. If this results in a pooled site still having fewer than the prespecified number of ITI-007 patients, 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 site, the same site pooling algorithm will be applied again, but this time pooling sites with a larger prespecified 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.

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

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

12.4.1 Patient Disposition, Analysis of Demographics and Other Baseline Characteristics

Patient disposition will be summarized by treatment group, when applicable, and overall, 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 discontinuation due to all reasons, AEs (all, AEs associated with worsening of bipolar depression, and AEs not associated with bipolar depression), lack of efficacy, or due to any reason of special interest will be evaluated using the Kaplan-Meier method, where patients who complete the On-treatment Period or who discontinue for a reason other than the one being evaluated, will be censored. The Log-rank test will be used to compare the time to discontinuation between the treatment groups.

Demographic and baseline characteristics, including Bipolar Disorder diagnosis and baseline efficacy parameters, will be listed and summarized by treatment group. No inferential statistics will be presented.

12.4.2 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 will only be counted once within the preferred term.

During the study, a patient may be treated with zolpidem as described in Section 6.6. The number and percent of patients in the ITT Set receiving zolpidem and the total number of days on zolpidem will be summarized by treatment group for the Screening Period, for each week during the On-treatment Period and for post-treatment with ITI-007.

12.4.3 Study Medication Exposure and Treatment Compliance

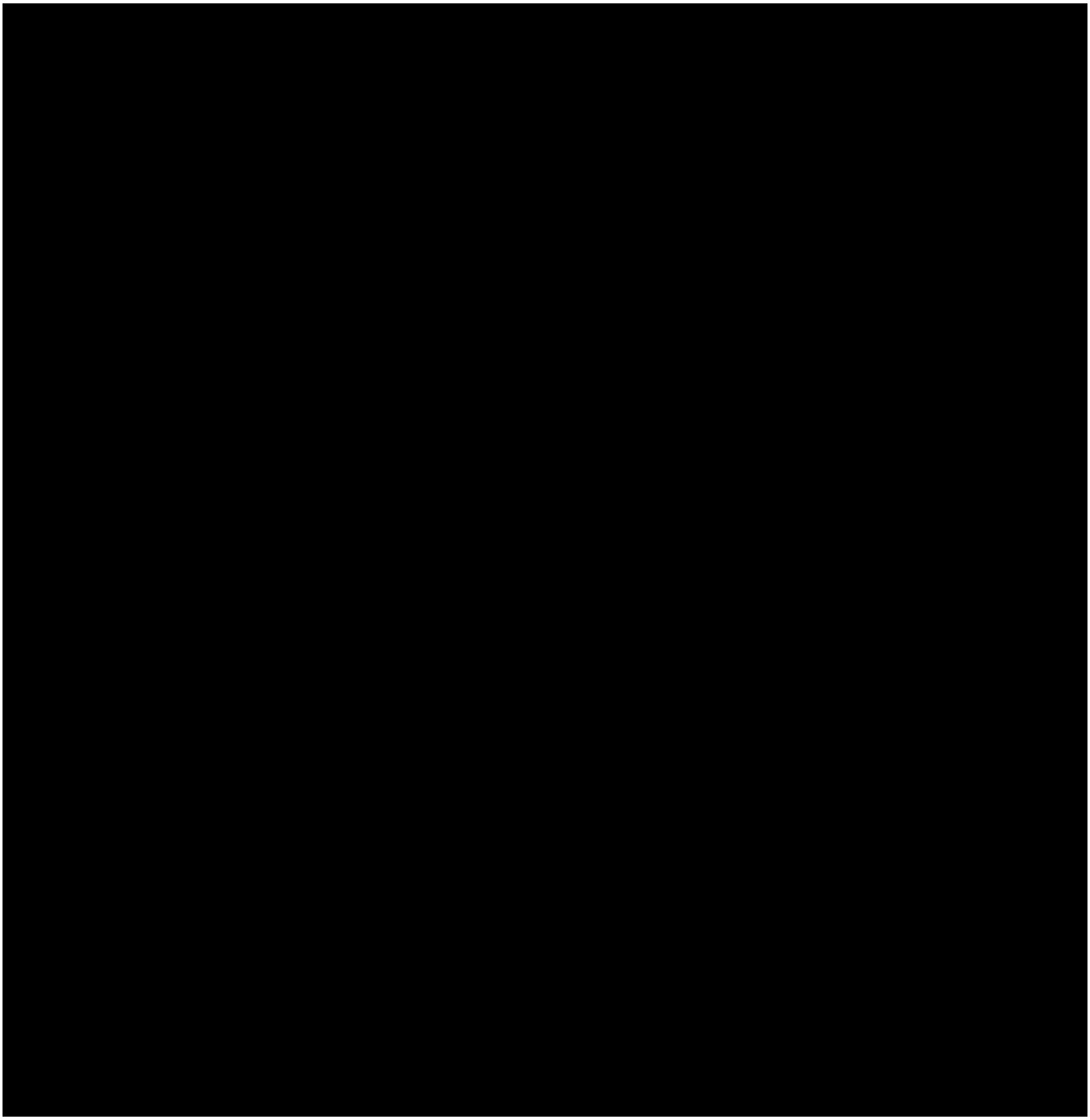
Exposure to study medication and treatment compliance will be presented using the ITT and Safety Analysis Sets. Duration of exposure (days) and dosing compliance (%) will be calculated and summarized by treatment group. Additionally, the number and percentage of patients exposed to study medication will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

