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Study ID: ITI-007-403

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) or Major Depressive Disorder

Protocol Amendment 4.0 Date: January 27, 2023

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ITI-007-403

[redacted]

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

Original Protocol Version 1.0:	**November 7, 2019**
Amendment 2.0:	**November 2, 2020**
Amendment 3.0	**August 30, 2021**
Amendment 4.0:	**January 27, 2023**

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 Title 45: Public Welfare, part 46 (45 CFR Part 46) on the Protection of Human Subjects.

CONFIDENTIAL

INVESTIGATOR SIGNATURE PAGE

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The signature below constitutes the approval of this protocol and 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 product 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 Intra-Cellular Therapies, Inc. (the Sponsor).

Principal Investigator:

Signed: _____ Date: _____

Name:

Title:

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LIST OF ABBREVIATIONS

5-HT_{2A}	5-Hydroxytryptomine 2A Receptor
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
ARH	Heterogeneous Autoregressive
AST	aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
bITT	Bipolar Intent-to-treat
BMI	body mass index
bpm	beats per minute
C-SSRS	Columbia Suicide Severity Rating Scale
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression Scale–Severity
CI	confidence interval
CRF	case report form
CRO	Contract Research Organization
CSR	clinical study report
D_2	dopamine 2 receptor
DSM-5	Diagnostic and Statistical Manual, 5th Edition
eCRF	electronic Case Report Form
EAF	Eligibility Assessment Form
ECG	electrocardiogram
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
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITI	Intra-Cellular Therapies, Inc.
ITT	Intent-to-treat
IVRS	Interactive Voice Response System

IWRS	Interactive Web Response System
LDL	low-density lipoprotein
MADRS	Montgomery-Åsberg Depression Rating Scale
MAR	Missing at random
MDD	Major Depressive Disorder
MDE	major depressive episode
MedDRA®	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
mITT	Modified Intent-to-treat
MMRM	Mixed-effect Model for Repeated Measures
msec	Millisecond
PCS	Potentially Clinically Significant
PET	Positron Emission Tomography
QTcB	corrected QT Interval Using the Bazett Formula
QTcF	corrected QT Interval Using the Fridericia Formula
SAE	serious adverse event
SAS	Simpson Angus Scale
SERT	serotonin transporter
SAP	Statistical Analysis Plan
TEAE	treatment-emergent adverse event
TOEP	Toeplitz Structure
TOEPH	Heterogeneous Toeplitz Structure
ULN	upper limit of normal
US	United States
YMRS	Young Mania Rating Scale

1 PROTOCOL SYNOPSIS AND SCHEDULE OF EVENTS

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) or Major Depressive Disorder

Study Design: This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of lumateperone monotherapy in the treatment of patients with major depressive episodes (MDEs) associated with Bipolar I or Bipolar II Disorder (Bipolar Depression) or major depressive disorder (MDD) who also meet the Diagnostic and Statistical Manual of Mental Disorder, 5th Edition (DSM-5) criteria for mixed-features. The study consists of a Screening Period, a Double-blind Treatment Period, and a Safety Follow-up Period.

Screening Period (2 Weeks)

Potential patients will be evaluated during a Screening Period lasting up to 2 weeks.

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.

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 (lumateperone 42 mg or placebo) for a 6-week, double-blind treatment period.

Double-blind Treatment Period (6 Weeks)

Patients will take their first dose of study drug 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 attend clinic visits on Days 8, 15, 22, 29, 36, and 43.

The Double-blind 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 drug. Patients who withdraw prematurely should be seen for an early termination visit and will be asked to return to the clinic for a safety follow-up visit approximately 2 weeks after Visit 8/Early Termination (ET).

Objectives:

Primary Objective:

The primary objective of this study is to confirm the efficacy of lumateperone 42 mg administered orally once daily compared with that of placebo as measured by mean change from baseline to Day 43 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score in patients with bipolar depression with mixed features or MDD with mixed features.

Secondary Objectives

Key Secondary Objective:

The key secondary objective of this study is to confirm the efficacy of lumateperone 42 mg administered orally once daily compared with that of placebo as measured by mean change from baseline to Day 43 in Clinical Global Impression Scale–Severity (CGI-S) score in patients with bipolar depression with mixed features or MDD with mixed features.

Safety Objective:

The safety objective of this study is to determine the safety and tolerability of lumateperone administered orally once daily compared with that of placebo in patients with bipolar depression or MDD as assessed by adverse events (AEs); clinical laboratory results; vital sign measures; electrocardiogram (ECG) results; suicidality as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS); manic symptoms as assessed by the Young Mania Rating Scale (YMRS); and extrapyramidal symptoms (EPS) as assessed by Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson Angus Scale (SAS) scales.

Population:	Male and female patients between the ages of 18 and 75 years, inclusive, with a diagnosis of Bipolar I or Bipolar II Disorder with mixed features or major depressive disorder (MDD) with mixed features who are experiencing a major depressive episode (MDE) and who meet the following criteria may be eligible for participation in the study: • The start of the current MDE is at least 2 weeks but no more than 6 months prior to Screening (Visit 1); • The patient has at least moderate severity of illness as measured by MADRS total score ≥ 24 and CGI-S score ≥ 4 at Screening (Visit 1) and Baseline (Visit 2); • The patient has sufficient history and/or independent report verifying that the current MDE is causing clinically significant distress or impairment in social, occupational, or other important areas of functioning; • The patient has a YMRS total score between 4 and 16, inclusive, at Screening (Visit 1) and Baseline (Visit 2). Patients will be enrolled in multiple countries globally.
Phase:	3
Number of Sites:	Up to 60 sites, approximately
Description of Intervention:	Patients will be randomized to receive either lumateperone 42 mg or placebo. Patients will self-administer doses orally, once daily, each evening at home for the duration of the Double-blind Treatment Period. Study drug will be provided in blister cards containing capsules, and patients will be instructed to take 1 capsule per dose.
Study Duration:	For each patient completing the study, the study will last up to approximately 10 weeks (9 visits), including a Screening Period, a Double-blind Treatment Period, and a Safety Follow-up Period.
Statistical Methods:	**Efficacy Analyses** The primary efficacy endpoint is the change from baseline to Day 43 in MADRS total score. The analysis of the primary efficacy endpoint will be performed using a mixed-effects model for repeated measures (MMRM) with the change from baseline in the MADRS total score at each pre-specified postbaseline time point as the response variable; treatment group, visit, site (or pooled site), the stratification factor at screening (Bipolar Disorder or MDD diagnosis), and treatment group-by-visit interaction as factors; and the baseline

MADRS total score and visit-by-baseline MADRS total score interaction as covariates. An unstructured covariance matrix will be used to estimate the covariance among repeated measurements within patient. This analysis will be performed based on all post-baseline scores using only the observed cases without imputation of missing values. This primary efficacy analysis will first be performed based on the combined patient population of Bipolar Disorder with mixed features and of MDD with mixed features. If this primary analysis based on the combined population is statistically significant at 0.05 level, then by using a similar MMRM model the primary efficacy analyses will be performed separately for the subpopulation of Bipolar Disorder with mixed features and for the subpopulation of MDD with mixed features.

The key secondary efficacy endpoint is the change from baseline to Day 43 in CGI-S score. This endpoint will be analyzed using an MMRM model similar to the one proposed for the analysis of the primary efficacy endpoint replacing MADRS total score with CGI-S score for the baseline and baseline-by-visit interaction terms as covariates in the model. The key secondary efficacy analysis will first be performed based on the combined patient population of Bipolar Disorder with mixed features and of MDD with mixed features. If the key secondary analysis is statistically significant at 0.05 level, then by using a similar MMRM model, the key secondary efficacy analyses will be performed separately for the subpopulation of Bipolar Disorder with mixed features and for the subpopulation of MDD with mixed features.

Multiple comparisons for the primary and key secondary efficacy endpoints will be addressed using a fixed-sequence (hierarchical) gatekeeping strategy combined with Hochberg procedure. The key secondary efficacy endpoint will be tested and its 2-sided p-value compared with 0.05 level for statistical significance only if the comparison for the primary efficacy endpoint is significant for the combined and two separate subpopulations at 2-sided $\alpha = 0.05$ overall level. Otherwise, the p-value for the key secondary efficacy endpoint will be reported as nominal.

The efficacy conclusion will be based on the analyses using the modified Intent-to-Treat (mITT) Analysis Set. The mITT Analysis Set is defined as all randomized patients enrolled after the implementation of Amendment 2.0 (dated 02 Nov 2020) who received at least 1 dose of study drug and had baseline and at least 1 post-baseline assessment of MADRS total score.

Descriptive analyses of the efficacy endpoints will be performed for patients enrolled before the implementation of Amendment 2.0 (dated 02 Nov 2020).

Safety Analyses

Safety data such as reported and observed AEs and SAEs, clinical laboratory results, vital signs, physical and neurological examination findings, ECGs, YMRS, EPS as measured by AIMS, BARS, and SAS, and C-SSRS, will be summarized descriptively 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.

The safety analysis will be performed using the Safety Analysis Set, defined as all randomized patients who received at least 1 dose of study drug.

