NCT02817906

Study ID: ITI-007-201

Title: A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study with an Open-Label Extension to Assess the Efficacy and Safety of ITI-007 in the Treatment of Agitation in Patients with Dementia, Including Alzheimer's Disease

Protocol Amendment 5.2 Date: 22 October 2018

CLINICAL STUDY PROTOCOL
ITI-007-201

IND 127595

A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study with an Open-Label Extension to Assess the Efficacy and Safety of ITI-007 in the Treatment of Agitation in Patients with Dementia, Including Alzheimer's Disease

Confidential

PROTOCOL ITI-007-201

Sponsor:

Intra-Cellular Therapies, Inc. (ITI)
430 East 29th Street
Alexandria Center for Life Science, Suite 900
New York, New York 10016

Sponsor Contacts:

Version of Protocol: Version 5.2

Date of Protocol: 22 October 2018

CONFIDENTIAL

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

Protocol Approval – Sponsor Signatory

Study Title	A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study with an Open-Label Extension to Assess the Efficacy and Safety of ITI-007 in the Treatment of Agitation in Patients with Dementia, Including Alzheimer's Disease
Protocol Number	ITI-007-201
Protocol Version	5.2
Protocol Date	22 October, 2018

[redacted]

[redacted]

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study with an Open-Label Extension to Assess the Efficacy and Safety of ITI-007 in the Treatment of Agitation in Patients with Dementia, Including Alzheimer's disease" and the accompanying associated Investigator's brochure issued.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 5.2, dated 22 October 2018, the International Council for Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with ITI or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer study treatment only to patients under my personal supervision or the supervision of a subinvestigator.

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

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

Signature of Principal Investigator Date

Printed Name of Principal Investigator

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Protocol Synopsis

Protocol Number:	ITI-007-201
Title:	A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study with an Open-Label Extension to Assess the Efficacy and Safety of ITI-007 in the Treatment of Agitation in Patients with Dementia, Including Alzheimer's Disease
Sponsor:	Intra-Cellular Therapies, Inc. (ITI)
Study Phase:	Phase 3
Study Sites:	Up to approximately 60 study sites in 1 country (United States)
Indication:	Agitation in Patients with Dementia
Rationale:	Intra-Cellular Therapies, Inc. is developing ITI-007, a new chemical entity, for the treatment of symptoms of agitation, including aggression, in patients with dementia, including Alzheimer's disease (AD). Dementia can be caused by a variety of conditions, the most common of which is AD. Typically patients develop signs of cognitive decline, including diminished capacity for concentration, calculation, language, comprehension, and memory. The behavioral disorders that commonly accompany this disease remain largely untreated by currently approved drugs. These behavioral disturbances include agitation, aggression, depression, apathy, delusions, hallucinations, and disrupted sleep/wake cycles. These symptoms have serious consequences for the patients and caregivers, leading to more rapid deterioration in patient health and increased burden of care. ITI-007 represents a novel, small molecule therapeutic agent designed specifically to combine in a dose-dependent manner potent serotonin 5-HT_{2A} receptor antagonism with mesolimbic/mesocortical selective modulation of phosphoprotein pathways downstream of dopamine receptors together with serotonin reuptake inhibition. As a dopamine receptor protein phosphorylation modulator, ITI-007 has dual properties, acting as a post-synaptic antagonist and as a pre-synaptic partial agonist at dopamine D_2 receptors in vivo with mesolimbic/mesocortical selectivity. ITI-007 also indirectly (i.e., through D1 receptor partial agonism) modulates

glutamatergic activity by increasing the phosphorylation of the NR2B subunit or GluN2B subunit of N-methyl-D-aspartate (NMDA) channels in extrastriatal dopamine-rich brain regions (e.g., nucleus accumbens). ITI-007 has been tested in a number of animal models that predict antipsychotic efficacy without movement disorders, antidepressant efficacy, and improved sleep. The in vitro and in vivo activities of ITI-007 support the development of low doses of this compound for the treatment of agitation and other behavioral disturbances associated with dementia and higher doses for the treatment of schizophrenia, bipolar depression, and other psychiatric and neurological indications.

To date, over 2,400 people have been exposed to doses ranging from 1 mg to 140 mg ITI-007 administered for up to 42 days. In all trials completed to date, ITI-007 has been well tolerated with a safety profile similar to placebo. The safety, tolerability, and appropriate pharmacokinetic (PK) profile of ITI-007 were demonstrated in a Phase 1/2 randomized, double-blind, placebo-controlled, multiple ascending dose clinical study in healthy geriatric subjects and patients with dementia, including Alzheimer's disease.

The available data support the development of ITI-007 for the treatment of agitation in patients with dementia.

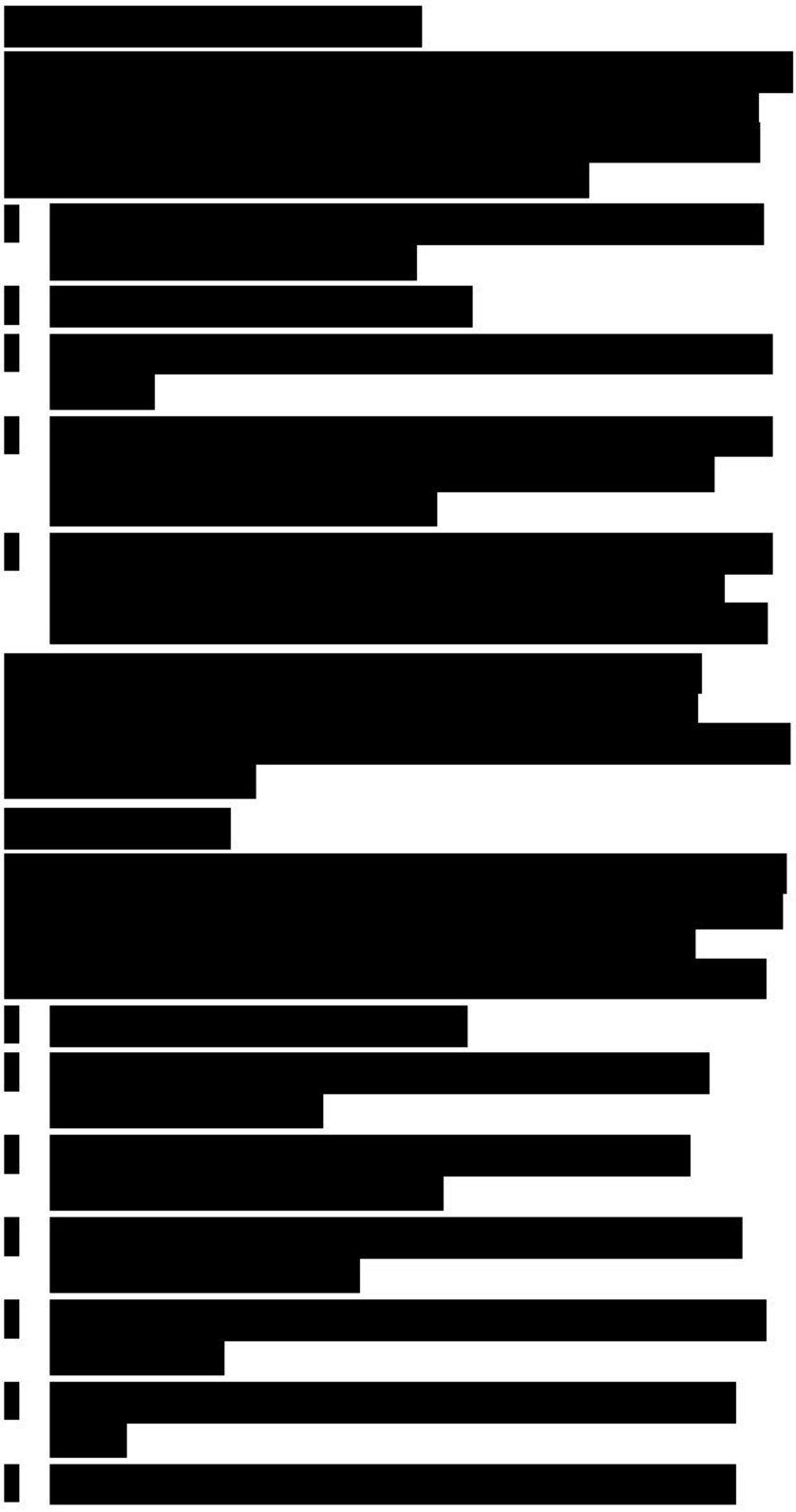
Objectives Part A (Double-blind, placebo-controlled phase):

