NCT05061706

Study ID: ITI-007-502

Title: A Randomized, Double-Blind, Placebo-controlled Multicenter Study to Assess the Efficacy and Safety of Lumateperone as Adjunctive Therapy in the Treatment of Patients with Major Depressive Disorder

Original Protocol Date: 18 Aug 2021

A Randomized, Double-Blind, Placebo-controlled Multicenter Study to Assess the Efficacy and Safety of Lumateperone as Adjunctive Therapy in the Treatment of Patients with Major Depressive Disorder

Protocol Number:	ITI-007-502
Original Protocol Date:	18 Aug 2021
Compound:	Lumateperone
Study Phase:	3
Sponsor:	[redacted]

Confidentiality Statement

The confidential information in this document is provided to you as an Investigator for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Acceptance of this document constitutes agreement that the information contained herein will not be disclosed to others without written authorization from Intra-Cellular Therapies, Inc. (ITI), the Sponsor. All financial and nonfinancial support for this study will be provided by the Sponsor. The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of ITI.

This study will be carried out in accordance with ICH GCP, US Code of Federal Regulations applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812), and all applicable local regulations.

PROTOCOL APPROVAL—SPONSOR SIGNATORIES

Protocol Title:	A Randomized, Double-blind, Placebo-controlled Multicenter Study to Assess the Efficacy and Safety of Lumateperone as Adjunctive Therapy in the Treatment of Patients with Major Depressive Disorder
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LIST OF ABBREVIATIONS

ADT	antidepressant therapy
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATRQ	Antidepressant Treatment Response Questionnaire
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CFR	Code of Federal Regulations
C-SSRS	Columbia–Suicide Severity Rating Scale
CGI-BP-S	Clinical Global Impression Scale, Bipolar version, Severity
CRO	Contract research organization
CSFQ	Changes in Sexual Functioning Questionnaire
CSR	Clinical study report
D_2	dopamine 2 receptor
DSM-5	Diagnostic and Statistical Manual, 5th edition
ECG	electrocardiogram, electrocardiographic
eCRF	electronic case report form
ECT	electroconvulsive therapy
EDC	electronic data capture
ET	early termination
FDA	Food and Drug Administration
RF	Federal Register
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
ICE	intercurrent event
ICF	informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	International Ethics Committee
IND	Investigational New Drug (application)
ITI	Intra-Cellular Therapies, Inc.
ITT	intent-to-treat
IWRS	interactive web response system

MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
MDE	major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed-effect Model for Repeated Measures
msec	millisecond
PCS	potentially clinically significant
PEER	Pre-Enrollment Eligibility Review
PET	positron emission tomography
PK	pharmacokinetic
PMM	pattern-mixture model
QIDS-SR-16	Quick Inventory of Depressive Symptomatology-Self Report-16 item
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/\langle RR\rangle^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/\langle RR\rangle^{1/3}$)
SAE	serious adverse event
SAS	Simpson Angus Scale
SAP	statistical analysis plan
SERT	serotonin transporter
SOC	system organ class
TEAE	treatment-emergent adverse event
UDS	urine drug screen
ULN	upper limit of normal
US	United States

1 PROTOCOL SYNOPSIS AND SCHEDULE OF EVALUATIONS

CLINICAL STUDY SYNOPSIS: Study ITI-007-502	
Title of Study	A Randomized, Double-blind, Placebo-controlled Multicenter Study to Assess the Efficacy and Safety of Lumateperone as Adjunctive Therapy in the Treatment of Patients with Major Depressive Disorder.
Study Centers (Country)	Approximately 60 study centers (United States and globally).
Development Phase	3
Objectives	**Primary Objective** • To evaluate the efficacy of lumateperone 42 mg administered once daily compared with placebo as adjunctive treatment to antidepressant therapy in patients with Major Depressive Disorder (MDD) who have an inadequate response to ongoing antidepressant therapy (ADT) as measured by change from baseline to Day 43 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score. **Key Secondary Efficacy Objective** • To evaluate the efficacy of lumateperone 42 mg administered once daily compared with placebo as adjunctive treatment to ADT in patients with MDD who have an inadequate response to ongoing ADT as measured by change from baseline to Day 43 in the Clinical Global Impression Scale-Severity (CGI-S).
Study Design	This is an international, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study in patients with a primary diagnosis of MDD according to criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) who have an inadequate response to ongoing ADT. The study will be conducted in three periods: • Screening Period (up to 2 weeks) during which patient eligibility will be assessed; • Double-blind Treatment Period (6 weeks) in which all patients will be randomized to receive placebo or lumateperone 42 mg/day in 1:1 ratio. • Safety Follow-up Period (1 week) in which all patients will return to the clinic for a safety follow-up visit approximately one week after the last dose of study treatment.
Number of Patients	Approximately 470 patients (235 per treatment group) are planned to be enrolled in the Double-blind Treatment Period.
Diagnosis and Main Criteria for Inclusion and Exclusion	***Main Inclusion Criteria*** Patients will be eligible for study participation if they meet the following inclusion criteria: 1. Provides written informed consent; 2. Male or female patients between the ages of 18 and 65 years, inclusive;

3. Meets DSM-5 criteria for MDD (MDD with psychotic features will be acceptable) as confirmed by the Investigator or Sponsor-approved rater using the MINI and meets all of the following criteria:
   a. The start of the current major depressive episode (MDE) is at least 8 weeks but not more than 18 months prior to Screening (Visit 1);
   b. Has at least moderate severity of illness based on rater-administered MADRS total score ≥ 24 at Screening (Visit 1) and at Baseline (Visit 2);
   c. Has at least moderate severity of illness based on CGI-S score ≥ 4 at Screening (Visit 1) and at Baseline (Visit 2);
   d. Has a Quick Inventory of Depressive Symptomatology-Self Report-16 item (QIDS-SR-16) score ≥ 14 at Screening (Visit 1) and at Baseline (Visit 2);
   e. Has sufficient history and medical record confirmation verifying the ADT and the current MDE is causing clinically significant distress or impairment in social, occupational, or other important areas of functioning.
4. Currently having an inadequate response to ADT (less than 50% improvement) as confirmed by the Investigator using the Antidepressant Treatment Response Questionnaire (ATRQ) and taking at least the minimum effective dose (per package insert) of one of the following antidepressants as monotherapy treatment for at least 6 weeks duration:
   a. citalopram/escitalopram
   b. fluoxetine
   c. paroxetine
   d. sertraline
   e. duloxetine
   f. levomilnacipran/milnacipran (if locally approved for MDD)
   g. venlafaxine/desvenlafaxine
   h. bupropion
   i. vilazodone
   j. vortioxetine

All Inclusion Criteria are presented in Section 6.3.1.