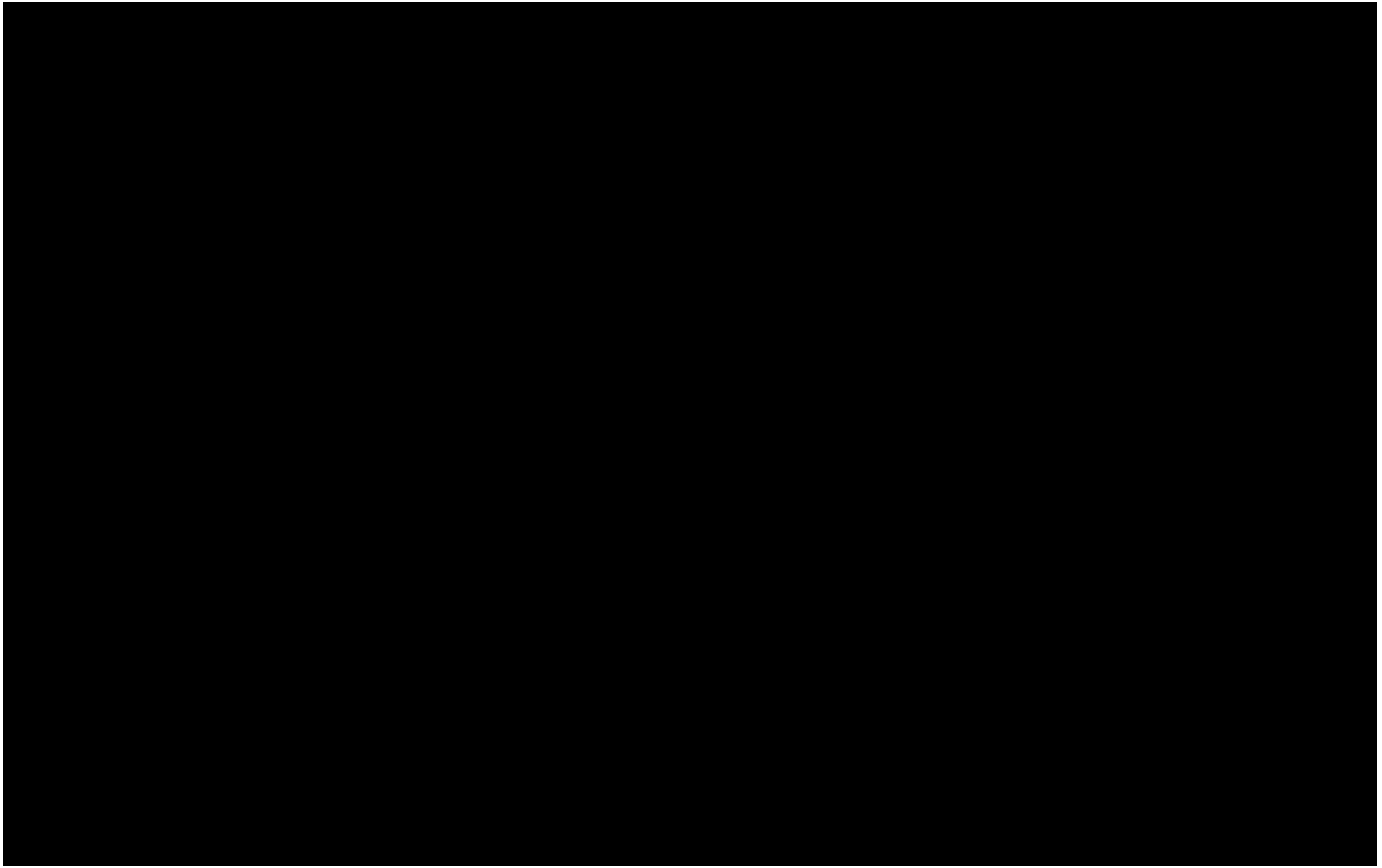
A statistical analysis plan (SAP) will be finalized prior to unblinding patients' treatment assignments.

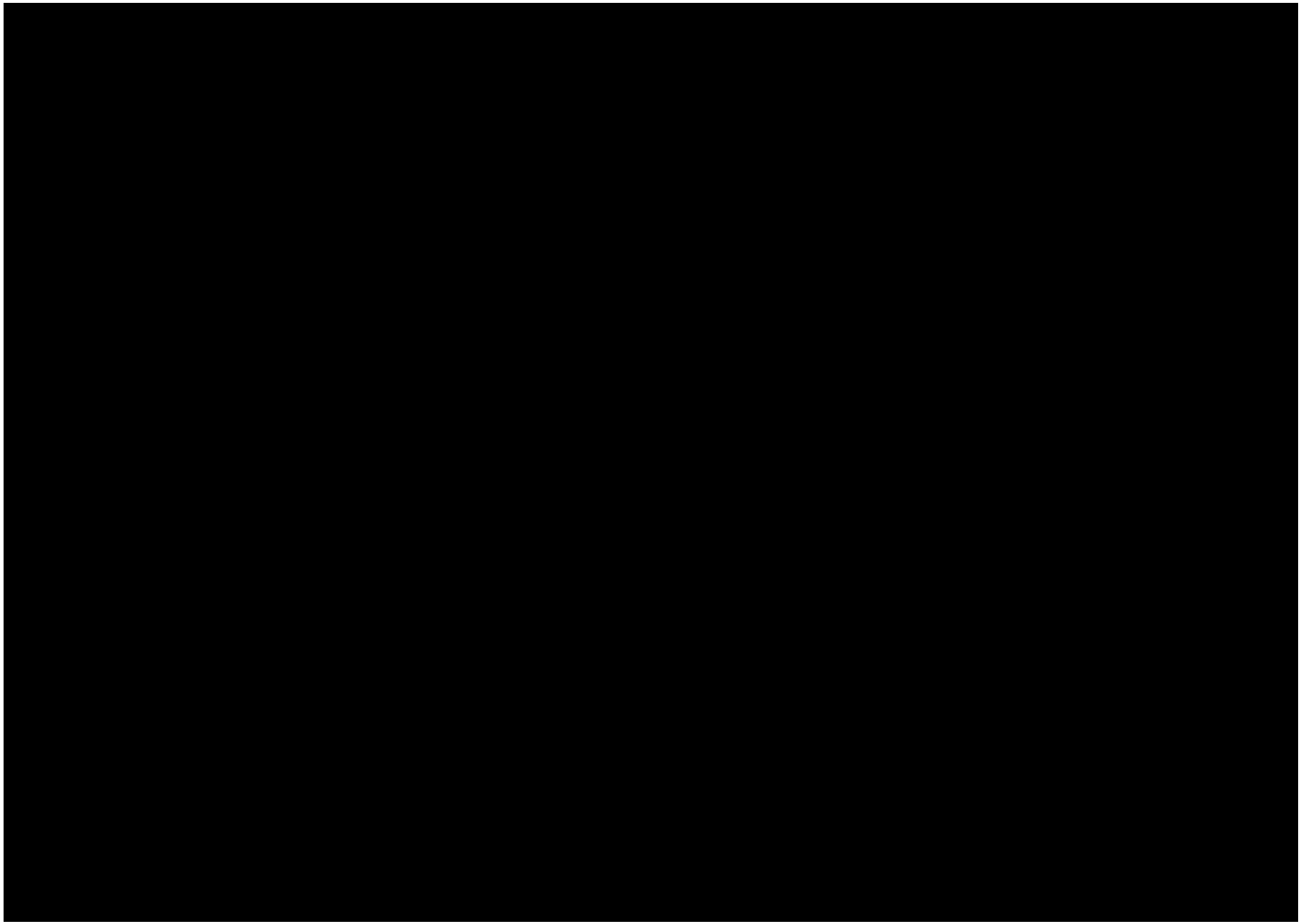
Sample Size:

The assumed effect size (treatment-group difference relative to pooled standard deviation) of 0.37 for lumateperone is based on a treatment difference of 3.3 units with a common pooled standard deviation of 9 for the primary efficacy parameter, change from baseline to Day 43 in MADRS total score. A sample size of 350 patients (175 per treatment group) enrolled after the implementation of Amendment 2.0 (dated 02 Nov 2020) will be needed to provide 90% power for primary analysis for the combined population of Bipolar Disorder with mixed features and MDD with mixed features based on a mixed-effect model for repeated measures (MMRM) using simulation method (Lu, 2012). The simulation assumes a correlation of 0.7 between the repeated measures and a dropout rate of 10% based on historical data.

The sample size and statistical power for the primary analyses in the subpopulations are presented in Section 9.1.

The study randomized approximately 100 patients under the original protocol before the implementation of Amendment 2.0 (dated 02 Nov 2020); therefore, the total enrollment for the study will be approximately 450 patients.





2 INTRODUCTION

2.1 Background Information

Major depressive disorder (MDD) is a serious psychiatric disorder characterized by the presence of one or more major depressive episodes (MDE) without a history of manic, mixed, or hypomanic episodes. Major depressive episodes may begin at any age; however, the average age of onset is in the mid-20s. The lifetime risk for MDD is estimated at 5% to 12% for men and 10% to 25% for women. MDD has a high mortality rate and up to 15% of patients with severe major depressive episodes die by suicide. In addition, individuals with MDD have high medical morbidity and are often plagued with more pain and physical illness than the general population.

Bipolar Disorder is a serious psychiatric disorder that may also result in major depressive episodes but is additionally characterized by manic or hypomanic episodes. Bipolar I Disorder is defined by the presence of mania with or without mixed features whereas Bipolar II Disorder is defined by the presence of hypomania, but both are often associated with MDEs. Bipolar Disorder affects approximately 5.7 million adult Americans a year, or about 2.6% of the U.S. population age 18 and older, 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 approved treatment options available.

In both MDD and Bipolar Disorder, MDEs may include some symptoms of hypomania or mania that do not meet the criteria for a manic or hypomanic episode. The recognition of this presentation has been noted in the DSM-5 (2013) as the specifier of “mixed features.” Mixed features associated with MDD have been noted to be a risk factor for the development of Bipolar I or Bipolar II disorder, highlighting the clinical utility of this specifier. Additionally, these “subsyndromic hypomanic” patients with either MDD or Bipolar Disorder may suffer from greater symptom severity, increased recurrence of mood episodes, higher comorbidity, and increased risk of suicidality. These poorer outcomes emphasize the need for effective treatments in this population.

Lumateperone (trade name CAPLYTA®) was approved by the Food and Drug Administration (FDA) on December 20, 2019, under NDA 209500 for the treatment of schizophrenia in adults. Intra-Cellular Therapies, Inc. (ITI, the Sponsor) is exploring the utility of lumateperone (ITI-007) for the treatment of MDEs with mixed features associated with Bipolar I or Bipolar II Disorder (bipolar depression) and MDD.