12.4.4 Analysis of Primary and Key Secondary Efficacy Endpoints

The study is designed to evaluate the efficacy profile of ITI-007 60 mg based on the following primary and key secondary efficacy endpoints:

- Primary Endpoint – Change from baseline to Day 43 in the MADRS total score.
- Key Secondary Endpoint – Change from baseline to Day 43 in the CGI-BP-S score.

[redacted]



Safety Analyses

All safety parameters will be summarized using the safety analysis set.

Safety data such as reported and observed AEs, treatment emergent AEs (TEAEs) and 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 laboratory parameters, ECG and weight. Parameters collected in duplicate or triplicate will be analyzed as an average of the measures for the relevant time point, including baseline.

Reported AE terms will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) will be defined as any AEs, regardless of the relationship to study drug, that occur or worsen in intensity after the first dose of study drug and on or before the date of last dose of study drug plus one day. 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 drug. If relationship to study drug 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 categories, and preferred terms. 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 drug 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.

Patients who discontinue study or study drug due to AEs will be listed and summarized by system organ class and preferred term. TEAEs will be categorized to monitor signals of potential abuse of ITI-007 and the number and percentage of patients with at least one abuse-related TEAE will be summarized by the pre-specified categories.

Additional summaries of TEAEs will be presented as deemed necessary and will be specified in the SAP.

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 certain abnormal criteria. Pre -specified 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. Any comparison between the treatment groups will be considered exploratory.

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

Additional details for analyses on safety assessments will be provided in the SAP.

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of patients. Study staff will permit authorized representatives of the sponsor and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

14 QUALITY CONTROL AND QUALITY ASSURANCE

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

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Ethical Standard

15.2 Independent Ethics Committee or Institutional Review Board

Federal regulations and the International Conference on Harmonisation (ICH) guidelines require that approval be obtained from an Institutional Review Board (IRB) or Independent Ethics Committee (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, 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.

15.3 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.

15.4 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all patient materials will be submitted to the IRB/IEC and local regulatory authorities (where applicable) for review and approval. Approval of both the protocol and the consent form must be obtained before any patient is enrolled. Any amendment to the protocol will require review and approval by the IRB/IEC as well as local regulatory authorities, before the changes are implemented in the study.

15.5 Informed Consent Process

15.6 Patient Information and Consent

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to patients and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the patient. Consent forms will be IRB/IEC-approved, and the patient is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the patient and answer any questions that may arise. The patient will sign the informed consent document prior to any study-related assessments or procedures. Patients will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to patients for their records. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the clinical or research record.