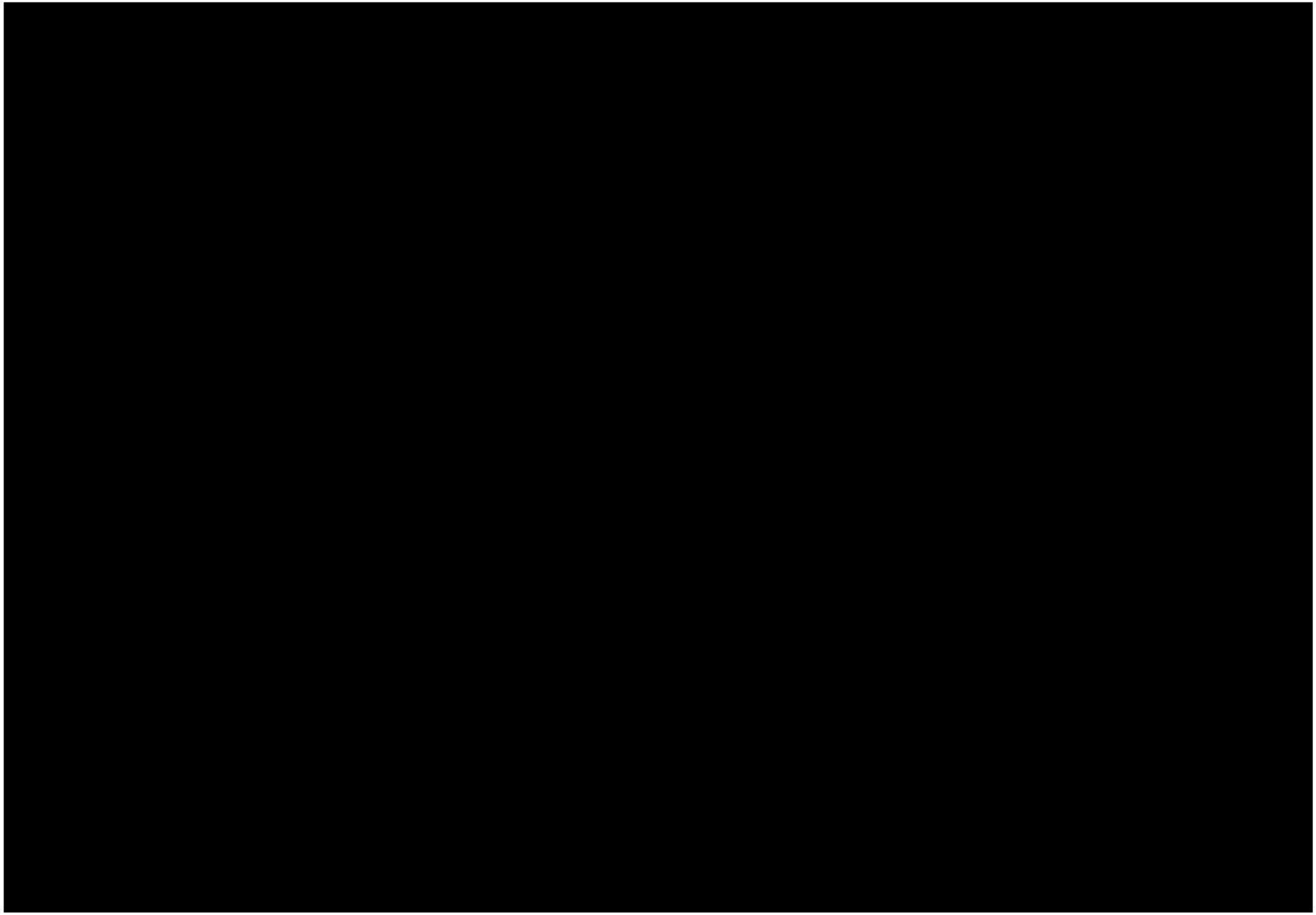
Main Exclusion Criteria

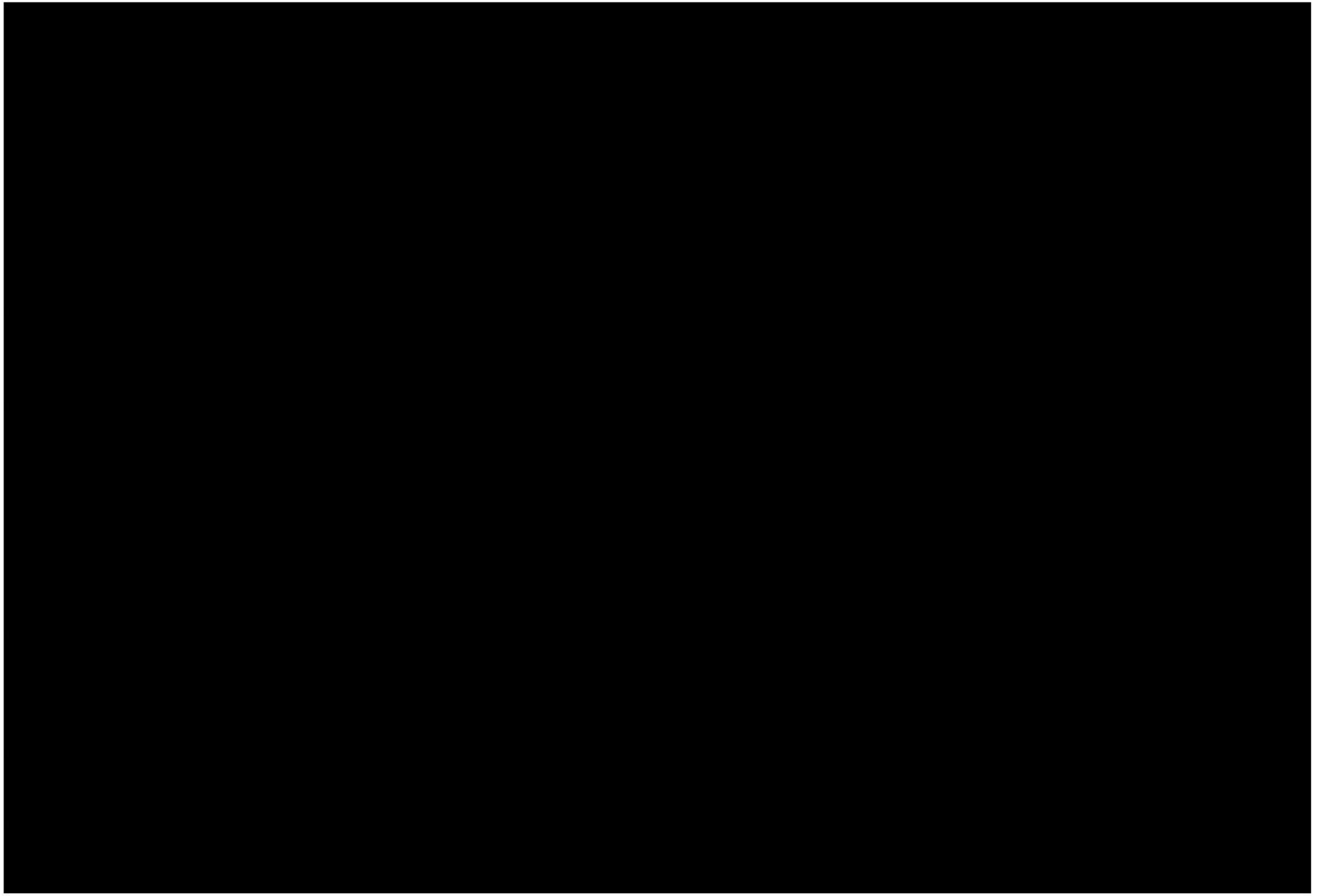
Patients who meet any of the following exclusion criteria will not be able to participate in the study:

1. Within the patient's lifetime, has a confirmed DSM-5 psychiatric diagnosis other than MDD, including:
   a. Schizophrenia, Schizoaffective Disorder, Schizophreniform Disorder or other psychotic disorder;
   b. Bipolar Disorder;
2. Within 6 months of Screening, has a confirmed DSM-5 psychiatric diagnosis other than MDD including:
   a. Anxiety disorders such as Panic Disorder or Generalized Anxiety Disorder; Obsessive-compulsive Disorder; Posttraumatic Stress Disorder as primary diagnoses. Note: Anxiety symptoms may be allowed if secondary to MDD, provided these symptoms do not require concurrent treatment;
   b. Eating disorder;
   c. Substance use disorders (excluding nicotine);

	d. Personality disorder of sufficient severity to have a major impact on the patient's psychiatric status; e. Within 12 months of Screening, has had any other psychiatric condition (other than MDD) that has been the main focus of treatment; 3. The patient experiences a ≥ 25% decrease in the MADRS total score between Screening (Visit 1) and Baseline (Visit 2); 4. The patient experiences a ≥ 25% decrease in the QIDS-SR-16 total score between Screening (Visit 1) and Baseline (Visit 2); 5. In the opinion of the Investigator, the patient has a significant risk for suicidal behavior during participation in the study or: a. At Screening (Visit 1), the patient scores "yes" on Suicidal Ideation Items 4 or 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) within 6 months prior to Screening, or at Baseline (Visit 2), the patient scores "yes" on Suicidal Ideation Items 4 or 5 since the Screening Visit; b. At Screening (Visit 1), the patient has had 1 or more suicide attempts within 2 years prior to Screening; c. At Screening (Visit 1) or Baseline (Visit 2), the patient scores ≥ 5 on MADRS Item 10 (Suicidal Thoughts), or d. The patient is considered to be in imminent danger to him/herself or others. 6. The patient has a first MDE at age 60 years or older. All Exclusion Criteria are presented in Section 6.3.2.
Duration of Treatment	Study duration will be approximately 9 weeks based on the following study periods: Screening Phase up to 2 weeks, a 6-week Double-blind Treatment Period, a 1-week Safety Follow-up Period.
Investigational Product, Dosage, and Mode of Administration	Lumateperone 42 mg capsules, 42 mg/day adjunctive to ongoing ADT, oral administration.
Reference Therapy, Dosage, and Mode of Administration	Placebo capsules, adjunctive to ongoing ADT administration, oral administration.
Criteria for Evaluation	
Primary Efficacy Endpoint	Change from Baseline (Visit 2) to Day 43 (Visit 8) in MADRS total score.
Secondary Efficacy Endpoint	Change from Baseline (Visit 2) to Day 43 (Visit 8) in CGI-S score.
Safety Measures	Adverse event (AE) recording, clinical laboratory measures, vital sign parameters, electrocardiograms (ECGs) and physical examinations. Measures of extrapyramidal symptoms: Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS), and Simpson-Angus Scale (SAS). Measure of suicidality: C-SSRS.
[redacted]	[redacted]

Statistical Methods	The primary efficacy endpoint will be change from Baseline to Day 43 in MADRS total score. Based on the primary hypothetical estimand strategy which assumes patients are on study treatment up to the primary time point (Day 43), efficacy data collected after discontinuation of study treatment (ie, efficacy assessment performed more than 3 days after last dose of study treatment) and/or after starting new ADT will be set to missing and will not be included in the primary analysis. Instead, these missing data will be assumed as missing at random. The primary analysis to estimate and compare the treatment effects of lumateperone vs placebo as defined by the primary estimand will be performed using a mixed-effects model for repeated measures (MMRM) with change from baseline at each study visit as the response variable, and treatment group, study site (or pooled site) and study visit as factors, baseline MADRS total score as covariate, and interaction terms for baseline MADRS total score-by-study visit and treatment group-by-study visit. An unstructured covariance matrix will be used to model the covariance of within-patient scores. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Treatment difference will be estimated via contrast based on treatment group and treatment group-by-study visit factors. The key secondary efficacy parameter will be the change from baseline to Day 43 in CGI-S score. The key secondary efficacy parameter will be analyzed using a similar MMRM as used for the primary analysis with the baseline CGI-S score for the covariate. A fixed sequence testing procedure will be used to control the overall Type I error of 0.05 with the primary endpoint tested first at the 2-sided 0.05 level, and if significant, the key secondary endpoint will be tested at the 2-sided 0.05 level. Primary efficacy analyses will be based on the modified Intent-to-Treat (mITT) Population, defined as all randomized patients who received at least 1 dose of study treatment, have an evaluable baseline assessment of MADRS total score, and have at least one evaluable post-baseline, on-treatment assessment of the MADRS total score (on-treatment MADRS assessments are those performed no later than 3 days after the last dose of study treatment). Key secondary efficacy analyses will also be based on the mITT Population. An estimation and comparison of the treatment effects of lumateperone vs placebo for the key secondary endpoint are based on the hypothetical estimand (similar to that defined for the primary analysis, using assessed CGI-S score up to 3 days after last study dose and not including those assessed after new ADT). All safety parameters will be summarized descriptively. Safety analyses will be based on the Safety Population defined as all randomized patients who received at least one dose of investigational product. Individual plasma concentrations will be listed and summarized by visit. Plasma concentrations will be analyzed using a population PK approach. The results from the population PK analyses will be presented in a separate report. Approximately 470 patients will be randomly assigned to 1 of the 2 treatment groups (lumateperone 42 mg or matching placebo). Assuming a common drop-out rate of 20% and a common correlation of 0.7 between the repeated measures, the sample size of 235 patients per treatment group will provide approximately 90% statistical power for the effect size of 0.33 (treatment difference of 3.3 and common pooled standard deviation of 10) for the primary efficacy endpoint.





2 ETHICAL CONSIDERATIONS

2.1 Institutional Review Board and Independent Ethics Committee

Approval by the Institutional Review Board (IRB) and Independent Ethics Committee (IEC) is required before the start of the study. A copy of the approval letter will be supplied to Intra-Cellular Therapies, Inc. (the Sponsor) or its designee along with a roster of IRB/IEC members. During the course of the study, the Investigator will provide timely and accurate reports to the IRB/IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate) and will notify the IRB/IEC of serious adverse events (SAEs) or other significant safety findings. The study protocol, informed consent form (ICF), information sheet advertisements, and amendments (if any) will be approved by the IRBs/IECs at the study centers in conformance with US CFR, Title 21, Part 56 and applicable local regulations.

2.2 Ethical Conduct of the Study

This clinical study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. This clinical study will comply with the ICH Guidance on General Considerations for Clinical Trials (ICH-E8; 62 FR 66113, 17 Dec 1997) and GCP (ICH-E6; 62 FR 25692, March 2018), as well as CFR Part 312 and applicable local regulations.