Lumateperone is a novel small molecule therapeutic agent designed specifically to combine serotonergic, dopaminergic, and glutamatergic modulation in a dose-dependent

manner. Lumateperone 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, lumateperone 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. Lumateperone also increases the phosphorylation of the NR2B, or GluN2B, subunit of N-methyl-D-aspartate channels in extrastriatal dopamine-rich brain regions (eg, nucleus accumbens) and indirectly modulates glutamatergic (NMDA 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. In addition, studies have also shown the potential for D_2 receptor antagonists in the treatment of MDEs with mixed features in MDD (Suppes et al, 2016; Swann et al, 2017) as well as mixed features in Bipolar Depression (McIntyre et al, 2015; McIntyre et al, 2020). The pharmacologic profile of lumateperone includes both the post-synaptic D_2 antagonism that appears efficacious in Bipolar Disorder and other pharmacological properties that may confer efficacy and better safety and tolerability than other D_2 antagonists. As a 5-HT_{2A} receptor antagonist and serotonin reuptake inhibitor, lumateperone is predicted to have antidepressant efficacy with fewer side effects than selective serotonin reuptake inhibitors (Meltzer et al, 1989). Lumateperone's indirect glutamatergic modulation in combination with serotonin reuptake inhibition predicts rapid-acting antidepressant response. Importantly, lumateperone lacks potent off-target interactions that have been associated with side effects of other antipsychotic drugs approved for the treatment of bipolar depression. For example, lumateperone 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 lumateperone are provided in the Investigator's Brochure.

Nonclinical data also suggest that lumateperone may have the potential to treat depression (Snyder et al, 2015). Antidepressant-like activity of lumateperone 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, lumateperone 1 mg/kg, 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 Study ITI-007-003, the

positron emission tomography (PET) Phase 1 clinical trial (Davis et al, 2015). PET 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 lumateperone administration. Lumateperone 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 the 10 mg dose (>85% occupancy). A dose of lumateperone 40 mg 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 lumateperone at dopaminergic and serotonergic brain targets. An additional PET study in patients with schizophrenia (Study ITI-007-008) demonstrated an average of approximately 40% striatal D_2 receptor occupancy at 60 mg, at plasma steady state, lower than that observed with most antipsychotic drugs. Relatively low striatal D_2 receptor occupancy likely contributes to a relatively low liability for extrapyramidal side effects and hyperprolactinemia compared with most antipsychotic drugs.

Clinical data from 3 well-controlled studies in patients with schizophrenia (Studies 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 addition to improving psychotic symptoms, lumateperone also improved symptoms of depression in patients with schizophrenia and comorbid depression at baseline. Safety data from these studies and other trials with lumateperone, which has been administered to more than 1500 individuals, show lumateperone to be well tolerated across a dose range from 0.7 to 98 mg, administered once daily for up to 42 days with a safety profile similar to placebo.

In previously conducted bipolar depression studies (Studies ITI-007-401, ITI-007-404, and ITI-007-402) lumateperone was well-tolerated with a favorable safety profile. Studies ITI-007-401 and ITI-007-404 were randomized, double-blind, fixed-dose, placebo-controlled, outpatient clinical trials designed to evaluate lumateperone as monotherapy in patients with major depressive episodes associated with either Bipolar I or II Disorder. Study ITI-007-402 was a randomized, double-blind, fixed-dose, placebo-controlled, outpatient clinical trial designed to evaluate lumateperone as adjunctive to lithium or valproate in patients with major depressive episodes associated with either Bipolar I or II Disorder.

In Study ITI-007-404, which was conducted globally, once-daily lumateperone 42 mg met the primary endpoint with statistically significant improvement over placebo at Week 6 (study endpoint), as measured by change from baseline in MADRS total score. Lumateperone 42 mg also met the key secondary endpoint of statistically significant improvement on the CGI-BP-S total score and demonstrated statistically significant improvement on the CGI-BP-S subscale that specifically assesses depression. Positive

effects were demonstrated in patients with either Bipolar I or Bipolar II Disorder. Additionally, a post hoc analysis of patients with 4 ≤ YMRS ≤ 12 showed statistically significant improvement over placebo at Week 6, as measured by change from baseline in MADRS and CGI-BP-S total score.

In Study ITI-007-402, which was conducted globally, once-daily lumateperone 42 mg adjunctive to lithium or valproate met the primary endpoint with statistically significant improvement over placebo at Week 6 (study endpoint), as measured by change from baseline in MADRS total score. Lumateperone 42 mg also met the key secondary endpoint of statistically significant improvement on the CGI-BP-S depression subscale.

In Study ITI-007-401, which was conducted solely in the United States, neither lumateperone dose (28 mg or 42 mg) met the primary endpoint of statistical separation from placebo as measured by change from baseline in MADRS total score. There was a high placebo response in this trial.

The purpose of this study is to confirm the efficacy of lumateperone 42 mg administered orally once daily compared with that of placebo as measured by mean change from baseline to Day 43 in the MADRS total score in patients with bipolar depression with mixed features or MDD with mixed features.

2.2 Rationale

The screening phase permits evaluation of diagnosis of Bipolar I or Bipolar II Disorder with mixed features or MDD with mixed features. Laboratory and ECG assessments enable confirmation of eligibility for inclusion into the study. Unless an extension of screening is approved by the Medical Monitor or Sponsor designee, the screening phase will be no longer than 2 weeks (14 days).

At Baseline (Visit 2), patients will be randomly assigned in a 1:1 ratio to 1 of 2 treatment groups (lumateperone 42 mg or placebo) and will receive treatment for up to 6 weeks. In order to ensure patient safety, a mandatory follow-up visit will be performed approximately 2 weeks after Visit 8/ Early Termination (ET). 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.

Lumateperone 42 mg was selected to evaluate the efficacy seen with this dose in bipolar depression studies ITI-007-404 and ITI-007-402. This dose delivers 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 lumateperone indicate that a dose as low as 10 mg is associated with >85% occupancy of cortical 5-HT_{2A} receptors, while the 42-mg dose demonstrates approximately 40% striatal D_2 receptor occupancy. SERT occupancy has been demonstrated to be comparable to D_2 receptor occupancy. Moreover, in patients with schizophrenia and

bipolar depression, once-daily oral administration of lumateperone 42 mg has been well tolerated with no dose titration needed and with a safety profile similar to placebo with up to 6 weeks' treatment duration. There is evidence that MDD patients with mixed features respond to similar doses of D2 receptor antagonists as bipolar depression patients with mixed features (Suppes et al, 2016*;* Swann et al, 2017). Therefore, a fixed-dose design will be employed in this study with once daily oral administration of lumateperone 42 mg (or placebo).

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

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

The hypothesis of this study is that lumateperone 42 mg will demonstrate efficacy based on a 2-sided test for the treatment of MDEs associated with Bipolar I or II Disorder or with MDD, with statistically significant superiority vs placebo on the primary outcome measure: mean change from baseline to Day 43 in MADRS total score in patients with bipolar depression or MDD who meet DSM-5 criteria for mixed features.

2.3 Potential Risks and Benefits

Patients will be monitored carefully for their mental health status and general health. Symptoms of bipolar depression may or may not improve during participation in this study; approximately half of the patients in this study will receive placebo. However, the information obtained from this study may help to treat people with bipolar depression in the future. More detailed information about the known and expected benefits and risks and reasonably expected AEs is provided in the lumateperone Investigator's Brochure.

3 STUDY OBJECTIVES

3.1 Primary Efficacy Objective

The primary objective of this study is to confirm the efficacy of lumateperone 42 mg administered orally once daily compared with that of placebo as measured by mean change from baseline to Day 43 in the MADRS total score in patients with bipolar depression with mixed features or MDD with mixed features.

This study will evaluate the efficacy of lumateperone 42 mg based on the following three sets of patients:

1. All patients enrolled after the implementation of Amendment 2.0, which includes all patients associated with Bipolar Depression with mixed features and all patients associated with MDD with mixed features;
2. All patients with Bipolar Disorder (I or II) with mixed features enrolled after the implementation of Amendment 2.0;
3. All patients associated with MDD with mixed features.

3.2 Secondary Efficacy Objectives

[redacted]

[redacted]

[redacted]

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

3.3 Safety Objectives

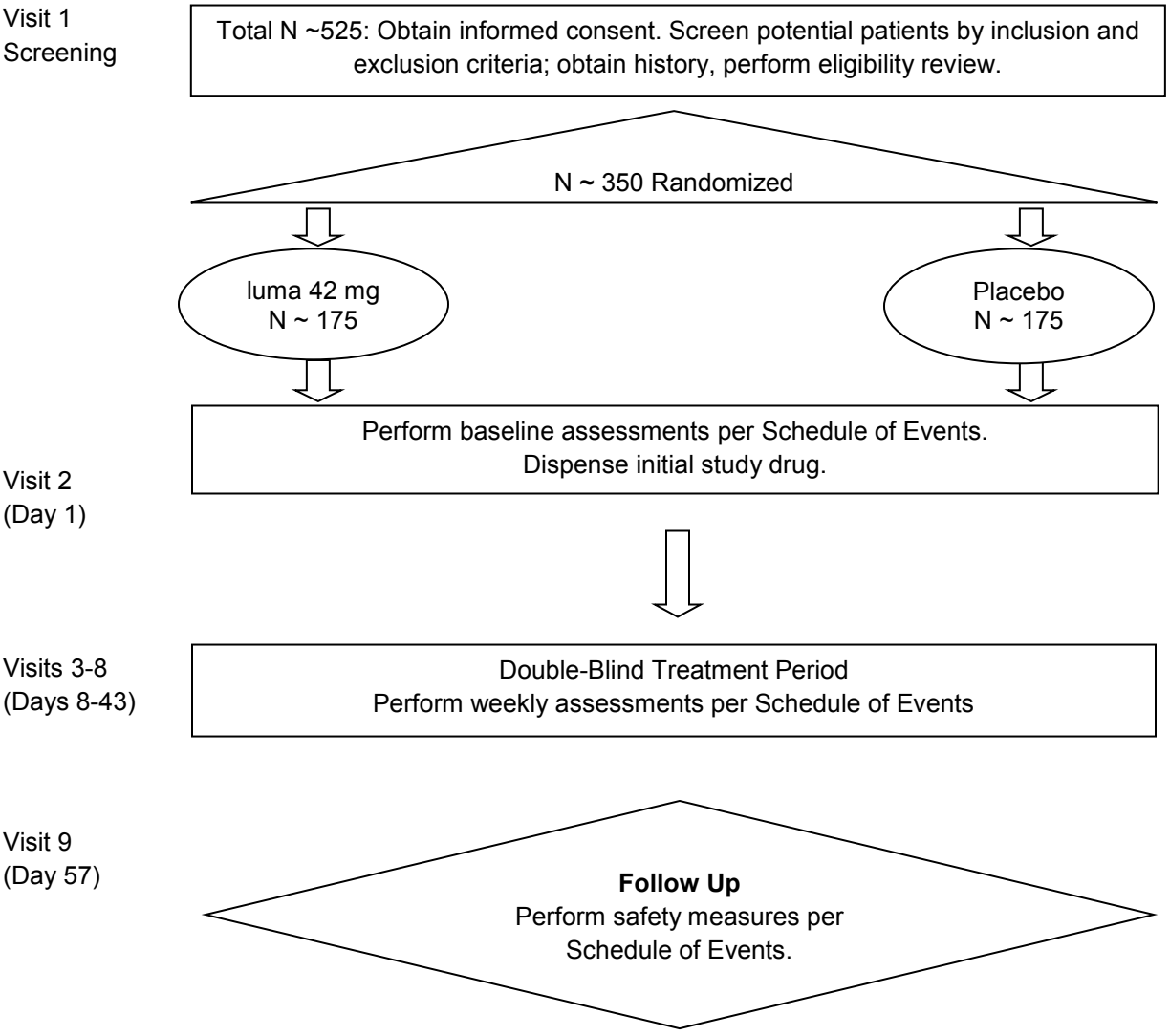
The safety objective of this study is to determine the safety and tolerability of lumateperone 42 mg administered orally once daily compared with that of placebo in patients with bipolar depression and MDD as assessed by AEs; clinical laboratory results; vital sign measures; ECG results; suicidality as assessed by the C-SSRS; manic symptoms as assessed by the YMRS; and extrapyramidal symptoms (EPS) as assessed by Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson Angus Scale (SAS) scales.