Primary Objective

The primary objective of Part A of this study is to compare the efficacy, measured as change from baseline to Day 29 in the Cohen-Mansfield Agitation Inventory – Community version (CMAI-C) symptoms related to aggressive behavior, non-aggressive agitated behavior and/or verbally agitated behavior, for 9 mg ITI-007 administered orally once daily in the evening (QPM) to that of placebo in patients with dementia.

Key Secondary Efficacy Objective

Key secondary objective of Part A of this study is to compare the efficacy of 9 mg ITI-007 administered orally QPM to that of placebo in relation to the difference in the change from baseline to Day 29 in the Clinical Global Impression scale for Severity (CGI-S) of illness (e.g., CGI-S of Agitation and/or CGI-S of Aggression).



[redacted]

Patient Population:

Inclusion Criteria - Part A:

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

1. Has ability to provide written informed consent or have written informed consent provided on behalf of the patient by a legally authorized representative (LAR);
2. Patients able to attend clinic visits who have a primary caregiver with the ability to provide written informed consent for joint participation in study.

[redacted]

[redacted]

3. Is a male or female, > 55 years of age at the time of screening;
4. Has a clinical diagnosis of probable AD according to the National Institute on Aging- Alzheimer's Association (NIA-AA) guidelines (McKhann, 2011; Appendix A);
5, Has an MMSE score of 8 to 26 (inclusive) at screening;
6. Has clinically significant symptom(s) of agitation secondary to probable AD, consistent with the International Psychogeriatric Association consensus definition (see Appendix B);
7. At screening, according to NPI-C, has verbally agitated behavior, physically agitated nonaggressive behavior, or physical aggressive behavior occurring at least several times a week defined as ratings of frequency scores on items comprising the domains of Agitation and/or Aggression i.e., at least one behavior occurring at a frequency of 3 (several times a week but less than every day) or 4 (once or more per day), or at least two behaviors occurring at a frequency of 2 (about once per week), or at least three behaviors occurring at a frequency of 1 (less than once per week). This will be assessed over the past 4 weeks before screening;
8. At baseline according to the CMAI-C, has agitation and/or aggressive behavior as measured by any of the items in the Factor Composite occurring at least several times a week, i.e., at least one behavior occurring at a frequency of 4, or two behaviors occurring at a frequency of 3, or three behaviors occurring at a frequency of 2, at baseline (as assessed over the past 2 weeks before baseline);

9. In the opinion of the investigator, has frequent agitation that is clinically significant and warrants treatment with a pharmacological agent;
10. Has a CGI-S of Agitation or CGI-S of Aggression score of ≥ 4 (moderately ill) at screening and baseline;
11. Is maintained on a stable dose of any allowed standard of care medications for at least 3 months prior to Day 1 (baseline) [unless a shorter duration is reviewed and approved by the medical monitor] and for the duration of study participation. This includes stable doses of cholinesterase inhibitors and memantine;
12. Has a body mass index (BMI) between 19.0 and 38.0 kg/m^2, inclusive, and a minimum body weight of 46 kg at screening;
13. Has a score of ≤ 4 on a modified Hachinski Ischemia Scale;
14. Has normal serum B12 and folate levels (patients with abnormally low serum B12 and folate levels at screening can be re-screened following supplementation).

Exclusion Criteria - Part A:

1. Is bedridden;
2. Is, in the opinion of the investigator, unable to comply with study procedures;
3. Has clinical symptoms suggestive of other neurological disease such as evidence of infection, tumor, infarction, or other focal (e.g., subdural hematoma) or generalized lesions (e.g., hydrocephalus) that could account for the subject's dementia;

   [Note: if magnetic resonance imaging (MRI) or computed tomography (CT) scan of the head is available within the last 12 months, it should be negative];

4. Has, in the opinion of the investigator, and/or as assessed by the C-SSRS at screening (suicidal ideation of type 4 or 5 on the C-SSRS within 6 months prior to screening or any suicidal behavior in the last 2 years prior to screening, as indicated by any "yes" answers on the suicidal behavior section of the C-SSRS), a significant risk for suicidal behavior during the course of their participation in the study or is considered to be an imminent danger to themselves or others;
5. Has any clinically significant systemic illness or unstable or severe medical condition(s) that could put the patient at risk during the study, interfere with outcome measures, or affect compliance with the protocol procedures, such as:
    a. History of myocardial infarction within 3 months prior to screening, unstable or severe cardiovascular disease including uncontrolled angina or congestive heart failure with symptoms at rest within 2 years before enrollment or history of a clinically significant cardiac arrhythmia including antipsychotic drug-induced QTc prolongation;
    b. Endocrine-related disease (including insulin-requiring diabetes or poorly controlled diabetes as judged by the investigator; uncorrected hypothyroidism within the last 2 years)