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 clinical study 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.

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.

15.7 Patient 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 other local regulatory authorities, 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.

15.8 Future Use of Stored Specimens and Other Identifiable Data

Residual blood samples collected for pharmacokinetic analysis may be maintained after the study is complete. Patients will provide informed consent form for the future use of his/her samples. The sponsor or designee will maintain the samples up to 10 years following the completion of the study for pharmacokinetic analysis purposes only. Confidentiality will be protected for any future studies with the stored samples or data de-identified (identified by patient identification number only). Genetic testing will not be performed.

16 DATA HANDLING AND RECORD KEEPING

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R1) 8.2 and Title 21 of the US Code of Federal Regulations (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 subinvestigator listed on Form FDA 1572
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after study completion.
- IRB/IEC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardian, and
- Laboratory certifications and normal ranges for any local laboratories used by the study site, in accordance with 42 CFR 493

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 M.I.N.I., laboratory reports, and ECG strips.

After database lock, each study site will receive a CD-ROM containing all of their study site-specific eCRF data as entered into the EDC, including full discrepancy and audit history. Additionally, a CD-ROM copy of all of the study site's data will be created and sent to the sponsor for storage. The CRO will maintain a duplicate CD-ROM copy for their records. In all cases, patient initials will not be collected or transmitted to the sponsor.

16.1 Data Management Responsibilities

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

16.2 Data Capture Methods

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

16.3 Types of Data

Types of data that will be collected includes efficacy outcome assessments, safety outcome assessments, and pharmacokinetic assessments.

16.4 Schedule and Content of Reports

The sponsor or designee will be responsible for clinical monitoring plans and reports, safety monitoring plans, data management plans, statistical analysis plans and the clinical study report. Masking procedures and breaking the blind are described in Sections 5.4.2 and 5.4.3, respectively.

16.5 Study 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.

16.6 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 or local regulatory authority regulations or ICH GCP guidelines, and will lead to the patient being withdrawn from the study (Section 5.5).

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.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

18 LITERATURE REFERENCES

Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry. 1989;154:672-6.

Davis RE, Vanover KE, Zhou Y, et al. ITI-007 demonstrates brain occupancy at serotonin 5-HT_2A and dopamine D_2 receptors and serotonin transporters using positron emission tomography in healthy volunteers. Psychopharmacology (Berl). 2015;232(15):2863-72.

Endicott J, Nee J, Harrison W, Blumenthal R. Quality of Life Enjoyment and Satisfaction Questionnaire: A new measure. Psychopharmacology Bull. 1993;29:321-326.

Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. Rockville: U.S. Department of Health Education, and Welfare; 1976. 616 p.

Loebel A, Cucchiaro J, Silva R, et al. Lurasidone monotherapy in the treatment of Bipolar I Depression: a randomized, double-blind, placebo-controlled study. Am J Psychiatry. 2014a;171(2):160-8.

Loebel A, Cucchiaro J, Silva R, et al. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of Bipolar I Depression: a randomized, double-blind, placebo-controlled study. Am J Psychiatry. 2014b;171(2):169-77.

Montgomery SA and Åsberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382-389.

Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-77.

Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar G. The Mini International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview. J Clin Psychiatry. 1998;59(suppl 20):22-33.

Simpson GM. Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiat Scand Suppl. 1970;212:11–9.

Snyder GL, Vanover KE, Zhu H, et al. Functional profile of a novel modulator of serotonin, dopamine, and glutamate neurotransmission. Psychopharmacology (Berl). 2015;232(3):605-21.

Spearing MK, Post RM, Leverich GS, et al. Modification of the Clinical Global Impressions (CGI) Scale for use in Bipolar illness (BP): the CGI-BP. Psychiatry Res. 1997;73(3):159-71.

Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 1978;133:429–35.

Young AH, Calabrese JR, Gustafsson U, et al. Quetiapine monotherapy in Bipolar II depression: combined data from four large, randomized studies. Int J Bipolar Disord. 2013;1:10.

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]