4 STUDY DESIGN

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of lumateperone monotherapy in the treatment of patients with MDEs associated with Bipolar Disorder with mixed features or MDD with mixed features. The study consists of a Screening Period, Double-blind Treatment Period, and a Safety Follow-up Period.

Figure 4-1 presents the study-design schematic. The numbers of patients enrolled and randomized are based on the patients to be enrolled after the implementation of Amendment 2.0.

Figure 4-1: Schematic of Study Design



luma = lumateperone

Screening Period (2 Weeks)

Potential patients will be evaluated during a Screening Period lasting up to 2 weeks unless an extension of the Screening Period is approved by the Medical Monitor or Sponsor Designee.

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

At Baseline (Visit 2), patients who continue to meet all eligibility criteria will be randomized to 1 of the 2 treatment arms (lumateperone 42 mg or matching placebo) for a 6-week, double-blind treatment period.

Double-blind Treatment Period (6 Weeks)

Patients will take their first dose of study drug on the evening of Baseline (Visit 2, Day 1). A single dose will be taken each day in the evening, with or without food, for the duration of the 6-week Double-blind Treatment Period.

Following randomization, patients will attend outpatient study visits on Days 8, 15, 22, 29, 36, and 43.

With approval from the Sponsor or Sponsor's representative, sites will be permitted to conduct remote visits if the patient is unable to travel to the site for an in-person visit or if the site is unable to schedule an in-person visit. However, all Screening and Baseline (Visit 2) assessments must be performed in person.

A patient will be defined as a treatment completer if the patient completed the double-blind treatment period (all scheduled visits up to and including Visit 8).

Safety Follow-up Period (2 Weeks)

All patients should return to the clinic for the Safety Follow-up Visit approximately 2 weeks after Visit 8/ET.

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. Male and female patients between the ages of 18 and 75 years, inclusive, at the start of screening;
3. Meets the Diagnostic and Statistical Manual of Mental Disorder, 5th Edition (DSM-5) criteria for Bipolar I or Bipolar II Disorder with mixed features or MDD with mixed features, as confirmed by the Investigator or Sponsor-approved rater using the Mini-International Neuropsychiatric Interview (MINI) and meets all of the following 4 criteria:
    a. The start of the current MDE is at least 2 weeks but no more than 6 months prior to the Screening (Visit 1);
    b. Has at least moderate severity of illness, as measured by a rater-administered MADRS total score ≥24 and corresponding to a CGI-S score of ≥ 4 at Screening (Visit 1) and Baseline (Visit 2);
    c. Has 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. Has a rater-administered YMRS total score between 4 and 16, inclusive, at Screening (Visit 1) and Baseline (Visit 2).
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 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 ≥ 25% decrease in the rater-administered MADRS total score between Screening (Visit 1) and Baseline (Visit 2);
2. In the opinion of the Investigator, the patient has a significant risk for suicidal behavior during the course of his/her participation in the study or
    a. At Screening (Visit 1), 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 (Visit 1), the patient has had 1 or more suicidal attempts with reference to a 2-year period prior to screening; or
    c. At Baseline (Visit 2), 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 (Visit 1) or Baseline (Visit 2), 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 (Visit 1). On Day 1 (Baseline/Visit 2), female patients of childbearing potential must have a negative urine pregnancy test prior to study drug administration;
4. Within 12 months of screening, the patient has a confirmed DSM-5 psychiatric diagnosis other than Bipolar Disorder or MDD, including:
    a. Schizophrenia or other psychotic disorder;
    b. Anxiety disorders such as panic disorder, obsessive-compulsive disorder, general anxiety disorder, or post-traumatic stress disorder as a primary diagnosis (however, anxiety symptoms may be allowed, if secondary to Bipolar Disorder or MDD, provided these symptoms do not require current treatment);
    c. Eating disorder;
    d. Personality disorder;
    e. Moderate or severe substance use disorder (including for cannabis, excluding for nicotine);
    f. Any other psychiatric condition (other than Bipolar Disorder or MDD) 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 or MDD, as described in Exclusion Criterion #4;
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 prior to study enrollment
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 his/her lifetime.
8. For patients with bipolar depression, the patient has had at least 4 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 for the treatment of MDD or medications approved for the treatment of bipolar depression at an adequate dose (per locally-approved label) for an adequate duration (at least 6 weeks);
10. The patient is currently receiving formal cognitive behavioral therapy (CBT), 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 Screening (Visit 1) or presents evidence of either withdrawal from or acute intoxication with cocaine, opiates, amphetamines (including methamphetamine), alcohol, barbiturates, or hallucinogens or similar compounds. A negative urine drug screen/test is required for study enrollment. Repeat testing is prohibited for positive alcohol, cocaine, phencyclidine, and amphetamine results;
13. The patient has used 1 of the following agents under the specified conditions:
    a. Any previous exposure to lumateperone (including participation in previous clinical study of lumateperone) 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 Baseline/Visit 2 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 which may be taken as needed, but no more than 3 times per week 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 and medical foods are excluded unless approved by the Medical Monitor. Daily multivitamin use is not excluded;

14. The patient has abnormal laboratory values or clinical findings at screening that are judged clinically significant including, but not limited to:

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

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

    c. Alkaline phosphatase >2.0 × ULN;

    d. Gamma-glutamyl transpeptidase >2.0 × ULN;

    e. Total bilirubin >1.5 × ULN;

    f. Serum creatinine >1.5 × ULN;

    g. Blood urea nitrogen >1.5 × ULN;

    h. Thyroid-stimulating hormone (TSH) outside of the normal limits and clinically significant, as determined by the Investigator. Free T3 and free T4 will be measured if TSH level is out of range. The patient will be excluded if the free T3 or T4 level is clinically significant;

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

    Note: medical conditions that are stable with medication (eg, diabetes, hypertension, high cholesterol, and thyroid abnormalities) 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.

15. 12-lead ECG (in a supine position after a rest of approximately 10 minutes at the screening visit) corrected QT interval using the Fridericia formula (QTcF) >450 msec for males or females, corrected QT interval using the Bazett formula (QTcB) >450 msec for males or >470 msec for females, and/or heart rate ≤ 50 bpm, or evidence of clinically significant bundle-branch blocks. Repeat ECG testing will not be permitted;

16. 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] > 7.0% [>53 mmol/mol] at screening with no HbA1c re-test allowed); 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/she participates in the study (in the opinion of the Investigator);
17. The patient has a known history of human immunodeficiency virus (HIV) infection;
18. The patient has a positive test for hepatitis B surface antigen and/or hepatitis B core antibody immunoglobulin M at screening;
19. The patient has a positive hepatitis C antibody at screening, with the exception of a patient for whom the reflex HCV RNA test is negative
20. 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);
21. The patient is judged by the Investigator to be inappropriate for the study;
22. The patient is an employee of the Investigator or study site, or immediate family (ie, spouse, parent, child, or sibling, whether biological or legally adopted) of such employees, the Investigator, the Sponsor, or contract research organizations (CROs) conducting the study.

5.3 Strategies for Recruitment

Strategies for recruitment will be determined by individual participating clinical study sites using Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved recruitment 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 (lumateperone 42 mg or matching placebo) for a 6-week Double-blind Treatment Period.

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 9.4 or newer 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). Patients will be stratified based on their Bipolar Disorder or MDD diagnosis. Also, patients with Bipolar Disorder will be further stratified by Bipolar I or Bipolar II diagnosis.

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 that patient data 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 drug will be supplied in identical treatment cards and packaging, and will be similar in color, smell, taste, and appearance, thereby enabling double-blind conditions.

5.4.3 Breaking the Blind

A patient's treatment assignment will not be broken until after the end of the study unless medical treatment of the patient depends on knowing the study drug 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 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. The date on which the code was broken together with the identity of the person responsible must also be documented.

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

5.5 Discontinuation of Patients

A premature discontinuation will occur when a patient who signed the ICF ceases participation in the study, regardless of circumstances, before the completion of all study visits and procedures. Patients can be prematurely discontinued from the study after careful consideration for one of the following reasons:

- Death
- AE or SAE
- Lack of efficacy
- Lost to follow-up
- Pregnancy
- Physician decision
- Protocol violation
- Study terminated by Sponsor
- Withdrawal by subject or withdrawal of consent

***NOTE**:* If a patient discontinues due to withdrawal of consent and either a concurrent AE was reported or concurrent lack of efficacy was documented, the study site should query and confirm the primary reason for discontinuation and record the primary reason for discontinuation on the electronic case report form (eCRF).

All patients who prematurely discontinue from the study regardless of cause should be seen for final assessments as soon as possible at Visit 8/ET. All patients who prematurely discontinue from the study should also return for the Safety Follow-up Visit (Visit 9).