       [Note: if on thyroid replacement medication, dose should be stable for at least 3 months prior to screening and remain stable during trial participation, unless a shorter duration is reviewed and approved by the medical monitor];
    c. Uncontrolled hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg);
    d. History of clinically significant liver disease, coagulopathy or Vitamin K deficiency within the last 2 years prior to screening;
    e. History of clinically significant renal disease;

f. Clinically significant obstructive pulmonary disease or asthma;

g. Clinically significant and unstable gastrointestinal disorder;

h. Documented and confirmed clinically significant neurological or psychiatric disease (e.g., Parkinson's disease, multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus [based upon clinical judgment], brain tumor, progressive supranuclear palsy, seizure disorder including epilepsy, subdural hematoma, schizophrenia, major depressive disorder, significant anxiety and/or phobic disorder(s), multiple sclerosis, arteriovenous malformation or history of significant head trauma and/or subdural hematoma followed by persistent neurologic deficits or known structural abnormalities, substance-induced persisting dementia, dementia due to multiple etiologies or dementia not otherwise specified) [Note: with the exception of rapid eye movement (REM) sleep behavior disorder, sleep disorders are allowed, but should be carefully documented, including but not limited to insomnia (sleep induction and/or sleep maintenance insomnia), periodic limb movements of sleep, and sleep apnea as determined by the STOP-bang questionnaire];

i. Malignancy (including any malignancy and/or chemotherapy within the 2 years prior to screening; malignancy more than 2 years prior to screening must have been local and without metastasis and/or recurrence, and if treated with chemotherapy, without nervous system complications; some malignancies, such as basal cell carcinoma, may not preclude participation and will be individually reviewed);

j. Metabolic, psychiatric or other condition that might be detrimental to the patient if he or she participates in the study in the opinion of the investigator;

6. Has abnormal laboratory values or clinical findings at screening that are judged clinically significant by the investigator (one re-test is allowed to confirm reproducibility of results; results must be available prior

to the baseline visit and must have returned to non-clinically significant range). Absolute value exclusions are listed in item 6b and 6c below:

a. Thyroid stimulating hormone (TSH) outside of the normal limits and clinically significant as determined by the investigator. Free thyroxine (T4) levels may be measured if TSH level is high. Patient will be excluded if Free T4 level is judged clinically significant by investigator;

b. 12-lead ECG (in a supine position at rest at screening or baseline visit; note: baseline ECG measures for determining inclusion into the study are based on the investigator/site read ECG data, though the database will reflect centrally read ECG data) mean of triplicate QTcF > 500 ms (independent from sex) and/or heart rate (HR) ≤50 beats per minute. Bundle branch blocks deemed clinically significant by investigator will be excluded. [Note: If it is the opinion of the investigator that a lower HR is physiological in a well-fit subject or due to stable concomitant medications, this will be reviewed and approved by the medical monitor on a case by case basis];

c. Alanine transaminase (ALT), aspartate transaminase (AST), or creatine phosphokinase values > 3 times the upper limit of normal (ULN);

d. Any other clinically significant abnormal laboratory result at the time of the screening as determined by the investigator.

7. Is a female of childbearing potential as determined by the investigator;

8. Has a history of neuroleptic malignant syndrome induced by any antipsychotic medication;

9. Has a history of human immunodeficiency virus (HIV) infection or demonstration of HIV antibodies;

10. Has a history of Hepatitis B or C infection AND evidence of active disease defined as elevated ALT, AST or bilirubin levels > 2 × ULN;
11. Has demonstrated Hepatitis B surface antigen or Hepatitis C antibodies at screening AND evidence of active disease defined as elevated ALT, AST or bilirubin levels > 2 × ULN;
12. Meets Diagnostic and Statistical Manual – 5th Edition (DSM-5) criteria for moderate to severe substance use disorder;
13. Has a positive urine drug or alcohol test at screening or evidence of either withdrawal from, or acute intoxication with cocaine, (meth) amphetamines, alcohol, barbiturates, or hallucinogens or similar compounds;

14. Has a likely allergy or sensitivity to ITI-007 or any psychoactive drug based on history;
15. Has used any of the following agents under the specified conditions:
    a. Lifetime exposure to ITI-007 or, who has had exposure to any investigational product within 3 months of baseline visit or participated in the past 4 years in > 2 clinical studies of an

investigational product with a central nervous system indication;

b. Any strong or moderate CYP450 3A4 inhibitor or inducer within 7 days (or 5 half-lives, whichever is greater) prior to the baseline visit;

c. Certain drugs with known psychotropic properties or any non-psychotropic drugs with known or potential significant central nervous system effects within 5 half-lives before the baseline visit unless noted below to be discontinued by the baseline with taper, if appropriate (see Section 5.8), including:

    i. Anxiolytics (except lorazepam as described in Table 5-7)

    ii. Sedative hypnotics

    iii. Central opioid agonists/antagonists including tramadol (Ultram). Except: following review by medical monitor for treatment of stable condition on case by case basis

    iv. Antipsychotics may be tapered and must be discontinued by the baseline visit

    v. Methotrexate

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

    vii. Immunosuppressants

    viii. St. John's Wort must be discontinued by the baseline visit

    [Notes: Anticonvulsants, mood stabilizers, and antidepressants (such as SSRI or SNRI) may be allowed, but the dose should be stable for at least 3 months prior to screening and remain stable during trial participation, unless a shorter duration is reviewed and approved by the medical monitor. Dietary supplements,

medical foods, or pharmaceuticals used specifically for the treatment of dementia, agitation, or sleep, containing omega3 fatty acids, melatonin, kava kava, Vitamin B12, folate, or valerian root may be allowed, but the dose should be stable for at least 3 months prior to screening and remain stable during trial participation, unless a shorter duration is reviewed and approved by the medical monitor. Multivitamin as daily supplement is allowed. All stable psychotropic medications or supplements require review and approval by the medical monitor.];

16. Is unable to be safely discontinued from current above-mentioned psychotropic medications;
17. Is unable to swallow oral medication;
18. Is judged by the investigator to be inappropriate for the study;
19. Is an immediate family (i.e., spouse, parent, child, or sibling, whether biological or legally adopted) of the investigator, ITI or CROs conducting the study.

[redacted]

[redacted]

[redacted]

Study Design:

The study will be conducted in two parts, Part A and Part B. Part A is a randomized, double-blind, placebo-controlled, adaptive two-stage design with a single interim analysis and a

final analysis. In Part B, patients who completed participation in Part A safely may be enrolled in an open-label extension.

Part A Study Periods (up to Approximately 8 Weeks, Including Screening/Baseline)

Part A of the study consists of the following periods: screening/baseline period, on-treatment period, and safety follow-up period.