2.3 Patient Information and Informed Consent

A written informed consent in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50 regulations and relevant country regulations shall be obtained from each patient before entering the study or performing any study-specific procedure that involves risk to the patient. If the ICF is revised during the study, all active participating patients must sign the revised form. The informed consent statement shall contain all the elements of informed consent listed in Appendix I.

Before any screening procedures, each prospective patient will be given a full explanation of the study and be allowed to read the approved ICF. After receiving an explanation of study procedures, patients will have the opportunity to have any questions answered before signing the ICF. The Investigator must address all questions raised by the patient. Each patient will read, assent to an understanding of, and sign the ICF or other locally applicable authorization form. Each patient will be made aware that he/she may withdraw from the study at any time.

The Investigator will also sign the ICF and provide a copy of the ICF to the patient.

3 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

A list of Sponsor personnel responsible for study oversight is provided in the Study Reference Manual.

4 INTRODUCTION

Major depressive disorder (MDD) is a serious psychiatric disorder characterized by the presence of one or more major depressive episodes (MDE). 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. Depression can have damaging effects on health and wellbeing, and leave one at risk for social withdrawal, alcohol abuse, and disrupted work, family, and social life (Kupferberg et al, 2016). 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.

Despite a number of approved antidepressants, a substantial percentage of individuals with MDD have inadequate response to conventional antidepressants alone or in various combinations (Little, 2009). In STAR*D (Sequenced Treatment Alternatives to Relieve Depression), the largest randomized trial of the treatment of MDD, a representative sample of outpatients with MDD received one to four successive acute treatment steps. Those who did not achieve remission at each treatment step were able to move to the next step. Only 36.8% of patients achieved remission at step 1, the first course of antidepressant treatment (Rush et al, 2005). More than 20% of those who failed to improve with the first treatment stopped taking medication, primarily within the first 2 weeks (Warden, 2007). Depressed patients who have an inadequate response to ADT represent a particularly vulnerable, at risk 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. ITI, the Sponsor, is exploring the utility of lumateperone as adjunctive therapy in the treatment of 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 NR_2B, or $GluN_2B$, 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 (D_1) receptor activation.

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 may also play a role in antidepressant response. Importantly, lumateperone lacks potent off-target interactions that have been associated with side effects of other antipsychotic drugs approved as adjunctive treatment of MDD. 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.

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.

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. Similar improvements in depression symptoms were also seen in a one-year open label study of lumateperone in patients with schizophrenia (ITI-007-303). In this study, the favorable safety and tolerability profile was sustained.

Clinical data from 3 well-controlled bipolar depression studies (Studies ITI-007-401, ITI-007-404, and ITI-007-402) demonstrated efficacy in bipolar depression and confirmed lumateperone's tolerability and favorable safety profile.

In Study ITI-007-404, 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 Montgomery-Åsberg Depression Rating Scale (MADRS) total score. Lumateperone 42 mg also met the key secondary endpoint of statistically significant improvement on the Clinical Global Impression Scale, Bipolar version, Severity (CGI-BP-S) total score and demonstrated statistically significant improvement on the CGI-BP-S depression.

In Study ITI-007-402, 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, 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. Patients who completed Study ITI-007-401 were eligible to participate in an optional, 6-month open-label extension. On average, patients improved and did not worsen on lumateperone 42 mg with respect to their depressive symptoms.

Safety data from these studies and other trials with lumateperone, which has been administered to more than 3300 individuals for up to one year, show lumateperone to be well tolerated across a dose range from 0.7 to 126 mg, with a safety profile similar to placebo.

The purpose of the current study is to confirm the efficacy, safety and tolerability of lumateperone as adjunctive therapy for the treatment of patients with MDD. Patients will be monitored carefully for their mental health status and general health. Symptoms of 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 depression in the future. More detailed information about the known and expected benefits and risks and reasonably expected AEs is provided in the current lumateperone Investigator's Brochure.

5 STUDY OBJECTIVES

5.1 Efficacy Objectives

5.1.1 Primary Objective

The primary efficacy objective of this study is to evaluate the efficacy of lumateperone 42 mg administered once daily compared with placebo as adjunctive treatment to antidepressant therapy (ADT) in patients with MDD who have an inadequate response to ongoing ADT as measured by change from baseline to Day 43 in the MADRS total score.

The proposed estimand strategy to address the primary objective is as follows:

- Target Population: Patients with MDD who have an inadequate response to ongoing ADT
- Treatment: Lumateperone 42 mg vs placebo as adjunctive therapy to existing ADT
- Variable (Endpoint): Change from baseline to Day 43 in the MADRS total score
- Intercurrent events (ICE) and corresponding strategies (see Table 5-1)
- Summary measure: Difference in treatment means between lumateperone 42 mg and placebo.

[redacted]

[redacted]

Policy estimand eliminating potential effect of newly initiated ADT is proposed as supportive

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5.1.2 Key Secondary Efficacy Objective

The key secondary efficacy objective of this study is to evaluate the efficacy of lumateperone 42 mg administered once daily compared with placebo as adjunctive treatment to ADT in patients with MDD who have an inadequate response to ongoing ADT as measured by change from baseline to Day 43 in the Clinical Global Impression Scale-Severity (CGI-S).

The proposed estimand strategy to address the secondary objective is the same as the proposed

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5.2 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 MDD who have an inadequate response to ongoing ADT as assessed by AEs; clinical laboratory results; vital sign measures; ECG results; suicidality as assessed by the C-SSRS; and extrapyramidal symptoms (EPS) as assessed by Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson Angus Scale (SAS).

6 INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan

Study ITI-007-502 is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, and tolerability of lumateperone as adjunctive therapy for the treatment of patients with MDD. This study will be performed at approximately 60 study centers in the United States and globally.

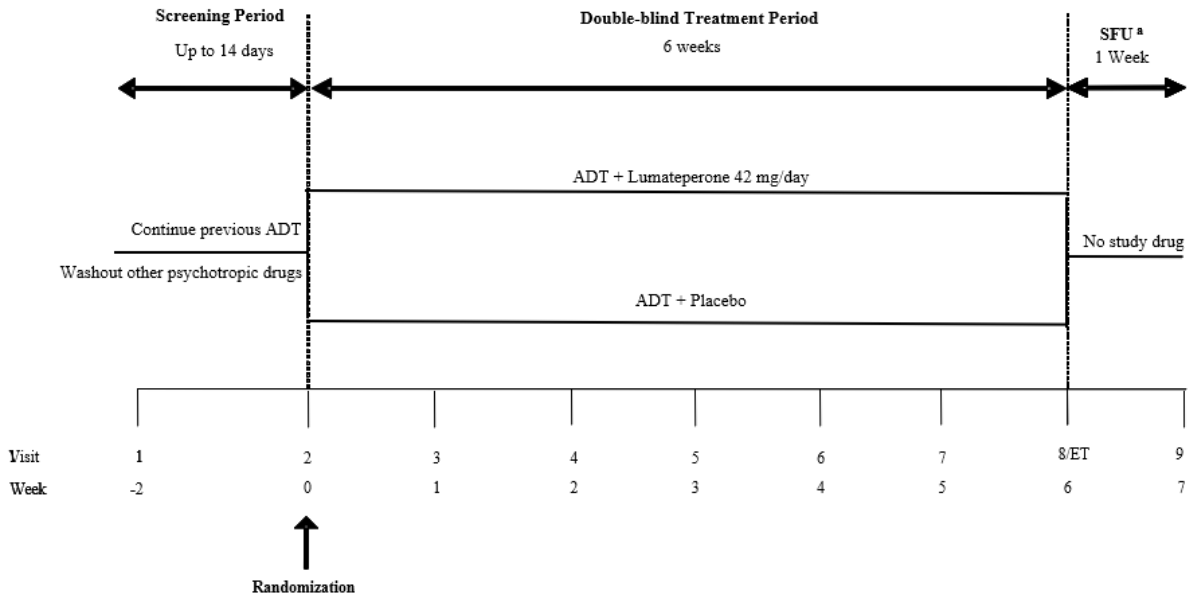
The study will be conducted as follows:

- A Screening Period of up to 2 weeks
- A 6-week Double-blind Treatment Period
- A 1-week Safety Follow-up (SFU) Period

The maximum study duration for each patient will be approximately 9 weeks.

The study design schematic is provided in Figure 6-1. The Schedule of Evaluations is presented in Table 1-1. Detailed descriptions of the procedures conducted at each study visit are provided in Section 8.5.

Figure 6-1: Schematic of Study Design



ADT = antidepressant treatment; ET = early termination; SFU = Safety Follow-up.

[a] Eligible patients who complete 6 weeks of double-blind treatment and provide informed consent to rollover into the Open-label Safety Study will not enter the SFU Period.

6.2 Scientific Rationale for Study Design

6.2.1 Study Design

Screening Period (up to 2 Weeks)

Potential patients will be evaluated during a Screening Period lasting up to 14 days. With approval from the Sponsor or designee, short extensions to the Screening Period may be granted in exceptional circumstances. After obtaining written informed consent, diagnostic interviews, determination of inadequate response to current ADT, 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 will be required to continue their current ADT but will be required to discontinue other psychotropic drugs.

Evaluation of diagnostic validity and eligibility of each patient will be undertaken by the Sponsor or designee.

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

Double-blind Treatment Period (6 Weeks)

Patients will self-administer his/her first dose of study treatment on the evening of the Baseline visit (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. Antidepressant treatment will also continue as previously prescribed. The dose and frequency of ADT must not change during the Screening Period or for the duration of the Double-blind Treatment Period.

Patients will attend outpatient study visits on Days 8, 15, 22, 29, 36, and 43. With approval from the Sponsor or designee, sites will be permitted to conduct remote visits if a site-based visit is not feasible. However, all Screening (Visit 1) and Baseline (Visit 2) assessments must be performed in person.

A patient will be defined as a treatment completer if the patient completes the Double-blind Treatment Period (all scheduled visits up to and including Visit 8). Patients who withdraw prematurely should be seen for an Early Termination (ET) visit as soon as possible and will also be asked to return for a safety follow-up visit approximately one week after Visit 8/ET.

Safety Follow-up Period (1 Week)

All patients should return to the clinic for the SFU visit approximately 1 week after Visit 8/ET. Any ongoing AEs at the SFU visit must be followed until resolution, until the AE stabilizes, until it is determined to be not clinically significant, or until the patient is lost to follow-up.