Patients who discontinue from the study and do not return to the study site for the ET Visit must be requested in writing to return to the study site for a final assessment. A copy of the letter, together with the source documentation, will be kept in the Investigator's files. The reason for premature discontinuation from the study will be recorded on the Study Termination Page of the eCRF. Study site staff may be contacted by the Sponsor after

each premature discontinuation to ensure that proper characterization of the reason for discontinuation is recorded.

5.6 Premature Study Termination or Study Suspension

The Sponsor reserves the right to terminate the study in its entirety or at a specific study site before study completion.

5.7 Patient Replacement Procedures

Patients who prematurely discontinue from the study during the Double-blind Treatment Period will not be replaced.

6 STUDY TREATMENTS

6.1 Study Drug Description

Lumateperone 42 mg and placebo will be supplied as capsules. Placebo capsules are identical in appearance to lumateperone and have the same excipient ingredients as lumateperone but do not have the active compound.

[redacted]

Descriptions of study drug supplies and formulation for the ***original*** supply (lumateperone Swedish orange opaque capsule) and for the ***new*** supply (lumateperone white opaque capsule) are provided in Table 6-1 and Table 6-2, respectively.

Table 6-1: Study Drug Dosage and Composition—Original Supply

Study drug	**Lumateperone 42 mg**	**Placebo**
Dose frequency	Once daily in the evening	Once daily in the evening
	Composition (mg)	
Lumateperone dose	42 (60 mg lumateperone tosylate)	0
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Table 6-2: Study Drug Dosage and Composition—New Supply

Study drug	Lumateperone 42 mg	Placebo
Dose frequency	Once daily in the evening	Once daily in the evening
	Composition (mg)	
Lumateperone dose	42 (60 mg lumateperone tosylate)	0
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

6.1.1 Formulation, Packaging, and Labeling

Lumateperone and matching placebo will be prepared according to current Good Manufacturing Practice standards in blister cards and shipped under ambient conditions. Each blister card will contain a sufficient quantity of capsules for 1 patient for 1 week:

- The ***original*** supply contains 7 doses, plus 1 extra dose, to be dispensed at every visit during the 6-week treatment period.
- The ***new*** supply will contain 7 doses, plus 3 extra doses, to be dispensed at every visit during the 6-week treatment period.

The blister card for study drug in the ***original*** supply contains one 1×8 strips of capsules; the blister card for study drug in the ***new*** supply will contain one 1×10 strips of capsules (see Table 6-3 and Table 6-4).

Table 6-3: Weekly Study Drug Cards—Original Supply

Treatment	Card Contents
Lumateperone 42 mg	One 1×8 strip of lumateperone 42-mg capsule
Placebo	One 1×8 strip of lumateperone-matched placebo

Note: Each card will hold 8 capsules.

Table 6-4: Weekly Study Drug Cards—New Supply

Treatment	Card Contents
Lumateperone 42 mg	One 1×10 strip of lumateperone 42-mg capsule
Placebo	One 1×10 strip of lumateperone-matched placebo

Note: Each card will hold 10 capsules.

Each lumateperone dosing container will be labeled according to local laws and regulations.

6.1.2 Product Storage and Stability

Study drug must be stored in a secure area (eg, a locked cabinet) while in storage at the study site, protected from moisture, and kept at room temperature. Patients will be instructed to store the blister card at room temperature at home, out of the reach of children.

6.2 Dosage and Administration of Study Drug

Patients will be randomized to receive either lumateperone 42 mg or placebo. Study site personnel will receive a treatment card number from the IVRS/IWRS for each patient at every clinic visit (eg, at Baseline/Day 1, Visit 3/Day 8, Visit 4/Day 15, Visit 5/Day 22, Visit 6/Day 29, and Visit 7/Day 36) to ensure that the correct study drug is dispensed.

Patients will be instructed to take 1 capsule per dose. Patients will self-administer study drug orally, once daily in the evening for the duration of the Double-blind Treatment Period. Study drug should be administered with or without food and at approximately the same time each evening.

6.3 Modification of Study Treatment Administration

Patients who do not tolerate the study drug should be discontinued from the study. No dose modifications are allowed. See Section 5.5 for details regarding patient discontinuation.

6.4 Study Drug Accountability Procedures

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

6.5 Assessment of Patient Compliance with Study Drug Administration

Patient compliance will be assessed by capsule counts of unused study drug at each visit during the double-blind treatment period. Any irregularities in medication adherence should be discussed with the patient. Any exceptions to non-compliance with the study drug regimen due to unusual circumstances should be discussed with the Medical Monitor.

All errors in medication dispensing or administration must be carefully documented. These errors may include providing the wrong dose, not taking dose as prescribed, or losing medication. 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

Use of the following products during the study is prohibited: 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.

Zolpidem may be taken no more than 3 times per week during the screening period and the first 2 weeks of the double-blind treatment period only (Section 5.2, Exclusion 13). If zolpidem is not available in specific regions, another sedative hypnotic may be approved by the Medical Monitor.

Patients considered potentially eligible for participation will be required to discontinue their current antidepressant treatment and/or other psychotropic drugs for the duration of the study.

Use of all concomitant medications will be recorded in the patient's eCRF. Drug name and dates of administration must be recorded for 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 complete details regarding the medication are recorded 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.

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8 EFFICACY, SAFETY, AND OTHER ASSESSMENTS

8.1 Diagnostic and Other Screening Period Assessments

8.1.1 Mini International Neuropsychiatric Interview

To be included in this study, a patient must meet the DSM-5 criteria for diagnosis of Bipolar I or Bipolar II Disorder with mixed features or MDD with mixed features, as confirmed by the MINI (7.0.2; 8/8/16 version). The MINI is a validated clinical tool (Sheehan et al, 1998) that will be used at screening only and will be completed by a Sponsor-approved rater.

8.1.2 Young Mania Rating Scale

The YMRS is an 11-item, clinician-administered mania rating scale with established reliability, validity, and sensitivity that assesses 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 YMRS total score assesses baseline severity of manic symptoms and treatment-emergent manic symptoms in patients. It will be completed by the Sponsor-approved rater.

8.1.3 Medical History and Other Information

Medical history information will be collected at screening and should include demographic information, current and past medical conditions, and current and past medications. Prior to study drug administration, medical history must be documented in the patient's study chart and also recorded in the appropriate eCRF. In addition to 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.

Patients will be checked for previous participation in an ITI-007 clinical study and for duplicate enrollment by study site staff through Verified Clinical Trials (VCT).

[redacted]

8.1.5 Patient Placebo Questionnaire and Training

A brief training module will be provided describing placebo response at Baseline (Visit 2). 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.

8.2 Efficacy Assessments

8.2.1 Montgomery-Åsberg Depression Rating Scale (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 Sponsor-approved rater on a scale of 0 to 6 in which a score of 6 represents the most severe symptoms for each item assessed. The MADRS total score ranges from 0 to 60.

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

8.2.2 Clinical Global Impression–Severity (CGI-S)

The Clinical Global Impressions Scale-Severity provides the clinician's assessment of the overall severity of the patient's psychopathology (Guy, 1976). The CGI-S asks the clinician: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" which is rated on the following seven-point scale: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients. The CGI-S will be completed by a Sponsor-approved rater.

8.3 Safety Assessments

All patients who receive study drug will be evaluated for safety. Safety assessments will include incidence of AEs, C-SSRS assessment for suicidality, YMRS assessment of manic symptoms, EPS assessments as measured by AIMS, BARS, and SAS scales, clinical laboratory evaluations, ECG evaluations, vital sign measurements, and physical examination and neurological findings. Additional details pertaining to safety assessments are provided in the Schedule of Events (Table 1-1).

8.3.1 Adverse Events

8.3.1.1 Definition of Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not it is considered related to the medicinal product (ICH-E2A; 21 CFR 312.32[a]).

NOTE: Medical procedures scheduled prior to obtaining informed consent but occurring during the study should not be captured as AEs but the medical reason for the procedure should be listed in the medical history if related to a pre-existing condition.

8.3.1.2 Definition of Serious Adverse Event

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

- Results in death;
- Is life threatening;

  Note: The term “life threatening” refers to an event in which the patient is at risk of death at the time of the event.

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

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of study medication dependency or drug abuse.

Emergency room visits that do not result in hospitalization should be evaluated for one of the other serious outcomes to determine whether they qualify as SAEs.

Pre-planned hospitalizations (eg, elective procedures for pre-existing conditions that did not worsen, such as cosmetic surgery and hysterectomy) are excluded from SAE reporting.

Expectedness of SAEs

The Sponsor or designee will be responsible for determining whether an SAE is expected or unexpected. An SAE 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.

8.3.1.3 Classification of Adverse Events and Serious Adverse Events

8.3.1.3.1 Causality Assessment

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

The Investigator will assess the causality/relationship between the study drug and the AE. Table 8-1 presents the AE causality categories, one of which should be selected based on medical judgment and all contributing factors.

Table 8-1: Adverse Event 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 (eg, concomitant disease, environmental factors, or other drugs or chemicals).

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

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

8.3.1.3.2 Severity

The Investigator will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the patient's eCRF. *Severity,* which is a description of the intensity of manifestation of the AE, is distinct from *seriousness,* which implies a patient outcome or AE-required treatment measure associated with a threat to life or functionality (Section 8.3.1.2). Severity will be assessed according to the following scale (Table 8-2):

Table 8-2: Adverse Event Severity Categories

Category	Definition
Mild	A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research
Severe	A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Any change in intensity of signs and symptoms will be captured by recording a new AE with the amended intensity grade and the date of the change in intensity. If changes in AE intensity occur more than once a day, the maximum intensity of the AE should be recorded for that day.

8.3.1.4 Time Period and Frequency of AE Assessment and Follow-up

The Investigator will report all AEs and SAEs from the time informed consent was obtained until 30 days after the final protocol-defined study visit or the last known dose of study drug (if the final visit does not occur).

All AEs must be 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 clinically stable.

8.3.1.5 Adverse Event Reporting Procedures

8.3.1.5.1 Reporting Adverse Events

All AEs, including overdose of study medication or other medication, must be recorded on the appropriate AE reporting page of the patient's eCRF whether or not they are considered causally related to study medication. For every AE, the Investigator must:

- Provide an assessment of the seriousness of the event (ie, is it an SAE?), as well as the severity and casual relationship. See Section 8.3.1.2 for the definition of SAEs and Section 8.3.1.5.2 for SAE reporting procedures.
- Document all actions taken with regard to study medication
- Detail any other treatment measures taken for the AE

Any AEs that are ongoing at the time of the final protocol-defined study visit will be followed until the condition returns to pre-study status, has resolved or stabilized, or can be explained as being unrelated to study medication.