Screening/Baseline Period (up to 2 Weeks)

Potential patients will be evaluated during the screening period lasting up to 2 weeks, starting with a screening visit (Visit 1). In an effort to retain patients and reduce caregiver burden, every effort should be made to schedule the baseline visit (Visit 2) for randomization and to start study drug within 1 week of screening, but up to 2 weeks are allowed for flexibility of scheduling and to ensure that prohibited medications are tapered and/or sufficiently washed out. Extension to the screening period may be approved by the Sponsor or representative in extenuating circumstances related to the patient or caregiver.

After obtaining written informed consent, diagnostic interviews and modified physical examinations (including height and weight) will be conducted; vital signs (3-positional blood pressure and pulse rate, respiration rate, and oral body temperature) and 12-lead ECGs will be assessed; and blood samples for laboratory assessments (hematology and serum chemistry) will be collected. Suicidal ideation and behavior will be assessed by the C-SSRS. Patients considered potentially eligible for participation will be required to discontinue prohibited medications. Patients on excluded medications, including long-acting medications, that cannot be washed out safely, including any taper that might be appropriate, should be considered not eligible for the study.

[redacted]

[redacted]

On-Treatment Period (4 Weeks)

Patients will take their first dose of study drug the evening of their baseline randomization visit (Visit 2). A single dose will be taken each day in the evening during the on-treatment period.

Following randomization, study visits will be conducted at Day 15 (Visit 4) and Day 29 (Visit 6). Interim 'visits' will be conducted by phone on Day 8 (Visit 3) and Day 22 (Visit 5) to check on patient status, adverse events, and any change in medication.

The on-treatment period will be a total of 4 weeks.

At the end of the on-treatment period, patients can be restarted on prior medications or be started on other medications [redacted] as deemed appropriate by the investigator following all study procedures at the end of the last treatment visit at Visit 6; any and all post-study treatment medications should be recorded.

Safety Follow-up Period (2 Weeks)

[redacted] a safety follow-up visit (Visit 7) will occur at Day 43, approximately 2 weeks following the last dose of study drug. If possible, patients who withdraw prematurely will be seen in the research clinic for an early termination visit (within 1 week of early termination, where possible) and approximately 2 weeks following withdrawal for a safety follow-up. The final safety follow-up, for both completed patients and following early termination visits, will be completed as a study clinic visit.

At any time during the study, a visit to the research clinic can be conducted as an unscheduled visit to address any safety concerns.

[redacted]

[redacted]

Estimated Study Duration:

In Part A, the study will last a maximum of up to 8 weeks, including the screening/baseline period (7 scheduled visits).

In Part B, the duration of individual patient participation in the [redacted]

Efficacy Assessments:

The following assessments will be performed by qualified personnel:

- CMAI-C
- CGI-S of Agitation
- CGI-S of Aggression
- NPI-C
- MMSE

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Study Drug, Dosage, and Route of Administration:

In Part A, patients will be assigned to receive either ITI-007 (9 mg) or placebo. All doses will be administer orally once daily at home, each evening, during the on-treatment period.

[redacted]

[redacted]

Analysis Sets:

In Part A, the following analysis sets will be used in for the analyses:

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

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

Primary, secondary, and exploratory efficacy analyses will be performed using the Full Analysis Set (FAS), which will contain all randomized patients who received at least one dose of study drug and who had a valid (pre-dose) baseline and at least one valid post baseline measurement of CMAI-C. Patients will be classified according to the randomized treatment.

The Per Protocol Set (PPS) will contain all randomized patients who completed the study treatment and who did not have any major protocol deviations. Patients will be classified according to the randomized treatment.

The Safety Analysis (SA) Set will contain all randomized patients who received at least one dose of study drug. Patients will be classified according to the treatment received.

The PK Set is defined as all patients who received at least one dose of the study drug, had a baseline measurement and at least one post baseline measurement of CMAI-C, had at least one PK sample collected and analyzed, and for whom a valid assay result (according to laboratory guidelines) has been obtained. Patients will be classified according to the treatment received.

[redacted]

Sample Size:

In Part A, approximately 292 patients (if no sample size adjustment is made after the interim analysis) will be randomly assigned in a 1:1 ratio to one of the two treatment groups. A sample size of 292 patients will provide approximately 264 patients assuming an approximately 9% discontinuation rate before the first post baseline assessment of the primary efficacy outcome measure (CMAI-C). 132 patients per treatment group will provide approximately 90% power, assuming an effect size of 0.4, at a two-sided significance level of 5%.

[redacted]

Statistical Methods:

Patient Disposition, Demographics, and Other Baseline Data

The incidence of patients who were screened, screen failed, completed or discontinued treatment, and completed or discontinued the study, including the corresponding reasons for early withdrawal, will be presented overall, by part, and by treatment group (Part A), if applicable. Time to discontinuation due to all reasons, AEs, lack of efficacy, or due to any reason of special interest will be summarized by part and compared between the treatment groups (Part A).

Demographic and baseline characteristics, including efficacy parameters and safety assessments, will be summarized by part and by treatment group (Part A).

Efficacy Analysis – Part A

Efficacy analysis in Part A will be performed on the FAS. The primary efficacy endpoint(s) will be evaluated using a mixed model repeated measures (MMRM) analysis. For each of the primary efficacy endpoint(s), the model will include change from baseline to each pre-specified time point as the response variable and treatment, visit, the stratification variable, defined by the MMSE score at screening, site (or pooled site), baseline score of the corresponding endpoint, and interaction terms for treatment-by-visit and baseline-by-visit as fixed effects and patient as a random effect. The model will specify an unstructured variance/covariance matrix. In the event the convergence cannot be attained with the unstructured correlation

matrix, pre-specified alternative structures will be evaluated. The Kenward-Roger's correction will be used to estimate the denominator degrees of freedom in the model. Summary statistics of change from baseline, as well as LSM estimates for change from baseline, standard errors and 95% CI for LSM will be presented for each visit at which they were measured by treatment group. Contrast estimates for the comparison of ITI-007 versus placebo, the corresponding 95% confidence intervals, and p-values will be reported.

The key secondary efficacy endpoints, change from baseline to Day 29 in the CGI-S of Agitation and/or CGI-S of Aggression, will be analyzed similar to the primary efficacy endpoint(s).

A multiplicity adjustment based on a parallel gatekeeping procedure will be applied to control the overall Type I error rate (familywise error rate) in the strong sense across the primary and key secondary endpoints at alpha=0.05 (two-sided). This gatekeeping procedure will apply a multiple test derived from the Holm test (known as the truncated Holm test) in the family of primary endpoint(s). This family will serve as a parallel gatekeeper for the key secondary endpoint(s) in the sense that a key secondary endpoint(s) will be tested if and only if the treatment effect on at least one primary endpoint is significant. Details of this gatekeeping procedure will be provided in the statistical analysis plan.