6.2.2 Separate Open-label Safety Study

Patients who complete the 6-week Double-blind Treatment Period, who are considered to be appropriate by the Investigator, and who meet eligibility criteria may enroll in the 6-month Open-label Safety Study at the Visit 8/Week 6 visit. This rollover visit to the Open-label Safety Study at Visit 8/Week 6 must be in person. A patient who enters the Open-label Safety Study will not have a SFU visit (Visit 9/Week 7).

6.2.3 Dose Selection

Lumateperone 42 mg was selected based on 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. 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 indication. The 6-week treatment period duration 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 MDD, with statistically significant superiority vs placebo on the primary outcome measure: Change from baseline to Day 43 in MADRS total score in patients with MDD.

6.3 Study Population

6.3.1 Inclusion Criteria

To be eligible to participate in the study, patients must meet the following inclusion criteria:

1. Provide written informed consent obtained from the patient before the initiation of any study specific procedures. See Appendix I for informed consent requirements;

2. Male or female patients between the ages 18 and 65 years; inclusive;

3. Meet DSM-5 diagnostic criteria for MDD (a diagnosis of MDD with psychotic features will be acceptable) as confirmed by the Investigator or Sponsor-approved rater using the Mini-International Neuropsychiatric Interview (MINI), and meet all the following criteria:

    a. The start of the current MDE is at least 8 weeks but no more than 18 months prior to the Screening (Visit 1);

b. Has at least moderate severity of illness, based on rater administered MADRS total score ≥ 24 at Screening (Visit 1) and at Baseline (Visit 2);

c. Has at least moderate severity of illness based on CGI-S score of ≥ 4 at Screening (Visit 1) and at Baseline (Visit 2);

d. Has a QIDS-SR-16 score of ≥14 at Screening (Visit 1) and at Baseline (Visit 2);

e. Has sufficient history and medical record confirmation (as defined in the Study Reference Manual) verifying ADT and the current MDE is causing clinically significant distress or impairment in social, occupational, or other important areas of functioning;

4. Currently having an inadequate response to ADT (less than 50% improvement) as confirmed by the Investigator using ATRQ and is taking at least the minimum effective dose (per package insert) of one of the following antidepressants as monotherapy treatment for at least 6 weeks duration, and:

    a. citalopram/escitalopram

    b. fluoxetine

    c. paroxetine

    d. sertraline

    e. duloxetine

    f. levomilnacipran/milnacipran (if locally approved for MDD)

    g. venlafaxine/desvenlafaxine

    h. bupropion

    i. vilazodone

    j. vortioxetine

5. Is currently an outpatient, and is anticipated to maintain outpatient status for the duration of the study;

6. Has a body mass index (BMI) of 19–40 kg/m^2, inclusive;

7. Ability to follow study instructions and likely to complete all required visits.

6.3.2 Exclusion Criteria

Patients who meet any of the following exclusion criteria will not be eligible to participate in the study**.**

Psychiatric Criteria:

1. Within the patient's lifetime, has a confirmed DSM-5 psychiatric diagnosis other than MDD, including:
    a. Schizophrenia, Schizoaffective Disorder, Schizophreniform Disorder or other psychotic disorder;
    b. Bipolar Disorder.
2. Within 6 months of Screening, has a confirmed DSM-5 psychiatric diagnosis other than MDD, including:
    a. Anxiety disorders such as Panic Disorder or Generalized Anxiety Disorder; Obsessive-compulsive Disorder; Posttraumatic Stress Disorder as primary diagnoses. ***Note***: anxiety symptoms may be allowed if secondary to MDD, provided these symptoms do not require concurrent treatment;
    b. Eating disorder;
    c. Substance use disorders (excluding nicotine)
    d. Personality disorder of sufficient severity to have a major impact on the patient's psychiatric status;
    e. Within 12 months of Screening, has had any other psychiatric condition (other than MDD) that has been the main focus of treatment.
3. The patient experiences a ≥ 25% decrease in the MADRS total score between Screening (Visit 1) and Baseline (Visit 2);
4. The patient experiences a ≥ 25% decrease in the QIDS-SR-16 total score between Screening (Visit 1) and Baseline (Visit 2);
5. In the opinion of the Investigator, the patient has a significant risk for suicidal behavior during his/her participation in the study or
    a. At Screening (Visit 1), the patient scores "yes" on Suicidal Ideation Items 4 or 5 of the C-SSRS within 6 months prior to Screening or, at Baseline (Visit 2), the patient scores "yes" on Suicidal Ideation Items 4 or 5 since the Screening Visit;
    b. At Screening (Visit 1), the patient has had 1 or more suicidal attempts within the 2 years prior to Screening; or
    c. At Screening (Visit 1) or Baseline (Visit 2), the patient scores ≥ 5 on MADRS Item 10 (Suicidal Thoughts); or
    d. The patient is considered to be an imminent danger to him/herself or others.
6. The patient has a first MDE at age 60 years or older.

Treatment Criteria:

7. In the current MDE, the patient has had > 2 ADTs administered at adequate dose (per product label) and for an adequate duration (at least 6 weeks);
8. In the current MDE, the patient has not responded to treatment with an antipsychotic for MDD administered at an adequate dose (per product label) and for an adequate duration (at least 3 weeks);
9. The patient is considered treatment-resistant, defined as having a lifetime history of treatment resistance (no remission) to $\geq$ 3 treatments with medications approved for the treatment of MDD at an adequate dose (per product label) and for an adequate duration of at least 6 weeks for monotherapy and 3 weeks for adjunctive therapy);
10. The patient has received electroconvulsive therapy (ECT), vagal nerve stimulation, or repetitive trans-cranial magnetic stimulation within the past 5 years or had a failure in response to ECT at any time;
11. The patient has known hypersensitivity or intolerance to lumateperone, or to any of the excipients;
12. The patient is currently participating in psychotherapy, or has plans to initiate psychotherapy therapy during the study;
13. The patient has used 1 of the following agents under the specified conditions:
    a. Any strong cytochrome P450 3A4 inhibitor or any P450 3A4 inducer within 7 days prior to the baseline visit;
    b. Monoamine oxidase inhibitors within 14 days prior to the baseline visit;
    c. Other drugs with known psychotropic properties or any non-psychotropic drugs with known or potentially significant central nervous system effects as reviewed by the Sponsor or designee, taken after screening, including, but not limited to:
        i. Benzodiazepines or sedative hypnotics (exceptions for zolpidem and other alternative treatments for insomnia are described in Section 7.7.3-Rescue Medications);
        ii. Central opioid agonists/antagonists including tramadol;
        iii. Anticonvulsants, mood stabilizers, antidepressants other than background antidepressant treatment, stimulants, antipsychotics, and non-benzodiazepine anxiolytics;
        iv. Dietary supplements and medical foods unless approved by the Sponsor or designee. Daily multivitamin use is not excluded;
14. The patient has participated in a previous clinical trial with lumateperone, *or* has had exposure to any investigational product within 3 months of the baseline visit *or* participated in the past 3 years in > 2 clinical studies of an investigational product with a central nervous system indication;
15. The patient is unable to be safely discontinued from prohibited psychotropic or non-psychotropic medication (in the opinion of the Investigator).

Other Medical Criteria:

16. The patient is male, or female of childbearing potential, and does not agree to use a highly effective method of birth control (defined as those methods, alone or in combination, that result in a failure rate less than 1 percent per year when used consistently and correctly) beginning with signing the Informed Consent Form through the end-of-study follow-up period. (Females of non-childbearing potential (defined as either permanently sterilized) or post-menopausal females (defined as at least one year with no menses without an alternative medical explanation) are exempt from the birth control requirement;

17. The patient is breast-feeding or pregnant. Female patients of childbearing potential must have a negative serum pregnancy test 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 treatment administration;

18. The patient has a positive test for drugs of abuse (eg, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, methadone, opiates, or phencyclidine) at Screening (Visit 1). Exceptions may include prescription treatments (eg, opioids, benzodiazepines) if the use is not chronic and is able to be discontinued as per the Investigator with the concurrence of the Sponsor or designee. A repeat drug test is allowed with the approval of the Sponsor or designee. A negative urine drug screen (UDS) is required for randomization.

19. The patient has abnormal laboratory values or clinical findings at Screening (Visit 1) that are judged to be clinically significant including, but not limited to:

    a. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2 × the upper limit of normal (ULN);

    b. Total bilirubin > 1.5 × ULN;

    c. Hemoglobin < 8 g/dL (80 g/L) for females and < 9 g/dL (90 g/L) for males;

    d. Absolute neutrophil count (ANC) < 1200 cells/µL (1.2×10^9/L);

    e. Thyroid-stimulating hormone (TSH) outside of normal reference range AND free T3 or free T4 outside of the reference range. Free T3 and Free T4 will only be evaluated if TSH is outside of reference range;

    f. HbA1c >7.5% [>58 mmol/mol];

    g. Positive test for hepatitis B surface antigen and/or hepatitis B core antibody immunoglobulin M at screening; positive hepatitis C antibody at screening (Visit 1), with the exception of a patient for whom the reflex HCV RNA test is negative;

    h. Any other clinically significant abnormal laboratory result obtained at Screening (Visit 1);

20. The patient has corrected QT interval using the Fridericia formula (QTcF) >450 msec for males or > 470 msec for 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;
21. The patient has any of the following conditions:
    a. Cardiac: 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);
    b. Malignancy: Any diagnosis of cancer (except basal or squamous cell skin carcinoma), unless in remission for at least 5 years;
    c. Gastrointestinal: history of gastric bypass or any other condition that results in malabsorption;
    d. Endocrine: hypo- or hyperthyroidism unless treated and stable with no medication changes for at least three months prior to screening, diabetes, unless considered stable with no changes in treatment for at least three months prior to screening;
    e. Hepatic: Hepatitis B or Hepatitis C; moderate or severe hepatic impairment (Child Pugh B or C)
    f. Pulmonary: history of diagnosed and untreated obstructive sleep apnea;
    g. Neurological: history of epilepsy, seizure or convulsion, or electroencephalogram with clinically significant abnormalities, delirium, dementia, amnestic, or central sleep apnea, or significant brain trauma, or other cognitive disorder;
    h. Infectious: History of human immunodeficiency virus (HIV) infection.

Note: Any other medical condition, or medical conditions that are stable with treatment (eg, hypertension, hypercholesterolemia, or thyroid abnormalities) are allowed as long as the condition has been stable for at least 3 months prior to Screening (Visit 1); treatments for these conditions are documented, kept stable, and are expected to be unchanged during the study; and the condition is not thought to affect safe participation in the study or relevant study outcomes in the opinion of the Investigator and confirmed by the Sponsor or designee.

Other Criteria:

22. The patient is judged by the Investigator to be inappropriate for the study;
23. 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.