8.3.1.5.2 Reporting Serious Adverse Events

The Sponsor is required to inform regulatory authorities of SAEs that meet specific criteria. Therefore, the Sponsor must be notified immediately regarding any SAE that occurs after informed consent is obtained.

For the initial SAE report, the Investigator will complete, sign, and date 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 (eg, hospital reports, consultant reports, autopsy reports), with the study patient's personal identifiers removed. All relevant information obtained by the Investigator through review of these documents will be recorded and 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 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.

8.3.2 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 partner of a patient during study participation must be reported by completing a Pregnancy Reporting Form. The patient must stop study drug immediately after pregnancy is discovered and have an ET visit as soon as possible. Additionally, each pregnancy must be reported to ITI within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the patient was discontinued from the study.

Pregnancy complications and elective terminations for medical reasons should not be reported as an AE or SAE. If the pregnancy is associated with an SAE (eg, spontaneous miscarriage or if the mother is hospitalized for hemorrhage), a separate SAE form must be filed as described in Section 8.3.1.5.2 with the appropriate serious criterion (eg, hospitalization) indicated in addition to the Pregnancy Reporting Form.

8.3.3 ECG Assessments

A 12-lead ECG will be performed during the Double-blind Treatment Period at the visits specified in the Schedule of Evaluations (Section 1). ECGs will be performed and electronically transmitted to a central ECG laboratory for analysis according to the instructions provided by the central ECG laboratory. Measurements (in msec) will be recorded for the following parameters: PR interval, QRS duration, and uncorrected QT

interval; QTcB (Bazett corrected QT interval) and QTcF (Fridericia corrected QT interval) will be calculated.

The overall interpretation and determination of the clinical significance of ECG findings using the interpretation from the central ECG laboratory will be the responsibility of the Investigator and will be recorded in the patient's eCRF. For eligibility criteria, the values reported on the central ECG interpretation report, not the values that are printed on the tracing itself, are used.

8.3.4 Vital Sign Assessments

Vital signs (pulse rate, systolic and diastolic blood pressure [BP], body temperature, body weight, and waist circumference) will be assessed at every visit. Height will be assessed at Screening/Visit 1 only; BMI will be calculated at Screening/Visit 1 and Visit 8/ET.

BP and radial pulse rate will be measured twice: once in the supine position for at least 5 minutes followed by once in the standing position. The standing measurements should be assessed after at least 2 minutes to allow the BP to equilibrate in the standing state.

BP may be measured manually or by machine, but radial pulse rate should only be measured manually and for a sufficient time to acquire an accurate measurement.

Patients should be instructed not to wear clothing with tight sleeves when they come for clinic visits. Additionally, patients should be kept as calm and undisturbed as possible while BP and pulse rate measurements are taken (eg, there should be no talking while the BP is being measured). The same arm and BP cuff (appropriate to the arm circumference) should be used for all BP measurements.

Whenever possible, the patient's weight should be measured at the same time of day; the patient should wear his/her usual indoor clothing but take off his/her jacket and shoes. For each patient, body weight should be determined using the same equipment during the study after ensuring its proper calibration.

8.3.5 Clinical Laboratory Evaluations

Blood and urine samples for clinical laboratory tests will be collected during the study as detailed in the Schedule of Evaluations (Table 1-1). During screening, the Investigator/sub-Investigator should assess the clinical significance of any values that are outside the reference ranges provided by the central laboratory; patients with abnormalities judged to be clinically significant will be excluded from the study. Laboratory results should be reviewed by the Investigator/sub-investigator throughout the study.

Patients are required to fast overnight (≥ 10 hours) before arriving at the study site for appointments involving the collection of clinical laboratory blood tests.

The following clinical laboratory analytes will be evaluated:

Hematology: hematocrit; hemoglobin; HbA_{1c} (Screening/Visit 1 and Visit 8/ET); 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 platelet count.

Clinical chemistry: albumin; alkaline phosphatase; blood urea nitrogen; gamma-glutamyl transferase; calcium; creatinine; glucose; insulin; cholesterol (high-density lipoprotein [HDL] and low-density lipoprotein [LDL] [calculated] and LDL will be reported, and LDL will be reflexed if a patient's triglycerides are >400 mg/dL); triglycerides; phosphate; potassium; prolactin; ALT; AST; lactate dehydrogenase; sodium; chloride; bilirubin (total, direct); total protein; uric acid; creatine phosphokinase; and TSH (reflex free T3 and free T4 at Screening/Visit 1 and at Visit 8/ET only).

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

8.3.5.1 Hepatitis Screening

Blood samples will be collected at screening from all patients in order to perform hepatitis B surface antigen, hepatitis B core antibody IgM, and hepatitis C antibody (immunoglobulin G) testing. Test results will be sent to the study site and must be reviewed before Baseline (Visit 2, Day 1). Any patient who tests positive for hepatitis B surface antigen and/or hepatitis B core antibody IgM or positive hepatitis C antibody with a positive confirmatory hepatitis C RNA result will be excluded from participating in the study. Details regarding sample collection, processing, and shipping are provided in the Laboratory Manual.

8.3.5.2 Urine Drug and Alcohol Screening

Urine drug (amphetamines, barbiturates, benzodiazepines, cannabinoids [THC], cocaine metabolites, methadone, opiates, phencyclidine, propoxyphene) and alcohol tests will be performed. Any patient who tests positive for alcohol or any drug, excluding prescription benzodiazepines, prescription opiates, and cannabinoids, at screening will be excluded from participating in the study. Positive drug screen results may undergo confirmative

testing. Repeat testing is prohibited for positive alcohol, cocaine, phencyclidine, and amphetamine results.

Additional information regarding sample collection, processing, and shipping is provided in the Laboratory Manual.

8.3.5.3 Urine and Serum Pregnancy Test

Female patients who are of childbearing potential will undergo serum and urine pregnancy tests at the study clinic at Screening (Visit 1), at Baseline (Visit 2, Day 1), and, at the discretion of the Investigator, at an Unscheduled Visit. At Visit 5 and Visit 8/ET, urine pregnancy tests will be administered.

Serum pregnancy testing will be performed using blood collected as part of protocol-specified sample; urine pregnancy testing will use a urine dipstick.

If the urine and serum pregnancy tests at screening are positive, the patient will not be eligible to participate in the study. If a urine pregnancy test is negative and the associated serum pregnancy test is positive, the patient will be discontinued from the study.

8.3.6 Other Safety Assessments

8.3.6.1 Extrapyramidal Scales

8.3.6.1.1 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” in 2 or more categories or a score of “moderate” or “severe” in any 1 category results in a positive AIMS score (ie, the scores are not averaged). Additionally, overall severity is scored on the basis of severity of abnormal movements and incapacitation due to abnormal movements. The patient’s awareness of and distress caused by the abnormal movements are also noted. The AIMS is to be completed at baseline and periodically in the study according to Schedule of Events (Table 1-1).

8.3.6.1.2 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 in the study according to Schedule of Events (Table 1-1).

8.3.6.1.3 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 dropping, glabella tap, tremor, and salivation are rated on a scale from 0 (normal) to 4 (extreme in severity). The SAS should be conducted by the investigator or an expert site-based rater in a room where the patient can walk a sufficient distance to allow a natural pace (eg, 15 paces). Each side of the body should be examined. The SAS is to be completed at baseline and periodically in the study according to Schedule of Events (Table 1-1).

8.3.6.2 C-SSRS

The C-SSRS is a clinician-rated instrument that reports the severity of both suicidal ideation and behavior (Posner, 2011). Suicidal ideation is classified on a 5-item scale:

- 1 (wish to be dead)
- 2 (nonspecific active suicidal thoughts)
- 3 (active suicidal ideation with any methods [not plan] without intent to act)
- 4 (active suicidal ideation with some intent to act, without specific plan); and
- 5 (active suicidal ideation with specific plan and intent).

The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation.

Suicidal behavior categories are:

- Actual attempt
- Interrupted attempt
- Aborted attempt
- Preparatory acts or behavior
- Presence of suicidal behavior

More than 1 classification can be selected provided it represents separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts.

The C-SSRS will be completed at all study visits. At Screening (Visit 1), the C-SSRS will be completed for the patient's lifetime history of suicidal ideation and behavior ("Baseline/Screening" version). At all other visits, the C-SSRS will be completed for suicidal ideation and behavior since the previous visit ("Since Last Visit" version). Before the patient leaves the study site, the Investigator or appropriately qualified designee will assess the patient's C-SSRS results.

The patient should not be released from the study center until the results of the C-SSRS are reviewed and the patient is not considered to be at risk. If there is doubt about whether a patient is at risk, the Investigator must obtain appropriate psychiatric consultation. The results of the C-SSRS will be recorded in the eCRF.

8.3.6.3 Modified Physical and Neurological Examination

A modified physical examination, including neurological and excluding genital/rectal examinations, will be performed. The examination should include evaluation of height (m; at Screening/Visit 1 only); 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.

9 STATISTICAL CONSIDERATIONS

A 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.

The study randomized 100 patients with Bipolar Disorder (Bipolar I or Bipolar II) before Amendment 2.0 (dated 02 Nov 2020). The efficacy data of these 100 patients will be combined with those of patients with Bipolar Disorder enrolled after Amendment 2.0 as a separate analysis.

Table 9-1 presents an overview of the statistical data analyses planned for all patients enrolled in the study.