Sensitivity and supportive analyses will be performed to assess the robustness of the MMRM results under different assumption of the mechanism of missing data.

[redacted]

[redacted]

Interim Analysis – Part A

One interim analysis (IA) is planned during Part A of the study after approximately 140 patients (53% of the 264 patients) have completed the 28-day On-Treatment Period or confirmed to have discontinued treatment or study after at least one post-baseline assessment of CMAI-C. The interim analysis will be conducted such that the ongoing study integrity is maintained, and will be reviewed by an independent Data Monitoring Committee (DMC).

The IA will be used to reassess the assumptions of variability and effect size. It may be used for a decision to terminate the study due to superior efficacy or futility or to adjust the sample size, at the discretion of the Sponsor. Additional details regarding the statistical analysis methodology will be provided in the SAP.

The operational details of the IA will be provided in the charter of the DMC (see section 7.5.8 Interim Analysis).

An analysis will report on the completion of Part A of the study, with the final analysis including both Parts A and B.

Date of Protocol: 22 October 2018

List of Abbreviations

Abbreviation	Definition
AD	Alzheimer's disease
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression for Severity scale
CI	confidence interval
CMAI-C	Cohen-Mansfield Agitation Inventory – Community version
CMH	Cochran-Mantel-Haenszel
CP	Conditional power
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
D_2	dopamine 2
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual, 5th Edition
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA_{1c}	glycated hemoglobin A_{1c}
HIV	human immunodeficiency virus
HR	Heart rate
IA	Interim analysis
ICF	informed consent form

Abbreviation	Definition
ICH	International Council for Harmonisation
IRB	Institutional Review Board
ITI	Intra-Cellular Therapies, Inc.
IVRS	interactive voice response system
IWRS	interactive web response system
LDL	low-density lipoprotein
LOCF	last observation carried forward
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed-model–repeated measures
MMSE	Mini Mental State Examination
MNAR	missing not at random
MRI	Magnetic Resonance Imaging
NIA-AA	National Institute on Aging – Alzheimer's Association
NPI-C	Neuropsychiatric Inventory Clinician
nTST	Nocturnal Total Sleep Time
RNA	Ribonucleic acid
PET	positron emission tomography
PK	Pharmacokinetic
PMM	pattern-mixture model
PPS	per-protocol set
QTcF	corrected QT interval using the Fridericia formula
SAE	serious adverse event
SA	safety analysis
SAP	statistical analysis plan
SAS	Simpson Angus Scale
SERT	serotonin transporter
TEAE	treatment-emergent adverse event
TSH	Thyroid stimulating hormone
ULN	upper limit of normal

1 Introduction

Dementia is a group of symptoms that affect mnemonic processes such as memory and reasoning. The World Health Organization estimates that 35.6 million people around the world are living with various forms of dementia. Dementia can be caused by a variety of conditions, the most common of which is Alzheimer's disease (AD). Alzheimer's disease is a progressive neurodegenerative disease, currently affecting 25 million worldwide. According to the 2014-2015 Alzheimer's Disease Progress Report published by the National Institute of Aging (NIA), as many as 5.1 million people over the age of 64 in the United States suffer from AD (www.nia.nih.gov/alzheimers). Typically patients first develop mild signs of cognitive decline, including diminished capacity for concentration, calculation, language, comprehension, and memory. Behavioral disorders that commonly accompany this disease remain largely untreated by currently approved drugs. These behavioral disturbances include agitation, aggression, depression, apathy, delusions, hallucinations, and disrupted sleep/wake cycles. These symptoms have serious consequences for the patients and caregivers, leading to more rapid deterioration in patient health. It has been estimated that up to 80% of patients with dementia exhibit behavioral disturbances during the course of the disease.

The NIA refers to dementia, including AD, as a growing public health crisis with a major impact on our economy and costs of care continuing to rise with the aging of our population. Behavioral disturbances in patients with dementia, including agitation, remains a significantly underserved medical need, with no Food and Drug Administration (FDA)-approved treatment options available. Treatment guidelines updated in 2014, recommends cautious (off-label) use of low doses of antipsychotics for the treatment of agitation and psychosis associated with dementia, given limited efficacy and severe adverse events (AEs) associated with these drugs (Rabins, 2014).

The Alzheimer's Association has raised concern over dementia-related behaviors in a 2015 statement (http://www.alz.org/about_us_statements.asp) in which it is recognized that such behaviors can be associated with serious clinical implications. Agitation, particularly physical aggression, can create an unsafe environment for the patient with dementia as well as for the caregiver. It is noted that failing to address the agitation may cause greater harm than the currently available medication options. There is clearly a need for treatments that can reduce the behavioral disturbances associated with dementia, including agitation and aggression, with decreased risk for motor side effects and with a favorable safety profile.

Intra-Cellular Therapies, Inc. (ITI) is developing ITI-007, a new chemical entity, for the treatment of symptoms of agitation in patients with dementia. ITI-007 is currently in Phase 3 clinical development in the United States for the treatment of schizophrenia and bipolar depression.

ITI-007 is a novel small molecule therapeutic agent designed specifically to combine, in a dose-dependent manner, potent serotonin 5-HT_{2A} receptor antagonism with both mesolimbic/mesocortical selective modulation of phosphoprotein pathways downstream of dopamine receptors and serotonin reuptake inhibition (Snyder, 2015). As a dopamine receptor protein phosphorylation modulator, ITI-007 has dual properties, acting as a post-synaptic antagonist and as a pre-synaptic partial agonist at dopamine 2 (D_2) receptors in vivo, with mesolimbic/mesocortical selectivity. ITI-007 also indirectly modulates glutamatergic activity by increasing the phosphorylation of the NR2B, or GluN2B, subunit of N-methyl-D-aspartate channels in extrastriatal dopamine-rich brain regions (e.g., nucleus accumbens), likely downstream from dopamine 1 (D_1) receptor activation. ITI-007 has been tested in a number of animal models that predict antipsychotic efficacy and reduced agitation without movement disorders, antidepressant efficacy, and improved sleep. The *in vitro* and *in vivo* activities of ITI-007 support the development of low doses of this compound for the treatment of agitation and other behavioral disturbances associated with dementia and higher doses for the treatment of schizophrenia and bipolar depression and other psychiatric and neurological indications.