6.4 Stopping Criteria

This section describes the patient-level discontinuation or stopping criteria as well as study-stopping criteria.

6.4.1 Discontinuation of Patients from Therapy or Assessment: Patient-level Stopping Criteria

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 treatment period for one of the following reasons:

- Death
- AE
- Lack of efficacy (patients whose MDD symptoms worsen or are determined by the Investigator to not be adequately controlled prior to completing the double-blind treatment period may be withdrawn from the study to start appropriate treatment at the Investigator's discretion)
- Protocol violation
- Study terminated by Sponsor
- Site terminated by Sponsor
- Withdrawal by subject or withdrawal of consent
- Lost to follow-up (every effort must be made to contact the patient; a certified/traceable letter must be sent)
- Pregnancy
- Other (such as physician decision, administrative reasons, etc)

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).

Patients who discontinue from the study and do not return to the study center for final assessments must be requested in writing to return to the study center 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 center staff may be contacted by the Sponsor or designee after each premature discontinuation to ensure that proper characterization of the reason for discontinuation is captured.

All patients who prematurely discontinue from the study regardless of cause should be seen for a final assessment at an ET Visit. All patients who prematurely discontinue from the study should return for the safety follow-up visit.

6.4.2 Study Stopping Criteria

This study will be regularly monitored for safety and tolerability based on routine review of safety data. On a quarterly basis during study conduct, all safety data (adverse events, clinical laboratory measures, vital signs, ECGs, and C-SSRS) will be reviewed in a blinded manner. If the Study

Physician determines at any point during the double-blind treatment period that the risk of study continuation outweighs the benefits, a determination to stop the study can occur in conjunction with discussions with the Head of Clinical Development or designee, the Head of Drug Safety and Pharmacovigilance, and the Chief Medical Officer.

6.5 Patient Replacement Procedures

Patients who prematurely discontinue from the study during the double-blind treatment period will not be replaced.

6.6 Changes in the Conduct of the Study

Any amendment to this protocol will be provided by the Sponsor in writing to the Investigator. No protocol amendment may be implemented before it has been approved by the IRB/IEC and Competent Authorities (if applicable), and the signature page, signed by the Investigator, has been received by the Sponsor. If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB/IEC and Competent Authority review and approval. However, the IRB/IEC and the Competent Authority must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits. Administrative changes, such as changes in study personnel, will be specified in the Study Reference Manual. Administrative changes will not require a protocol amendment.

7 STUDY TREATMENTS

7.1 Treatment Administered

Study treatment will be administered only to eligible patients under the supervision of the Investigator or sub-investigators or other designated personnel authorized to administer treatment.

Lumateperone 42 mg will be supplied as capsules. Placebo will be supplied as capsules, are identical in appearance to lumateperone, and have the same excipient ingredients as lumateperone but do not have the active compound. All study treatment will be provided in treatment cards.

Study treatment will be self-administered orally, at approximately the same time in the evening with or without food, once daily.

Table 7-1 provides formulation information for study treatment.

Table 7-1: Study Treatment Dosage and Composition

	Lumateperone 42 mg	**Placebo**
Dose Frequency	Once daily in the evening	Once daily in the evening
Route	Oral	Oral
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]

7.2 Supply, Storage, and Accountability of Study Treatment

Lumateperone and matching placebo will be provided in treatment cards and shipped under ambient conditions. Each blister card will contain a sufficient quantity of capsules for 1 patient for 1 week (7 doses, plus 3 extra doses), to be dispensed at every visit during the 6-week treatment period. The study treatment blister card will contain one 1×10 strip of capsules as described in Table 7-2.

Each lumateperone blister card will be labeled according to local laws and regulations.

Table 7-2: Weekly Study Treatment Cards

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.

7.2.1 Storage of Study Treatment

Study treatment must be stored in a secure area, eg, a locked cabinet, protected from moisture, and kept at room temperature. Sites must report any temperature excursions as described in the Study Reference Manual or contact the Sponsor or its designee for further instructions. Patients will be instructed to store the blister card at room temperature at home, out of the reach of children.

7.2.2 Study Treatment Accountability

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 treatment is dispensed and used by each patient in the study. Reasons for deviation from the expected dispensing regimen must also be recorded.

At the end of the study, all study treatment must be accounted for. In addition, at the end of the study, all unused study treatment and empty study treatment packages should be returned to the Sponsor or designee or destroyed, as per instructions provided by the Sponsor.

7.3 Method of Assigning Patients to Treatment Groups

After a patient signs the ICF at Screening (Visit 1), site personnel will register the patient in the interactive web response system (IWRS).

Study treatment will be labeled with medication kit numbers. The IWRS will provide the study center with the specific medication kit number(s) for each patient at the time of randomization. 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 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 7.5).

Study center personnel will dispense study treatment according to the IWRS instructions. Study center personnel will also log onto the IWRS at subsequent visits to obtain a study treatment kit number for dispensing study treatment. Study centers will receive the IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

7.4 Blinding

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

7.5 Unblinding

Unblinding at the study center should be done only in an emergency that requires the study treatment to be identified for the medical management of the patient. The Investigator must notify the Sponsor or designee immediately and a full written explanation must be provided if the blind is broken. Before study treatment is unblinded, every attempt should be made to discuss the case with the Sponsor or designee. Breaking the code at the study center will immediately disqualify the patient from further participation in the study.

Treatment codes may be broken by Drug Safety for regulatory reporting purposes. In such cases, the study center staff will be kept blinded and the patient will not need to be disqualified from the study.

For IWRS Unblinding

In an emergency, the Investigator can obtain the treatment assignment of any patient at his/her study center through the IWRS. In an emergency, the Investigator will access the IWRS to break the blind.

7.6 Monitoring Treatment Compliance

Study treatment adherence will be emphasized at every visit. Study treatment compliance during any period will be closely monitored. Compliance is based on the number of capsules prescribed and number of capsules taken. At every visit, study staff will count the number of capsules remaining in the blister pack. Any irregularities in study treatment adherence should be discussed with the patient. All errors in study treatment dispensing or administration must be carefully documented. These errors may include providing the wrong dose, not taking the dose as prescribed, or losing medication.

In addition, at every visit, study staff will ask the patient about compliance with prescribed ADT dosing regimen.

Any exceptions to non-compliance due to unusual circumstances should be discussed with the Sponsor or designee.

7.7 Prior and Concomitant Medications

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, eg, limited, acute prescribed opioid use. However, it is the responsibility of the Investigator to ensure that complete details regarding the medication are recorded in the eCRF.

7.7.1 Prior Medications

Tapering and discontinuation of psychotropic medications, with the exception of the ongoing antidepressant, will take place during the Screening Phase lasting up to 2 weeks. A washout is not required for non-psychotropic medications; however, certain medications do have stability requirements as presented in the eligibility criteria. Medication history, including the use of psychotropic medication or of any other medication, should be recorded at Screening (Visit 1). Thereafter, any changes in concomitant medications or new medications should be recorded in the eCRF.

7.7.2 Prohibited Medications

Use of the following products during the study is prohibited: alcohol, cannabis, illicit drugs, any known 5-HT_{2A} receptor antagonist or inverse agonist, any strong cytochrome P450 3A4 inhibitor or inducer, or any drugs with known psychotropic properties or any non-psychotropic drugs with potential central nervous system effects.

Patients who have been taking a low dose of quetiapine (< 50 mg) for the treatment of insomnia must discontinue quetiapine at the Screening Visit (Visit 1).

7.7.3 Rescue Medication

Medications for the acute treatment of extrapyramidal symptoms and akathisia are allowed.

Zolpidem may be taken for insomnia, in the evening at bedtime and prior to midnight, but no more than 3 times per week during the screening period and the first 2 weeks of the double-blind treatment period only (Section 6.3.2, Exclusion 13) for the treatment of insomnia. If zolpidem is not available in specific regions, another sedative hypnotic may be approved by the Sponsor or designee.

The date of each dose of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded on the eCRF.

7.8 Treatment After Discontinuation

Patients whose depressive symptoms worsen or are determined by the Investigator not to be adequately controlled prior to completing the Double-blind Treatment Period may, at the Investigator's discretion, be discontinued from the Double-blind Treatment Period in order to start appropriate treatment. This new treatment will not be provided by the Sponsor. Patients who initiate a new treatment during the study must be discontinued from the study and should also return for a Safety Follow-up visit.

All patients who prematurely discontinue from the Double-blind Treatment Period regardless of cause should be seen for a final assessment at the ET Visit. All patients who prematurely discontinue from the Double-blind Treatment Period should return for the Safety Follow-up visit.

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 Major Depressive Disorder, as confirmed by the MINI (7.0.2; 8/8/16 version). The MINI is a validated clinical diagnostic tool (Sheehan et al, 1998) that will be used at the Screening visit only and will be completed by a Sponsor-approved rater.

8.1.2 MGH Antidepressant Treatment Response Questionnaire (ATRQ)

The Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ) (Chandler et al, 2010) is a clinician-administered scale used to determine treatment resistance in Major Depressive Disorder. The scale defines 6 weeks on an adequate dose of antidepressant medication as an adequate duration of treatment. It also provides specific operational criteria for adequate dosage for each of the most commonly used antidepressants.

8.1.3 Medical History and Other Information

Medical history information will be collected at screening and should include demographic information (as allowed by local country legislation), current and past medical conditions, and current and past medications. Prior to study treatment administration, medical history must be documented in the patient's study chart and also recorded in the appropriate 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).

8.1.4 Eligibility Review Process

Eligibility of potential patients will be confirmed by the Sponsor or designee through a review of screening data, including safety and laboratory assessments, medical and psychiatric history, including the ATRQ, and psychiatric status, including DSM-5 diagnosis of MDD, as confirmed by the MINI, and MADRS, CGI-S, and QIDS-SR-16 scores. Further information regarding the eligibility review process and the Pre-Enrollment Eligibility Review (PEER) Form are provided in the Study Reference Manual.

8.1.5 Patient Placebo Questionnaire and Training

A brief training module will be provided describing placebo response at Baseline (Visit 2) prior to randomization. A placebo response questionnaire will be administered at Baseline (Visit 2) prior to randomization 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 study treatment.

8.1.6 Quick Inventory for Depressive Symptomatology-Self Report (QIDS-SR-16)

The QIDS-SR-16 is a 16-item patient-rated scale of symptom severity in depression. It assesses nine key symptoms of depression: insomnia/hypersomnia, low mood, appetite/weight changes, impaired self-perception, concentration difficulties, loss of interest/pleasure, suicidal ideation, psychomotor agitation and fatigue. Respondents use a 4-point Likert-type scale (0-3) to assess their behaviors and mood over the course of the past week. The total score ranges from 0-27, with higher scores indicating more severe depression.