Table 9-1: Overview of Statistical Data Analyses

Analysis	Patients Randomized before Protocol Amendment 2.0	Patients Randomized after Protocol Amendment 2.0			All Bipolar Patients (randomized before or after Amendment 2.0)	All Patients randomized before or after Amendment 2.0
		Bipolar Disorder with Mixed Features	MDD with Mixed Features	All Patients Randomized after Protocol Amendment 2.0		
Patient Disposition	Yes	Yes	Yes	Yes	Yes	Yes
Protocol Deviation	Yes	Yes	Yes	Yes		Yes
Demographic and baseline characteristics	Yes	Yes	Yes	Yes	Yes	Yes
Bipolar Diagnosis, Psychiatric Diagnosis and History	Yes	Yes	Yes	Yes	—	—
Medical History	Yes	Yes	Yes	Yes	—	—
Prior/Concomitant Medication	Yes	Yes	Yes	Yes	—	—
Exposure/ Compliance	Yes	Yes	Yes	Yes	Yes	Yes
Primary and Key Secondary Efficacy	Yes[1]	Yes	Yes	Yes	Yes	Yes
AE	Yes	Yes	Yes	Yes	Yes	Yes
Labs	—	Yes	Yes	Yes	Yes	Yes
Vital Signs	—	Yes	Yes	Yes	Yes	Yes
ECG	—	Yes	Yes	Yes	Yes	Yes
C-SSRS	—	Yes	Yes	Yes	Yes	Yes
YMRS	Yes	Yes	Yes	Yes	Yes	Yes
AIMS, BARS, and SAS[2]	—	Yes	Yes	Yes	Yes	—

AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; SAS = Simpson-Angus Scale; YMRS = Young Mania Rating Scale.

[1] Descriptive statistics only.

[2] AIMS, BARS, and SAS assessments were added after implementation of Protocol Amendment 2.0.

Blinded data reviews 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.

9.1 Sample Size Considerations

The assumed effect size (treatment group difference relative to pooled SD) of 0.37 for lumateperone is based on a treatment difference of 3.3 units with a common pooled SD of 9 for the primary efficacy parameter, change from baseline to Day 43 in MADRS total score. A sample size of 350 patients (175 per treatment group) will need to be enrolled after the implementation of Amendment 2.0 (dated 02 Nov 2020) to provide 90% power for primary analysis for the combined population of Bipolar Disorder with mixed features and MDD with mixed features based on an MMRM model using simulation method (Lu, 2012). The simulation assumed a correlation of 0.7 between the repeated measures and a dropout rate of 10% based on historical data.

The assumed values of drop-out rate of 10%, correlation of 0.7, and standard deviation of 9 are approximate estimates from a previous successful study of lumateperone for bipolar depression. The assumed treatment difference of 3.3 used to obtain the power of 90% is considered appropriate as the generated sample size can cover a wide range of clinically relevant treatment difference to be detected as statistically significant.

The study will enroll approximately equal number of patients (175) for the Bipolar Disorder with mixed features and for MDD with mixed features following Amendment 2.0. Assuming an effect size of 0.45, and same assumptions of drop-out rate and correlation between the repeated measures, this sample size (approximately 87 patients in each treatment group) for each of the two subpopulations is expected to provide approximately 80% statistical power for the primary efficacy analysis with the adjustment of multiplicity for the testing of the primary analysis in each of the subpopulations.

The study randomized approximately 100 patients under the original protocol before the implementation of Amendment 2.0 (dated 02 Nov 2020); therefore, the total enrollment for the study will be approximately 450 patients.

9.2 Planned Interim Analyses

No interim analysis is planned.

9.3 Analysis Sets

All Enrolled Set will contain all patients who signed the informed consent for the study.

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

Intent-to-treat (ITT) Analysis Set will contain all randomized patients who received at least 1 dose of study drug and who had a non-missing (pre-dose) baseline assessment and at least 1 non-missing post-baseline assessment of MADRS total score.

Modified Intent-to-treat (mITT) Analysis 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 total score and were enrolled after the implementation of Amendment 2.0 (dated 02 Nov 2020). Patients enrolled before the implementation of Amendment 2.0 will not be included in the mITT Analysis Set.

Sensitivity Set will contain all patients randomized after the implementation of Amendment 2.0 (dated 02 Nov 2020) and who received at least 1 dose of study drug and who had a valid (pre-dose) baseline assessment of MADRS total score. Patients enrolled before the implementation of Amendment 2.0 will not be included in the Sensitivity Set.

The Bipolar Intent-to-treat (bITT) Analysis Set will contain all randomized Bipolar Disorder patients who received at least 1 dose of study drug and had baseline assessment and at least 1 post-baseline assessment of MADRS total score. The bITT Analysis Set will be based on patients enrolled before the implementation of Amendment 2.0 as well as the patients of Bipolar Disorder with mixed features enrolled after the implementation of Amendment 2.0.Safety Analysis Set will contain all patients who received at least 1 dose of study drug.

9.4 Statistical Analysis Methodology

Categorical variables (eg, 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 (eg, MADRS total score) will be summarized using descriptive statistics including number of patients, mean, standard deviation, median, minimum, and maximum.

For analysis purposes, baseline is defined as the last non-missing measurement before the first dose of study drug. Assessments on Day 1 for which times are recorded will be

considered baseline if the assessment time is before the time of the first dose of study drug.

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).

For efficacy analyses in which study site is a factor, a small site will be defined as a site with less than 2 patients in at least one treatment group for each specific analysis set (ie, the mITT Set, the Bipolar Disorder with mixed features based on mITT Set, the MDD with mixed feature based on mITT Set, and the bITT Set). Small sites in each specific analysis set will be pooled to form pseudo-sites so that each treatment group includes at least 2 patients within the site. Pooling will be performed separately for each analysis set but using the same algorithm described as the following:

Based on the number of patients, small sites will be ordered from the largest to the smallest, and sites of the same size will be ordered from the largest site code to the smallest site code. The pooling process starts with the largest small site from the top, which will be pooled with the smallest from the bottom until a non-small site is formed. The process will be repeated using the small sites left out after the first pass. If any sites are left out at the end of the process, they will be pooled with the smallest pseudo site. If there is more than 1 smallest pseudo site, the pseudo site with the smallest site code will be selected. In case the pseudo site formed by pooling all small sites is still a small site, it will be pooled with the smallest non-small site. If there is more than 1 smallest non-small site, the one with the smallest site code will be selected.

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

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

9.4.1 Patient Disposition, Analysis of Demographics and Other Baseline Characteristics

Patient disposition will be summarized by treatment group, when applicable, and overall, including 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 or MDD will be summarized.

Demographic and baseline characteristics, including Bipolar Disorder or MDD diagnosis and baseline efficacy parameters, will be listed and summarized by treatment group as outlined in Table 9-1 for the Safety Analysis Set. No inferential statistics will be presented.

9.4.2 Prior and Concomitant Medications

Prior, concomitant, and post-treatment medications, defined by start and stop dates relative to study drug administration, will be summarized by Anatomical Therapeutic Chemical (ATC) code, preferred term and treatment group for the Safety Analysis Set as outlined in Table 9-1. 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 Safety Analysis 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 Double-blind Treatment Period and for post-treatment with lumateperone.

9.4.3 Study Drug Exposure and Treatment Compliance

Exposure to study drug and treatment compliance will be presented using the Safety Analysis Set as outlined in Table 9-1. 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 drug will be presented by study week, defined by the planned visits.

9.4.4 Analysis of Primary and Key Secondary Efficacy Endpoints

The study is designed to evaluate the efficacy of lumateperone 42 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-S score.

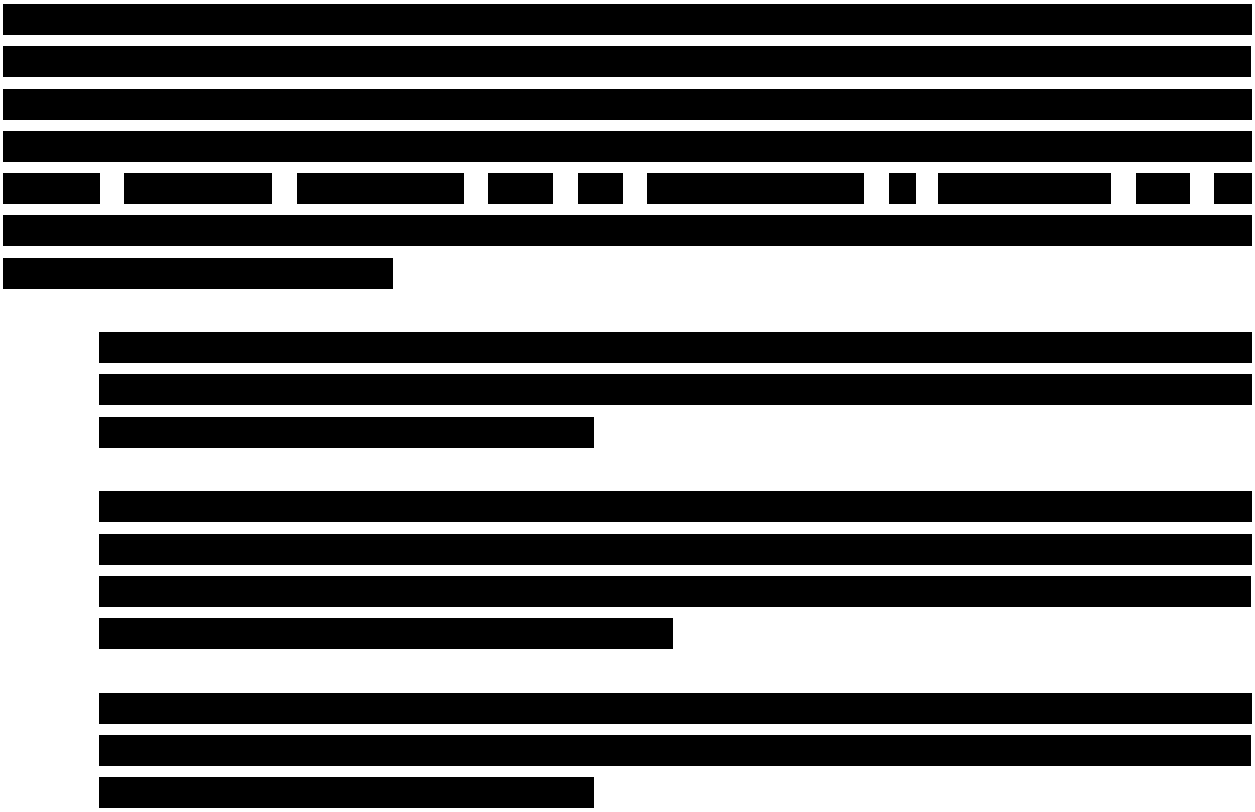
The treatment effect on the primary efficacy endpoint will be evaluated in the combined population of Bipolar Disorder with mixed features and MDD with mixed features using a mixed-effect model for repeated measures (MMRM) method based on the mITT Set. The model will include the change from baseline at each pre-specified time point in the MADRS total score as the response variable; treatment group (lumateperone 42 mg and placebo), visit, site (or pooled site), the stratification factor at screening (Bipolar I, Bipolar II, or MDD), and treatment group-by-visit interaction as factors; and the baseline MADRS total score and visit-by-baseline MADRS total score interaction as covariates. An unstructured covariance matrix will be used to estimate the covariance among repeated measurements within patient. In the event the convergence cannot be attained with the unstructured correlation matrix, the following alternative structures will be attempted in the specified order: heterogeneous Toeplitz structure (TOEPH), heterogeneous

autoregressive(1) (ARH(1)), heterogeneous compound symmetry (CSH), No Diagonal Factor Analytic (FA0(q), with q equal to the number of time points), Toeplitz structure (TOEP), autoregressive(1) (AR(1)), and compound symmetry (CS). Model parameters will be estimated using restricted maximum likelihood. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

The MMRM method described above will also be used for the primary efficacy analyses based on the subpopulation of Bipolar Disorder with mixed features in the mITT Set and based on the subpopulation of MDD with mixed features in the mITT Set.