The 5-HT_{2A} receptor antagonism by ITI-007 is predicted to reduce aggression, increase deep slow-wave sleep and improve sleep maintenance. The D_2 receptor modulation by ITI-007 is predicted to reduce irritability, agitation and aggression, and to improve sleep maintenance. In addition to a primary reduction in agitation and aggression, improved sleep maintenance by ITI-007 should translate to reduced nighttime agitation and reduced dementia-specific sleep-related behavioral disturbances, such as nighttime wandering and waking during the night thinking it is daytime. Serotonin reuptake inhibition by ITI-007 is predicted to reduce anxiety and depression. The D_1 receptor activation and indirect glutamatergic neurotransmission by ITI-007 is predicted to improve cognitive function. With its first-in-class pharmacological profile via all of these pharmacological pathways, ITI-007 is predicted to reduce the behavioral disturbances associated with dementia, including agitation, aggression, sleep-related behavioral disturbances, anxiety and depression, and to improve cognition.

Potent 5-HT_{2A} receptor antagonism combined with modest dopamine receptor modulation is predicted to be especially effective in reducing agitation and aggression. The 5-HT_{2A} receptor plays a particularly important role in the control of aggression in humans and in animals. In animal models, 5-HT_{2A} receptor antagonists attenuate aggressive behaviors and 5-HT_{2A} receptor agonists promote aggressive behavior (Sakaue, 2002; Higgins, 2003; Winstanley, 2004). Aggression has been shown to be directly correlated with platelet 5-HT_{2A} receptor binding in personality disordered patients, but not in healthy controls (Coccaro, 1991). In a postmortem study of human brain, 5-HT_{2A} receptor expression in prefrontal cortical areas was directly correlated with lifetime aggression history in those who committed suicide compared to those who died by other means (Oquendo, 2006). Aggression also is related to various human genetic polymorphisms of the 5-HT_{2A} receptor (Giegling, 2006; Nomura, 2006; Bjork, 2002). Further, 5-HT_{2A} receptor availability in the orbitofrontal cortex has been directly correlated with a clinical measure of aggression (Rosell, 2010). These findings are consistent with a model in which orbitofrontal 5-HT_{2A} receptors modulate aggression, and therefore, antagonism of 5-HT_{2A} receptors represents an attractive therapeutic target for controlling these kinds of behaviors.

While useful in treating some of the behavioral disturbances seen in patients with dementia, 5-HT_{2A} receptor blockade, as described above, may not be sufficient to alleviate the full range of behavioral disturbances experienced by patients with dementia. The other beneficial drug target interactions possessed by ITI-007 may be required to treat the full spectrum of behavioral symptoms in these patients. The addition of dopamine receptor modulation may be particularly useful in treating agitation and psychotic symptoms. It has been recognized that excessive dopamine neurotransmission can cause increases in agitation and psychosis (Engelborghs, 2008). Moreover, serotonin reuptake inhibition by ITI-007, the mechanism of action of the most current antidepressant drugs, may be useful in elevating mood in these patients.

Importantly, ITI-007 lacks potent off-target interactions that have been associated with side effects for other antipsychotic drugs used off-label for the treatment of agitation associated with dementia. For example, ITI-007 shows relatively weak affinity for 5-HT_{2C} and no measurable affinity for H_1 or muscarinic cholinergic receptors, which predict favorable body weight and metabolic profile responses to the extent that these receptors mediate such effects (Snyder, 2015). Additional details of the pharmacologic profile of ITI-007 can be found in the most recent version of the Investigator's brochure.

In animal models, ITI-007 demonstrated antipsychotic-like efficacy in a rat conditioned avoidance assay and antidepressant-like activity in a rat resident-intruder/social defeat model of chronic social stress (Snyder, 2015). These data suggest that ITI-007 will reduce agitation and psychosis and improve mood.

Human brain receptor target engagement was confirmed in healthy male volunteers in the ITI-007-003 PET Phase 1 clinical trial (Davis, 2015). Positron emission tomography was used to determine dopamine D_2 receptor, serotonin transporter (SERT), and serotonin 5-HT_{2A} receptor occupancy in the brain at various times following single dose oral ITI-007 administration. ITI-007 rapidly penetrated the brain, showed long-lasting and dose-related occupancy, and was safe and generally well-tolerated. Cortical 5-HT_{2A} receptors were shown to be fully occupied at 10 mg ITI-007 (>85% occupancy), while this dose was associated with an average of 12% striatal D_2 receptor occupancy. A dose of 40 mg ITI-007 achieved up to 39% striatal D_2 receptor occupancy (average of 29%) and up to 31% striatal SERT occupancy (average of 22%). Together, these data confirm a central mechanism for ITI-007 at dopaminergic and serotonergic brain targets. Projecting occupancy to higher doses based on plasma levels, it was estimated that a dose of 60 mg ITI-007 should achieve approximately 50% striatal D_2 receptor occupancy and similar or slightly less SERT occupancy. Additional clinical studies have demonstrated that 60 mg ITI-007, a dose that exhibited antipsychotic efficacy in randomized, placebo-controlled trials (ITI-007-005 and ITI-007-301), was associated an average of approximately 40% striatal D_2 receptor occupancy in patients with schizophrenia (ITI-007-008). This is lower than the D_2 receptor occupancy associated with antipsychotic efficacy of most other antipsychotic drugs and likely contributes to the improved motoric tolerability, similar to placebo for ITI-007.

The low dose strategy of 9 mg ITI-007 for the treatment of agitation in patients with dementia is estimated to be associated with approximately 10% striatal D_2 receptor occupancy and full cortical 5-HT_{2A} receptor occupancy.

To date, over 2,400 people have been exposed to doses ranging from 1 mg to 140 mg ITI-007 administered for up to 42 days. In all trials completed to date, ITI-007 has been well tolerated with a safety profile similar to placebo.

ITI has demonstrated the safety, tolerability and appropriate pharmacokinetic (PK) profile of ITI-007 in a Phase 1/2 randomized, double-blind, placebo-controlled, multiple ascending dose clinical study in healthy geriatric subjects and patients with dementia. This was a

single-center, randomized, double-blind, placebo-controlled, multiple oral dose escalation study. In Part A, doses of ITI–007 (7.5, 15, and 30 mg) were escalated in separate sequential groups of healthy geriatric subjects. Part B of the study evaluated 9 mg ITI-007 in a group of geriatric patients with dementia who were maintained on their standard-of-care medications for dementia. In both parts, study subjects received ITI–007 or placebo at least once daily for 7 days with a meal. Safety and tolerability were assessed, blood samples for PK analysis were collected, and pharmacodynamic measures were explored. In both parts, ITI-007 was safe and well tolerated with PK exposures in the range of those expected based on PK profiles in younger healthy adult subjects. There was no suggestion of any adverse interaction with the standard-of-care medications in the dementia cohort. Exploratory assessments indicated improvements in cognitive function with ITI-007.