8.2 Efficacy Assessments

8.2.1 Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS is a 10-item scale 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. Patients are rated on items assessing feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty in concentration, and lack of interest. The MADRS total score ranges from 0 to 60. The MADRS total score at screening is a major inclusion criterion of the study, as well as the primary outcome measure for the study. The MADRS will be completed by a Sponsor-approved rater.

8.2.2 Clinical Global Impression-Severity (CGI-S)

The Clinical Global Impression 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.

8.2.3 Changes in Sexual Functioning Questionnaire

The Changes in Sexual Functioning Questionnaire (CSFQ) is a structured interview/questionnaire designed to measure illness- and medication-related changes in sexual functioning (Keller et al, 2006). The CSFQ-14 uses a 5-point Likert scales to provide the patient an opportunity to self-evaluate his or her sexual behaviors or problems in a number of areas. For all items, higher scores reflect higher sexual functioning. For 12 of the 14 items, higher sexual functioning corresponds to greater frequency or enjoyment/pleasure (eg, 1 = never to 5 = every day). For two items (Item 10, assessing loss of interest after arousal for women and priapism for men, and Item 14, assessing painful orgasm), higher sexual functioning corresponds to lower frequency (eg, 1 = every day to 5 = never). Items 10 and 14 are included in the total score but not in any scale score. Gender-specific versions of the CSFQ-14 will be administered during the study.

8.3 Safety

All patients who receive study treatment will be evaluated for safety. Safety assessments will include incidence of AEs, C-SSRS assessment for suicidality, EPS assessment as measured by AIMS, BARS, and SAS scales, clinical laboratory evaluations, ECG evaluations, vital sign measurements, and physical examination. Additional details pertaining to safety assessments are provided in the Schedule of Evaluations (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 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 and for a pre-existing condition which did not worsen 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 any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening

NOTE: An AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/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 treatment 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.

8.3.1.3 Classification of Adverse Events and Serious Adverse Events

8.3.1.3.1 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:

Mild: A type of AE 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 AE 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 patient.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.3.1.3.2 Causality Assessment

For each reported AE and SAE, the Investigator must provide an assessment of causal relationship to study treatment. Causal relationship must be assessed by answering the following question:

Is there a reasonable possibility the study treatment caused the event?

Yes: **There is evidence to suggest a causal relationship between the study treatment and adverse event, ie:**

- There is a reasonable temporal relationship between the study treatment and the event, and/or
- The event is unlikely to be attributed to underlying/concurrent disease, other investigational products, or other factors, and/or
- Positive dechallenge and/or rechallenge exist

OR

No: There is no evidence to suggest a causal relationship between the study treatment and adverse event, ie:

- There is no reasonable temporal relationship between the study treatment and the event, or
- The patient did not take the study treatment, or

- The event is likely to be attributed to underlying/concurrent disease, other investigational products, or other factors.

There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor. The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. The causality assessment must be recorded on the appropriate AE reporting page of the patient's eCRF.

8.3.1.4 Time Period and Frequency of AE and SAE Reporting

The Investigator will report all AEs from the time informed consent was obtained until the final protocol-defined study visit or last known dose date of study drug + 1 day, whichever is later.

The Investigator will report all SAEs from the time informed consent was obtained until 30 days after the last known dose date of study drug.

At each visit, patients are to be queried regarding any AEs that have occurred since the previous visit. Patients will be asked to volunteer information with a nonleading question such as, "How do you feel since your last visit?"

8.3.1.5 Adverse Event Reporting Procedures

8.3.1.5.1 Reporting Adverse Events

All AEs, including overdose with sequelae or intentional overdose of study treatment 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 treatment.

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 treatment;
- 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 treatment. If a follow-up visit is deemed necessary for appropriate safety surveillance, it will take place within 30 days of the final protocol-defined study visit.

8.3.1.5.2 Reporting Serious Adverse Events

The Sponsor is required to inform worldwide 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. Within 24 hours of learning of any AE that meets one of the criteria for an SAE, study center personnel must report the event to ProPharma Group on the SAE Form. In addition to completing the SAE form, the Study Physician may also be notified by telephone.

If, during follow-up, any nonserious AE worsens and eventually meets any SAE criterion, that AE should be recorded as a new SAE.

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

The study center must email or fax the SAE form to the SAE email address below. Even if an initial report is made by telephone, the SAE form containing all available details must still be emailed or faxed within 24 hours of knowledge of the event at the study center.

Supplemental information should be submitted as soon as available and may include laboratory results, radiology reports, progress notes, hospital admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

The Investigator is expected to take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the patient's eCRF. All SAEs will be followed until resolution or stabilization. ***The Sponsor may contact the study center to solicit additional information or follow up on the event. A response is required within 24 hours of the request.***

SAE Reporting E-mail: clinicalsafety@propharmagroup.com
SAE Reporting Fax Number: +1 (866) 681-1063

Medical Emergency Phone Number: US: +1 (512) 686-1256; outside of US: +44 118 936 4096.

8.3.2 Potential Hy's Law Cases

Study center personnel must report every patient who meets potential Hy's Law criteria from the time the ICF is signed until 30 days after the final protocol-defined study visit or the last known dose of study treatment (if the final visit does not occur).
The criteria for potential Hy's law cases are as follows:

- ALT or AST ≥ 3 × ULN and
- Total bilirubin ≥ 2 × ULN and
- Alkaline phosphatase < 2 × ULN

Study center personnel must report every subject who meets these potential criteria. Typically, these analytes will be obtained from the same sample, but they may come from multiple samples

taken within a 24-hour period. This requirement applies from the time the ICF is signed for the study until 30 days after the last known dose of study treatment.

A laboratory alert for potential Hy's Laws cases will be in place, and the laboratory must notify Investigators and the Sponsor immediately when the above criteria have been met. The Sponsor must be notified of any potential Hy's Law case as soon as possible (within 24 hours of learning of a potential Hy's Law case). Refer to the SAE reporting procedures (Section 8.3.1.5.2) even if no AE has occurred.

Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring should be initiated in conjunction with the Study Physician and in accordance with the FDA Guidance for Industry: Drug Induced Liver Injury—Pre-Marketing Clinical Evaluation, July 2009.

8.3.3 Pregnancy

Female patients will not be eligible for inclusion in the study if they have a positive pregnancy test at the Screening or Baseline Visit. Any patient who becomes pregnant must be discontinued from the study.

Study center personnel must report every pregnancy, including pregnancies in female partners of male study patients, from the time consent was obtained until the final protocol-defined study visit or last known dose of study treatment (if a final visit does not occur).

Within 24 hours of learning of the pregnancy, study center personnel must report the event to the Sponsor on the Pregnancy Notification Form and email or fax it to the email address or fax number below even if no AE has occurred.

- While pregnancy itself is not considered to be an AE or SAE, any *pregnancy complication* or *elective termination* of a pregnancy for medical reasons will 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 8.2.1.5.2 with the appropriate serious criterion (eg, hospitalization) indicated in addition to the Pregnancy Notification/Outcome Form.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

Any pregnancy in a study patient or in a female partner of a male study patient/subject must be followed to term/termination. The outcome, including status of the mother and the child, must be reported to the Sponsor by completing a follow-up Pregnancy Outcome Form.

Pregnancy Reporting E-mail: clinicalsafety@propharmagroup.com
Pregnancy Reporting Fax Number: +1 (866) 681-1063.

8.3.4 Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected as specified in the Schedule of Evaluations (Table 1-1). Patients are required to fast for at least 10 hours before the collection of clinical laboratory blood tests at designated visits.

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 abnormal screening laboratory results judged to be clinically significant will be excluded from the study.

Laboratory results should be reviewed by the Investigator/sub-investigator throughout the study. For safety reasons or at the discretion of the Investigator, repeat laboratory assessments may be performed at an unscheduled visit.

The following clinical laboratory levels will be measured:

- **Hematology**: hematocrit; hemoglobin; 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.
- **Chemistry**: albumin; alkaline phosphatase; ALT; AST; bilirubin (total, direct); blood urea nitrogen; calcium; chloride; cholesterol (high-density lipoprotein [HDL] and low-density lipoprotein [LDL] will be calculated and reported); creatinine; creatine phosphokinase; gamma-glutamyl transferase; glucose; insulin; lactate dehydrogenase; phosphate; potassium; prolactin; sodium; triglycerides; total protein; uric acid. HbA1c and TSH (reflex free T3 and free T4) will be measured at Screening/Visit 1 and Visit 8/ET only.
- **Urinalysis**: macroscopic (pH, specific gravity, glucose, protein, ketones, bilirubin, nitrates, blood) and microscopic (red blood cells/high-power field, white blood cells/high-power field, casts, epithelial cells, crystals, granulation).
- **Urine Drug Screen (UDS)**: Urine drug tests for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, methadone, opiates, or phencyclidine will be performed. Any patient who tests positive for any drug at Screening, will be excluded from participating in the study. Exceptions may include prescription treatments (eg, opioids, benzodiazepines) if the use is not chronic and is able to be discontinued as per the Investigator with the concurrence of the Sponsor or designee. A repeat drug test is allowed with the approval of the Sponsor or designee. A negative UDS is required for randomization.

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

- **Urine and serum pregnancy tests**: Female patients who are of childbearing potential will undergo a serum pregnancy test at Screening (Visit 1) and a urine pregnancy test at Baseline (Visit 2) at the study clinic, and, at the discretion of the Investigator, at an Unscheduled Visit. Serum and urine pregnancy test will be administered at Visit 8 for patients who are rolling over into the Open-label Safety Study. 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 serum pregnancy test at screening is 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.
- **Hepatitis screening**: Blood samples will be collected at Screening (Visit 1) from all patients in order to perform hepatitis B surface antigen, hepatitis B core antibody IgM, and hepatitis C antibody (immunoglobulin G) testing. Confirmatory testing will be undertaken as needed. 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.

A central laboratory will be used to evaluate all urine and blood samples, which will be collected, processed, and stored according to the instructions provided in the Laboratory Manual.

8.3.5 Vital Signs

Vital signs (pulse rate, systolic and diastolic blood pressure [BP], body temperature, and body weight will be assessed at every visit during the study as specified in the Schedule of Evaluations (Table 1-1). Height and BMI is assessed at Screen (Visit 1) only and waist circumference will be assessed at Screen (Visit 1) and Visit 8/ET.