The key secondary efficacy endpoint, change from baseline to Day 43 in the CGI-S score, will be analyzed based on the mITT Set using an MMRM method similar to the one specified for the analysis of the primary efficacy endpoint, but replacing MADRS total score with CGI-S score for the baseline and baseline-by-visit interaction terms as covariates in the model.

The MMRM method for the key secondary efficacy endpoint will also be applied to the key secondary efficacy analyses based on the subpopulations of Bipolar Disorder with mixed features in the mITT Set and based on the MDD with mixed features in the mITT Set.



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9.4.6 Safety Analyses

All safety parameters will be summarized using the Safety Analysis Set as outlined in Table 9-1.

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, YMRS, AIMS, BARS, SAS, and C-SSRS) will be summarized by treatment group and by visit when appropriate. 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 and ECG. 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). TEAEs are defined as any AEs, regardless of the relationship to study drug, that occur or worsen in severity after the first dose of study medication and on or before the date of last dose of study medication 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 SAEs 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 lumateperone and the number and percentage of patients with at least one abuse-related TEAE will be summarized by the pre-specified categories.

Laboratory assessments, including hematology and chemistry, vital signs and ECGs, will be listed and summarized by treatment group and visit. Summaries may include actual and change from baseline, incidence of potentially clinically significant (PCS) values during the Double-blind Treatment Period according to normal range criteria and shifts from baseline to the end of Double-blind Treatment Period . Listings may be provided for patients meeting the PCS criteria.

For the C-SSRS, the number and percentage of patients who have suicidal ideation or suicidal behaviors will be summarized by treatment group. Supportive listings will be provided that include treatment group, assessment date, lifetime history, and postbaseline values for each patient. Intensity of suicidal ideation, suicidal behavior type, and lethality of suicidal behavior will also be included in these listings.

The observed and change from baseline in YMRS, AIMS, BARS, and SAS will be summarized by treatment group and by visit.

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

9.5 Protocol Deviations

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 or have any impact on the efficacy analyses. Significant deviations can include nonadherence to inclusion or exclusion criteria, enrollment of the patient without prior sponsor approval, or nonadherence to FDA or local regulations or ICH GCP guidelines and may lead to the patient being withdrawn from the study (Section 5.5).

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.

The IRB/IEC should be notified of all protocol deviations in a timely manner, according to local requirements.

Major protocol deviations observed during the Double-blind Treatment Period will be summarized by treatment group as outlined in Table 9-1 using the ITT Set.

10 ETHICS/PROTECTION OF HUMAN SUBJECTS

10.1 Institutional Review Board and Independent Ethics Committee

Federal regulations and the International Conference on Harmonisation (ICH) guidelines require that approval be obtained from an IRB or IEC before participation of human patients in research studies.

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.

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.

10.2 Ethical Conduct of the Study

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

10.3 Information and Informed Consent

A written informed consent in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50 shall be obtained from each patient before entering the study or performing any nonroutine procedure that involves risk to the patient. An informed consent template will 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 any screening procedure, a consent form describing in detail the study procedures and risks will be given to the patient. The patient is required to read and review the document or have the document read to him/her. The Investigator or designee will explain the research study to the patient and answer any questions that may arise. Once the Investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing the ICF 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.

The Investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient.

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.

10.4 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, 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.

11 INVESTIGATOR OBLIGATIONS

11.1 Documentation

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 by providing to the Sponsor the following essential documents, including but not limited to:

- A completed and signed Form FDA 1572. If, during the course of the study, any changes are made that are not reflected on Form FDA 1572, a new Form FDA 1572 must be completed and returned to the Sponsor for submission to the FDA
- A fully executed contract
- The curricula vitae for the Investigator and all sub-investigators listed on Form FDA 1572, including a copy of each physician's license
- Financial disclosure agreement completed and signed by the Investigator and all Sub-investigators listed on Form FDA 1572. The Investigator and all sub-investigators will provide an updated financial disclosure agreement to the Sponsor 1 year after the completion of the study.
- A copy of the original IRB/IEC approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals. All subsequent modifications must be submitted and approved by the IRB/IEC.
- A copy of the IRB/IEC-approved ICF
- A copy of the HIPAA authorization form, or other applicable local privacy forms
- A list of the IRB/IEC members or the US Department of Health and Human Services general assurance number
- A copy of the laboratory certifications and reference ranges
- The Investigator's Signature page in this protocol signed and dated by the Investigator

11.2 Performance

The Investigator must demonstrate reasonable efforts to recruit qualified patients for the study.

11.3 Use of Investigational Materials

The Investigator will acknowledge on the Investigator Signature page that the study drug supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Investigator or Sub-investigators listed on Form FDA 1572. Study drug supplies must be stored in a secured place and must be locked. At study initiation, a representative from the Sponsor will inventory the study drug supplies at the study center. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies as well as daily temperature logs. The Sponsor may supply forms on which to record the date the study drug was received and a dispensing record in which to record each patient's use. All unused study drug must be returned to the Sponsor-designated central depot.

11.4 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. However, if required by the applicable regulatory requirements or by an agreement with the Sponsor, these documents should be retained for a longer period. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

11.5 Clinical Site Monitoring

All aspects of the study will be carefully monitored by the Sponsor or its designee to ensure compliance with applicable government regulations, current GCP, and current standard operating procedures.

The Clinical Monitor, as a representative of the Sponsor, is obligated to closely monitor the study. In doing so, the monitor will visit the Investigator and study site at periodic intervals, in addition to maintaining necessary contact with the Investigator and study site. The Clinical Monitor will maintain current knowledge of the study through observation, review of study records and source documentation, and discussion of study conduct with the Investigator and study site personnel.

12 DATA HANDLING AND RECORD KEEPING

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 MINI, laboratory reports, and ECG tracings.

After database lock, each study site will receive documentation containing all of their study site-specific eCRF data as entered into the electronic data capture (EDC) system, including full discrepancy and audit history. Additionally, documentation of all of the study site's data will be created and sent to the Sponsor for storage. The CRO will maintain duplicate copy for its records.

In all cases, patient initials and other protected patient information will not be collected or transmitted to the Sponsor.

12.1 Data Monitoring

Before any patient enters the study, a representative of the Sponsor will meet with the Investigator and the study center personnel to review the procedures to be followed during the study. EDC functionality training is provided via computer-based training to train Investigators and authorized designees on recording the data in the eCRFs using the EDC system.

The Investigator will maintain complete source documents (eg, signed ICFs, written or electronic medical records, pharmacy records). Source documents provide evidence for the existence of study patients and substantiate the integrity of the data collected in the eCRF. The Investigator will make available to the Clinical Monitor or designee source documents (written notes and electronic medical records, if used), signed ICFs, and all other study-related documents.

Clinical Monitors, appointed by the Sponsor, will perform ongoing source document verification to confirm that data entered into the eCRF are accurate, complete, and verifiable from source documents; that the safety and rights of patients are protected; and that the study is conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. After the first patient is enrolled, the Clinical Monitor or designee, will periodically monitor the progress of the study by conducting on-site visits. In addition to on-site source document verification, Clinical Monitors will review study progress remotely, possibly warranting

more frequent communication and/or study center visits. Details of monitoring activities are provided in the Clinical Operations Plan.

12.2 Data Recording and Documentation

Data collection will involve the use of the EDC system, to which only authorized personnel will have access. Patient data are to be entered into the EDC system by the Investigator or designee using their assigned EDC user account. The Investigator or designee will record all patients' study data in the eCRF, unless the data are transmitted to the Sponsor electronically (eg, laboratory data). Data entered in the eCRF must be consistent with the source documents or the discrepancies must be explained. The Investigator is responsible for verifying that all data entries are accurate and correct. The Investigator may need to request previous or external medical records to support study data.

The Sponsor is responsible for the data management of this study, including quality checking of the data. The Sponsor or designee will review study data for completeness, logic, and protocol adherence, using a combination of manual review and programmatic edit checks. After data entry into the EDC system by the Investigator or designee, a combination of manual and programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol. As a result of these edit checks, data monitoring, and reviews, queries may be electronically issued to the study center and should be answered electronically via the EDC system. Each query will carry identifying information (assigned username, date, and time) to assist the Sponsor and the Investigator on the origin of the data clarification request and the response provided by the Investigator. All data changes made to the patient's data via a data query will be approved by the Investigator prior to final database lock.

The Investigator or designee will be responsible for approving all changes to the data and endorsing the patient data within the EDC system. This approval method will include applying an electronic signature linked to a uniquely assigned username and password that together will represent a traditional handwritten signature. After all data have been reviewed and all issues have been resolved, the database will be locked.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (eg, copies of eCRFs, laboratory reports, and regulatory documents) will be retained at the study center, along with adequate source documentation, according to FDA and ICH requirements. All study records must be available for inspection by the Sponsor, its authorized representatives, the FDA, or other health authorities.

Source documents will be used at the study centers and may include a patient's medical record, hospital charts, clinic charts, the Investigator's patient study files, as well as the results of diagnostic tests such as laboratory tests, ECGs, etc. A centralized clinical laboratory will be used for the analysis of all blood samples. Additional information on the collection and handling of samples is detailed in the Laboratory Procedure Manual.

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14 LITERATURE REFERENCES

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