The available data support the development of ITI-007 for the treatment of agitation, including aggression, in patients with dementia.

2 Study Objectives

2.1 Primary Objectives

2.1.1 Part A Primary Objective

The primary objective of Part A of this study is to compare the efficacy, measured as change from baseline to Day 29 in the Cohen-Mansfield Agitation Inventory – Community version (CMAI-C) symptoms related to aggressive behavior, non-aggressive agitated behavior and/or verbally agitated behavior, for 9 mg ITI-007 administered orally once daily in the evening (QPM) to that of placebo in patients with dementia.

[redacted]

2.2 Secondary Objectives

2.2.1 Part A Secondary Objectives - Efficacy

Key Secondary Efficacy Objective

The key secondary objective of Part A of this study is to compare the efficacy of 9 mg ITI-007 administered orally QPM to that of placebo in relation to the difference in the change from baseline to Day 29 in the Clinical Global Impression scale for Severity (CGI-S) of illness (e.g., CGI-S of Agitation and/or CGI-S of Aggression).

[redacted]

3 Investigational Plan

3.1 Study Design

The study will be conducted in two parts, Part A [redacted] Part A is a randomized, double-blind, placebo-controlled study comparing the efficacy and safety of ITI-007 versus placebo administered orally once daily in the treatment of agitation in patients with dementia, including Alzheimer's disease. [redacted] This study will be conducted at up to approximately 60 sites in 1 country (United States).

3.1.1 Part A Study Periods (up to Approximately 8 Weeks, Including Screening/Baseline)

Part A is an adaptive two-stage design with a single interim analysis and a final analysis. An interim analysis (IA) will be performed after a pre-specified number of patients have completed the 28-day treatment period, and will be reviewed by an independent data monitoring committee (DMC). The IA will be used to reassess the assumptions of variability and effect size, and correcting the sample size if needed. The interim data may be used for a decision to terminate the study due to superior efficacy or futility, at the discretion of the Sponsor.

Part A of the study consists of the following periods: screening/baseline period, on-treatment period, and safety follow-up period.

Screening/Baseline Period (up to 2 Weeks)

Potential patients will be evaluated during the screening period lasting up to 2 weeks, starting with a screening visit (Visit 1). In an effort to retain patients and reduce caregiver burden, every effort should be made to schedule the baseline visit (Visit 2) for randomization and to start study drug within 1 week of screening, but up to 2 weeks are allowed for flexibility of scheduling and to ensure that prohibited medications are tapered and/or sufficiently washed out. Extension to the screening period may be approved by the Sponsor or representative in extenuating circumstances related to the patient or caregiver.

After obtaining written informed consent, diagnostic interviews and modified physical examinations (including height and weight) will be conducted; vital signs (3-positional blood pressure and pulse rate, respiration rate and oral body temperature) and 12-lead ECGs will be assessed; and blood samples for laboratory assessments (hematology, serum chemistry, HIV

and Hepatitis) will be collected. Suicidal ideation and behavior will be assessed by the C-SSRS. Patients considered potentially eligible for participation will be required to discontinue prohibited medications. Patients on excluded medications, including long-acting medications, that cannot be washed out safely, including any taper that might be appropriate, should be considered not eligible for the study.

Adjudication of patient eligibility and caregiver suitability will be administered by remote, independent expert raters and/or medical monitor(s) in conjunction with the sponsor.

At baseline (Visit 2), patients who continue to meet all eligibility criteria will be randomized equally (1:1) to one of the two treatment arms for the double-blind on-treatment period, stratified by the MMSE score at screening. Patients will be randomized to 9 mg ITI-007 or matching placebo. Patients may receive the investigational product for a period of up to 4 weeks during the on-treatment period.

On-Treatment Period (4 Weeks)

Patients will take their first dose of study drug the evening of their baseline randomization visit (Visit 2). A single dose will be taken each day in the evening during the on-treatment period.

Following randomization, study visits will be conducted at Day 15 (Visit 4) and Day 29 (Visit 6). Interim 'visits' will be conducted by phone on Day 8 (Visit 3) and Day 22 (Visit 5) to check on patient status, adverse events and any change in medication.

The on-treatment period will be a total of 4 weeks.

At the end of the on-treatment period, patients can be restarted on prior medications or be started on other medications [redacted] as deemed appropriate by the investigator following all study procedures at the end of the last treatment visit at Day 29 (Visit 6); any and all post-study treatment medications should be recorded.

Safety Follow-up Period (2 Weeks)

[redacted] a safety follow-up visit (Visit 7) will occur at Week 6, approximately 2 weeks following the last dose of study drug. If possible, patients who withdraw prematurely will be seen in the research clinic for an early termination visit (within 1 week of early termination, where possible) 2 weeks following withdrawal for a

safety follow-up. The final safety follow-up, for both completed patients and following early termination visits, will be completed as a study clinic visit.

At any time during the study, a visit to the research clinic can be conducted as an unscheduled visit to address any safety concerns.

3.1.3 Rationale of Study Design

In Part A, the screening/baseline period permits evaluation of the laboratory and ECG assessments and enables confirmation of eligibility for inclusion into the study. The screening/baseline period will be no longer than 14 days, and is encouraged to be less than 7 days in an effort to retain patients and reduce caregiver burden. The screening/baseline period is appropriate to ensure washout of excluded medication, under the supervision of the investigator before baseline. During the screening/baseline period, baseline data will be collected for caregiver diaries and actigraphy. Patients will be randomly assigned in a 1:1 ratio to one of two treatment groups at the baseline visit and will receive treatment for up to 4 weeks. In order to ensure patient safety, a 14-day follow-up visit will be performed after administration of the last dose of study drug. Any ongoing AEs at the follow-up visit must be followed until resolution, until the AE stabilizes, until it is determined to be non-clinically significant, or until the patient is lost to follow-up.

The dose to be administered in the present study, 9 mg ITI-007, was shown to be well tolerated in a prior study (ITI-007-200) with no evidence of a need for drug titration. Therefore, a fixed-dose design will be employed in this study.

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

The Part A treatment duration of 4 weeks has been chosen because this is considered an appropriate duration to demonstrate efficacy in this patient population. Though not approved for the treatment of agitation in patients with dementia, a previous efficacy trial with risperidone showed statistically significant reduction in agitation compared to placebo after 4 weeks of treatment (Brodaty, 2003). It is desired to have rapid reduction in agitation to reduce patient distress, caregiver burden, and delay placement into nursing care facilities. Moreover, the primary endpoint clinical measure, CMAI, is validated looking at agitated and aggressive behavior over the previous 2 weeks (Cohen-Mansfield, 1989; Cohen-Mansfield, 1995). Capturing data after 2 weeks and again after 4 weeks of treatment allows for an interim measurement of efficacy in the case of early discontinuation by patients.