Blood pressure and pulse rate will be measured twice: once after the patient is resting quietly in the supine position followed by once after at least 2 minutes in the standing positions. BP may be measured either manually or by machine but using the same method consistently for each patient throughout the study.

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 without jacket and shoes. For each patient, body weight and height should be determined using the same equipment during the study after ensuring its proper calibration.

8.3.6 Electrocardiograms

A 12-lead ECG will be performed as specified in the Schedule of Evaluations (Table 1-1). Each ECG assessment will be conducted after the patient has been resting quietly in the supine position and will comprise ten-second epochs from 12-lead ECGs. ECG parameters to be measured include HR, QRS, PR, QT, QTcB, QTcF and RR intervals.

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. For eligibility criteria, the values reported on the central ECG interpretation report, not the values that are printed on the tracing itself, will be used.

8.3.7 Columbia–Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a clinician-rated instrument that reports the severity of both suicidal ideation and behavior (Posner, 2011). The C-SSRS will be completed by a Sponsor-approved rater.

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:

- Completed suicide
- Actual attempt
- Interrupted attempt
- Aborted attempt, and
- Preparatory acts or 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. The C-SSRS will be completed by a trained and Sponsor-approved rater.

8.3.8 Extrapyramidal Scales

8.3.8.1 Abnormal Involuntary Movement Scale (AIMS)

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. There are an additional 2 items on dental status that are answered yes or no. The AIMS is to be completed at Baseline (Visit 2) and Visits 4, 6 and 8/ET according to Schedule of Evaluations (Table 1-1).

8.3.8.2 Barnes Akathisia Rating Scale (BARS)

The BARS is a rating scale for drug-induced akathisia developed by Barnes (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 6-point scale from 0 to 5. The BARS is to be completed at Baseline (Visit 2) and Visits 4, 6 and 8/ET according to Schedule of Evaluations (Table 1-1).

8.3.8.3 Simpson-Angus Scale (SAS)

The SAS is a measure of extrapyramidal side effects (Simpson &Angus, 1970). The SAS is used for assessment of antipsychotic-induced parkinsonism in both clinical practice and research settings. 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 (Visit 2) and Visits 4, 6 and 8/ET according to Schedule of Evaluations (Table 1-1).

8.3.9 Modified Physical Examination

A modified physical examination, excluding genital/rectal examinations, will be performed at the visits specified in the Schedule of Evaluations (Table 1-1). The examinations will be performed by a professionally trained physician or health professional licensed to perform physical examinations.

The examination should include evaluation of height (at Screening/Visit 1 only); body weight (kg); waist circumference (cm) (at Screening and Visit 8/ET only); appearance and skin; head and neck; eyes, ears, nose, and throat; chest and lungs; heart; abdomen; and extremities. All physical examination findings must be documented in the patient's study chart and recorded in the eCRF.

[redacted]

9 STATISTICAL METHODS

9.1 General Considerations

The statistical analysis plan (SAP) will be finalized prior to unblinding the patients' treatment assignments and will provide a more technical and detailed description of the statistical analyses described in this section. 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.

9.2 Determination of Sample Size

The effect size (treatment group difference relative to pooled standard deviation) of 0.33 for lumateperone 42 mg is based on a treatment difference of 3.3 units with a common pooled SD of 10 for the primary efficacy endpoint, change from baseline to Day 43 in MADRS total score. A sample size of 470 patients (235 per treatment group) will be needed to provide approximately 90% power for primary analysis (lumateperone 42 mg vs placebo) based on an MMRM model using simulation method (Lu, 2012). The simulation assumed a correlation of 0.7 between the repeated measures and a common dropout rate of 20% based on historical data.

9.3 Analysis Populations

The following analysis populations will be considered in the statistical analysis of the study:

- **Randomized Population** includes all patients who were randomly assigned to study treatment;
- **Safety Population** includes all randomized patients who received at least 1 dose of study treatment. Patients will be analyzed according to the treatment they actually received;
- **Intent-to-Treat (ITT) Population** includes all randomized patients who received at least one dose of study treatment and have a baseline MADRS total score;
- **Modified Intent-to-Treat (mITT) Population** includes all randomized patients who received at least 1 dose of study treatment, have a baseline MADRS total score, and who have at least one on-treatment, post-baseline MADRS total score. On-treatment MADRS assessments are those performed no later than 3 days after the last dose of study treatment;
- [redacted]

9.4 Statistical Analyses

9.4.1 Patient Disposition

The number of patients in each study population will be summarized by treatment group and study center as follows:

- The number of patients who were screened will be summarized overall by study center.
- The number of patients in the Safety and mITT populations will be summarized overall and by treatment group and study center.

In addition, the number and percentage of patients who completed the Double-blind Treatment Period and who prematurely discontinue from the Double-blind Treatment Period will be summarized overall, by treatment group, and by reasons for premature discontinuation for the Double-blind Treatment Period. The reasons for premature discontinuation from the Double-blind Treatment period as recorded on the termination page of the eCRF will be summarized (number and percentage) by treatment group for the Safety Population.

9.4.2 Demographics and Other Baseline Characteristics

Demographic parameters as allowed by local country legislation (eg, age, sex, race, ethnicity, weight, body mass index) and other baseline characteristics will be summarized by treatment group for the Safety and mITT populations.

Prior medical and surgical history will be summarized by treatment group for the Safety Population.

Baseline efficacy parameters will be summarized by treatment group for the mITT Population.

9.4.3 Prior and Concomitant Medication

Prior medication is defined as any medication started and stopped before the date of the first dose of double-blind study treatment. A prior concomitant medication is any medication that started before the date of the first dose of double-blind study treatment and stopped or is ongoing after the date of the first dose of study treatment. Concomitant medication is defined as any medication taken on or after the date of the first dose of double-blind study treatment. Both prior and concomitant medication, including prior concomitant medication use, will be summarized as the number and proportion of patients in each treatment group who received each medication within each therapeutic class for the Safety Population. Multiple medications used by a patient will only be counted once.

Any concomitant medication started after the date of the last dose of double-blind study treatment will not be included in the summary but will be included in the patient data listings.

9.4.4 Extent of Exposure and Treatment Compliance

9.4.4.1 Extent of Exposure

Exposure to study treatment for the Safety Population will be summarized for treatment duration, calculated as the number of days from the date of the first dose of double-blind study treatment taken to the date of the last dose taken, inclusive. The number and percentage of patients with each treatment duration of ≥ 1 day, ≥ 7 days, etc, will be summarized by treatment group, respectively.

9.4.4.2 Measurement of Treatment Compliance

Dosing compliance for a specified period is defined as the total number of capsules of study treatment actually taken by a patient during the treatment period divided by the number of capsules of study treatment that were expected to be taken during the treatment period multiplied by 100.

The total number of capsules actually taken during the treatment period will be calculated from the study treatment record. Descriptive statistics for study treatment dosing compliance together with compliance category will be summarized by treatment group for the Safety Population.

9.4.5 Efficacy Analyses

The primary efficacy analyses and the sensitivity analysis will be based on the mITT and ITT Populations; other efficacy analyses will be based on the ITT Population, unless stated otherwise. The baseline for each specific efficacy endpoint is defined as the last measurement prior to the first dose of randomized treatment. All statistical hypothesis tests will be performed at the 2-sided 5% significance level for main effects. All confidence intervals (CIs) will be 2-sided 95% CIs, unless stated otherwise.

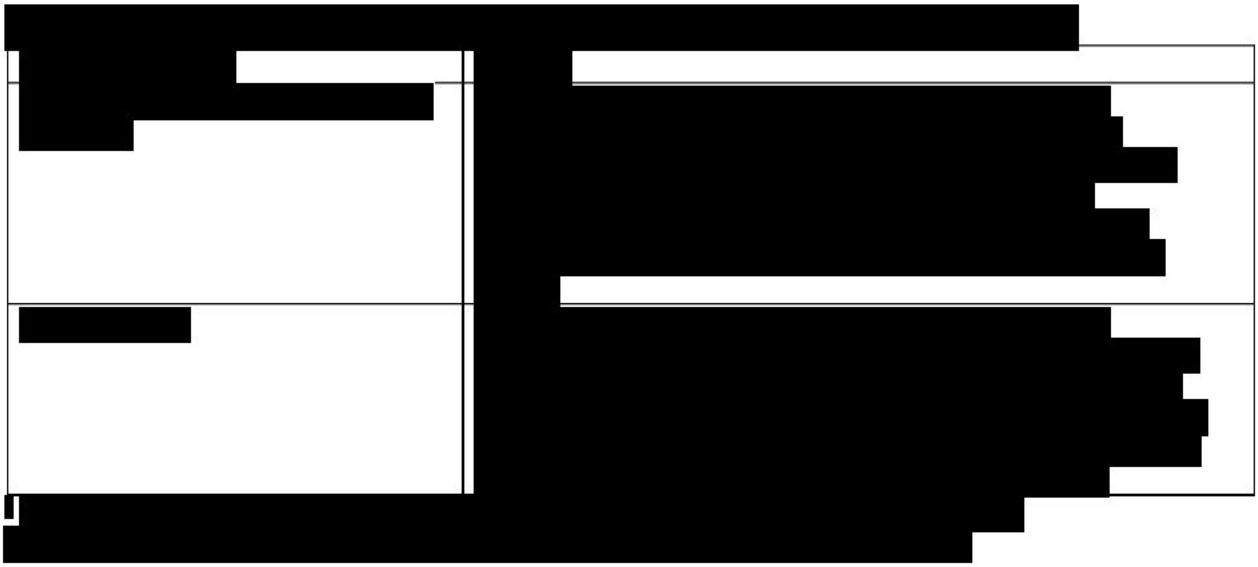
All investigative sites with fewer than 2 mITT patients per treatment group will be pooled as follows: The largest site with fewer than 2 mITT patients per treatment group will be pooled with the smallest site with fewer than 2 mITT patients per treatment group within the same country or geographic region. If this results in a pooled site still having fewer than 2 mITT patients per treatment group, this site will be pooled together with the next smallest investigative site within the same country or geographic region, if one exists; otherwise, no further pooling is needed. Sites with the same number of mITT patients will be ordered in ascending order of their numerical site identification number. This will serve as a tie-breaker rule in case multiple sites have the same number of mITT patients. Should the primary efficacy analysis model present convergence issues, after testing the sequence of correlation structures, then the site effect will be reconsidered and may be dropped from the model. These pooled investigative sites, as determined based on the primary efficacy response variable, will be used for any analysis that has investigative site as a fixed effect in the model. The actual investigative site numbers will be included in the listings. For analyses that are based on the ITT Population and include site as a factor, additional pooling will be performed starting from the mITT pooled sites. Sites with patients who are in ITT Population but not the mITT Population will be pooled, using the same algorithm as outlined above.

9.4.5.1 Primary Efficacy Endpoint

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

9.4.5.1.1 Primary Efficacy Analysis

The data to be included in the primary efficacy analysis will be decided by the intercurrent events as described in Table 9-1.



[redacted]

[redacted]

9.4.5.2 Key Secondary Efficacy Endpoint

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

9.4.5.2.1 Key Secondary Analysis

The key secondary efficacy endpoint will be tested using the same hypothetical estimand strategy as for the primary efficacy endpoint.

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9.4.6 Multiple Comparisons/Multiplicity

A fixed sequence testing procedure will be used to control the overall Type I error of 0.05 with the primary endpoint based on the primary estimand approach tested first at the 0.05 level, and if significant, the secondary endpoint will be tested at the 0.05 level.

9.4.7 Safety Analyses

Safety analyses will be performed using the Safety Population. The safety parameters will include AEs, clinical laboratory, vital signs, ECG, and EPS (AIMS, BARS, and SAS) and C-SSRS scales.

9.4.7.1 Adverse Events

Adverse events will be coded by system organ class (SOC) and preferred term using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

An AE will be considered a treatment-emergent AE (TEAE) if it was not present before the first dose of double-blind study treatment or was present before the first dose of double-blind study treatment but increased in severity after the first dose. If more than one AE is reported before the date of the first dose of double-blind study treatment and coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs occurring during the Double-blind Treatment Period that were also coded to that preferred term. An AE that occurs more than 1 day after the date of the last dose of double-blind study treatment will not be counted as a TEAE.

The number and percentage of patients reporting TEAEs in each treatment group will be tabulated by SOC and preferred term; by SOC, preferred term, and severity; and by SOC, preferred term, and relationship to study treatment. If more than one AE is coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the most severe and most related occurrence for the summary by severity and by relationship to study treatment.

The number and percentage of patients reporting serious AEs (SAEs) in each treatment group during double-blind treatment period will be tabulated by SOC and preferred term. Also, the number and percentage of patients reporting AEs leading to drug withdrawal in each treatment group during double-blind treatment period will be tabulated by SOC and preferred term.

9.4.7.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in International System of Units [SI] and conventional units) and changes from baseline values at each assessment timepoint will be summarized by treatment group for each clinical laboratory parameter.

The number and percentage of patients with potentially clinically significant (PCS) postbaseline clinical laboratory values will be tabulated by treatment group. The criteria for PCS laboratory values and details on additional laboratory analyses will be provided in the SAP.

The number and percentage of patients with shifts from baseline according to normal range criteria (for quantitative and categorical measurements) at the end of treatment will be provided. In addition, the number and percentage of patients with shifts from baseline according to PCS criteria at the end of treatment will be provided.

In addition, the number and percentage of patients meeting Hy's law criteria during the double-blind treatment period will be provided.

9.4.7.3 Vital Signs

Descriptive statistics for vital signs (eg, pulse rate, systolic and diastolic BP, body weight) and changes from baseline values at each visit, and at the end of the treatment period, will be presented by treatment group.

Vital sign values will be PCS if they meet the observed-value and the change-from-baseline-value criteria as detailed in the SAP. Details on additional vital sign analyses will be provided in the SAP.

9.4.7.4 Electrocardiogram

Descriptive statistics for ECG parameters (eg, ventricular heart rate, QTc interval, QRS interval) and changes from baseline values at each assessment timepoint will be summarized by treatment group.

The number and percentage of patients with PCS postbaseline ECG values will be summarized by treatment group. The criteria for PCS ECG values and details on additional analyses of ECG parameters will be provided in the SAP.

9.4.7.5 Other Safety Parameters

Descriptive statistics for EPS scales (AIMS, BARS, SAS) and C-SSRS will be summarized overall and by treatment group for the Double-blind Treatment Period, based on the corresponding Safety Populations.

[redacted]

[redacted]

9.5 INTERIM ANALYSIS

No interim analysis is planned for this study.

9.6 Data and Safety Monitoring Board

Not applicable.

9.7 Protocol Deviations

A deviation from the protocol is an unanticipated departure from the procedures or processes approved by the Sponsor and the IRB/IEC and the Competent Authority and agreed to by the Investigator. A major protocol 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 to the primary efficacy assessment. Major protocol deviations can include, for example, nonadherence to inclusion or exclusion criteria or nonadherence to ICH GCP guidelines and may lead to the patient being withdrawn from the study.

The Investigator or designee must document and explain any deviation from the approved protocol. The IRB/IEC should be notified of all major protocol deviations in a timely manner.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL MONITORING

10.1 Study Termination

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

10.2 Investigator Obligations

10.2.1 Documentation

The Investigator must provide the following to the Sponsor, before the start of the study:

- A completed and signed Form FDA 1572 or equivalent form, if applicable. If, during the course of the study, any changes are made that are not reflected on Form FDA 1572 or equivalent form, if applicable, a new form must be completed and returned to the Sponsor.
- A fully executed contract
- The curricula vitae for the Investigator and all sub-investigators listed on Form FDA 1572 or equivalent form, if applicable, 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 or equivalent form, if applicable
- 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
- 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
- The Investigator's Statement page in this protocol signed and dated by the Investigator.

10.2.2 Performance

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

10.2.3 Use of Investigational Materials

Study treatment must be stored in a secured place and must be locked. At study initiation, a representative from the Sponsor will inventory the study treatment at the study center. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. The Sponsor may supply forms on which to record the date the study treatment was received and a dispensing record in which to record each patient's use. All unused study treatment must be returned to the Sponsor-designated central depot.

10.2.4 Case Report Forms

All patient data relating to the study, except for data electronically transmitted (eg, central laboratory results), will be recorded on eCRFs to be provided by the Sponsor through the EDC system. The Investigator is responsible for verifying that all data entries in the eCRFs are accurate and correct by electronically signing the completed eCRFs submitted to the Sponsor. The Investigator must maintain and retain accurate documentation that supports the information entered into the EDC system for source document verification and possible regulatory inspection.

10.2.5 Retention and Review of Records

Records and documents pertaining to the conduct of this study, including eCRFs, source documents (eg, medical records, laboratory reports), consent forms, regulatory documents, and medication inventory records must be retained by the Investigator for a period of at least 15 years after study completion unless local regulations or institutional policies require a longer retention period or otherwise notified in writing by the Sponsor.

No study records shall be destroyed without notifying the Sponsor and providing the Sponsor the opportunity to arrange long-term storage for such study records or authorizing in writing the destruction of records after the required retention period.

The Investigator must permit access to any documentation relating to the study upon request of the Sponsor or applicable regulatory authorities. If the Investigator for the study retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a suitable alternate custodian employee of the institution or to a suitably qualified and responsible third party. The Sponsor must be notified in writing of the name and address of the new custodian in advance of the transfer.

10.2.6 Patient Confidentiality

All patient records will be identified by patient identification number only. Patients' names are not to be transmitted to the Sponsor. The Investigator will keep a master patient list on which the patient's identification number and the full name, address, and telephone number are listed. However, the list will never leave the site and will be archived at the site after the end of the study.

10.3 Data Quality Assurance

10.3.1 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. Electronic data capture (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 Sponsor or study monitor or designee source documents (written notes and electronic medical records, if used), signed ICFs, and all other study-related documents.

Study monitors or designee, 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 randomized, the study monitor or designee will periodically monitor the progress of the study by conducting on-site visits. In addition to on-site source document verification, study monitors will review study progress remotely, possibly warranting more frequent communication and/or study center visits. Details of monitoring activities are provided in the Monitoring Plan.

10.3.2 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 his/her designee using his/her assigned EDC user account. The Investigator or his/her 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 performed on 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 used in the past. 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 Manual.

10.4 Reporting and Publication

All data generated in this study are the property of the Sponsor. An integrated clinical and statistical report will be prepared and submitted within one year after the completion of the study.

11 APPENDICES

APPENDIX I. ELEMENTS OF INFORMED CONSENT

Procedures will comply with 21 CFR, Parts 50 and 312. Signed informed consent will be obtained for each patient participating in a clinical research study. This consent must include the following items:

- A statement that the study involves research and an explanation of the purposes of the research; a description of the procedures to be followed and the identification of any procedures that are experimental; and the expected duration of the patient's participation
- A description of any reasonably foreseeable risks or discomforts to the patient
- A description of any benefits to the patient or to others that may reasonably be expected from the research. If the patient is to be paid for participating in the study, the consent form must state the amount that he/she will receive and the schedule of payment (to ensure neither coercion nor undue influence).
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient.
- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA or other local health authority, the Sponsor, the IRB/IEC, or an authorized contract research organization may inspect the records
- For research involving more than minimal risk, an explanation of whether any medical treatment is available if injury occurs and, if so, what it consists of or where further information may be obtained
- An explanation of whom to contact, including the relevant telephone number, for answers to pertinent questions about the research and the research patient's rights and whom to contact in the event of a research-related injury to the patient. (Note: In some cases, it may be necessary to identify a person other than the Investigator as the contact. The guidance of the IRB/IEC may be required.)
- For EU countries, the ICF will include a statement of whom to contact, including relevant phone and email address, for questions about patient data confidentiality or data breach' per GDPR.
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject/patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled
- A statement that the treatment or procedures may involve risks to the patient (or to the embryo or fetus if the patient is, or may become, pregnant) that are at present unforeseeable
- The expected circumstances for which the patient's participation may be terminated by the Investigator without regard to the patient's consent

- Any additional costs to the patient that may result from participation in the research
- The consequences of a patient's decision to withdraw from the research and procedures for an orderly termination of the patient's participation
- A statement that significant new findings developed during the course of the research that may relate to the patient's willingness to continue participation will be provided to the patient
- The approximate number of patients involved in the study
- A statement of permission, providing consent for the patient to participate (eg, "I agree to participate . . .")
- A place for the patient's signature and date of signing of the ICF
- A statement indicating that information about this study has been, or will be, entered into a databank that is publicly accessible at www.ClinicalTrials.gov.
- A copy of the signed consent form must be given to the patient.

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13 INVESTIGATOR SIGNATURE PAGE

I agree to conduct the study in accordance with Amendment 1 to the Original Protocol for Study ITI-007-502, dated 18 Aug 2021, and with all applicable government regulations and GCP guidance, 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 disclose information regarding this clinical investigation or publish results of the investigation without prior authorization from Intra-Cellular Therapies, Inc.

_____	_____
Principal Investigator Signature	Date
_____	_____
Principal Investigator Name (printed)	Site Number