In Part A of the study, one interim analysis is planned to be performed. The interim data will allow evaluation of the validity of the assumptions used in the study design for which reliable prior information does not exist. If the assumptions appear inaccurate, a mid-study adjustment, such as sample size re-estimation, will improve the chance that the study will reach a definitive conclusion.

[redacted]

4 Patient Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 292 patients (in Part A, approximately 146 patients/treatment group) will be enrolled at approximately 60 study sites in the United States. In Part A patients will be randomly assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria. [redacted]

[redacted]

[redacted]

4.1.1 Part A Inclusion Criteria

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

1. Has ability to provide written informed consent or have written informed consent provided on behalf of the patient by a legally authorized representative (LAR);
2. Patients able to attend clinic visits who have a primary caregiver with the ability to provide written informed consent for joint participation in study.

[redacted]

[redacted]

3. Is a male or female, > 55 years of age at the time of screening;
4. Has a clinical diagnosis of probable AD according to the National Institute on Aging-Alzheimer's Association (NIA-AA) guidelines (McKhann, 2011; Appendix A);
5, Has an MMSE score of 8 to 26 (inclusive) at screening;
6. Has clinically significant symptom(s) of agitation secondary to probable AD, consistent with the International Psychogeriatric Association consensus definition (see Appendix B);
7. At screening, according to NPI-C, has verbally agitated behavior, physically agitated nonaggressive behavior, or physical aggressive behavior occurring at least several times a week defined as ratings of frequency scores on items comprising the domains of Agitation and/or Aggression i.e., at least one behavior occurring at a frequency of 3 (several times a week but less than every day) or 4 (once or more per day), or at least two behaviors occurring at a frequency of 2 (about once per week), or at least three behaviors occurring at a frequency of 1 (less than once per week). This will be assessed over the past 4 weeks before screening;
8. At baseline according to the CMAI-C, has agitation and/or aggressive behavior as measured by any of the items in the Factor Composite occurring at least several times a week, i.e., at least one behavior occurring at a frequency of 4, or two behaviors occurring at a frequency of 3, or three behaviors occurring at a frequency of 2, at baseline (as assessed over the past 2 weeks before baseline);
9. In the opinion of the investigator, has frequent agitation that is clinically significant and warrants treatment with a pharmacological agent;
10. Has a CGI-S of Agitation or CGI-S of Aggression score of ≥ 4 (moderately ill) at screening and baseline;
11. Is maintained on a stable dose of any allowed standard of care medications for at least 3 months prior to Day 1 (baseline) [unless a shorter duration is reviewed and approved

by the medical monitor] and for the duration of study participation. This includes stable doses of cholinesterase inhibitors and memantine;

12. Has a body mass index (BMI) between 19.0 and 38.0 kg/m^2, inclusive, and a minimum body weight of 46 kg at screening;
13. Has a score of ≤ 4 on a modified Hachinski Ischemia Scale;
14. Has normal serum B12 and folate levels (patients with abnormally low serum B12 and folate levels at screening can be re-screened following supplementation).

4.1.2 Part A Exclusion Criteria

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

1. Is bedridden;
2. Is, in the opinion of the investigator, unable to comply with study procedures;
3. Has clinical symptoms suggestive of other neurological disease such as evidence of infection, tumor, infarction, or other focal (e.g., subdural hematoma) or generalized lesions (e.g., hydrocephalus) that could account for the subject's dementia;

   [Note: if magnetic resonance imaging (MRI) or computed tomography (CT) scan of the head is available within the last 12 months, it should be negative];
4. Has, in the opinion of the investigator, and/or as assessed by the C-SSRS at screening (suicidal ideation of type 4 or 5 on the C-SSRS within 6 months prior to screening or any suicidal behavior in the last 2 years prior to screening, as indicated by any "yes" answers on the suicidal behavior section of the C-SSRS), a significant risk for suicidal behavior during the course of their participation in the study or is considered to be an imminent danger to themselves or others;
5. Has any clinically significant systemic illness or unstable or severe medical condition(s) that could put the patient at risk during the study, interfere with outcome measures, or affect compliance with the protocol procedures, such as:
   a. History of myocardial infarction within 3 months prior to screening, unstable or severe cardiovascular disease including uncontrolled angina or congestive heart failure with symptoms at rest within 2 years before enrollment or history of a clinically significant cardiac arrhythmia including antipsychotic drug-induced QTc prolongation;
   b. Endocrine-related disease (including insulin-requiring diabetes or poorly controlled diabetes); uncorrected hypothyroidism within the last 2 years)

[Note: if on thyroid replacement medication, dose should be stable for at least 3 months prior to screening and remain stable during trial participation, unless a shorter duration is reviewed and approved by the medical monitor];

c. Uncontrolled hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg);

d. History of clinically significant liver disease, coagulopathy or Vitamin K deficiency within the last 2 years prior to screening;

e. History of clinically significant renal disease;

f. Clinically significant obstructive pulmonary disease or asthma;

g. Clinically significant and unstable gastrointestinal disorder;

h. Documented and confirmed clinically significant neurological or psychiatric disease (e.g., Parkinson's disease, multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus [based upon clinical judgment], brain tumor, progressive supranuclear palsy, seizure disorder including epilepsy, subdural hematoma, schizophrenia, major depressive disorder, significant anxiety and/or phobic disorder(s), multiple sclerosis, arteriovenous malformation or history of significant head trauma and/or subdural hematoma followed by persistent neurologic deficits or known structural abnormalities, substance-induced persisting dementia, dementia due to multiple etiologies or dementia not otherwise specified) [Note: with the exception of rapid eye movement (REM) sleep behavior disorder, sleep disorders are allowed, but should be carefully documented, including but not limited to insomnia (sleep induction and/or sleep maintenance insomnia), periodic limb movements of sleep, and sleep apnea as determined by the STOP-bang questionnaire];

i. Malignancy (including any malignancy and/or chemotherapy within the 2 years prior to screening; malignancy more than 2 years prior to screening must have been local and without metastasis and/or recurrence, and if treated with chemotherapy, without nervous system complications; some malignancies, such as basal cell carcinoma, may not preclude participation and will be individually reviewed);

j. Metabolic, psychiatric or other condition that might be detrimental to the patient if he or she participates in the study in the opinion of the investigator;

6. Has abnormal laboratory values or clinical findings at screening that are judged clinically significant by the investigator (one re-test is allowed to confirm reproducibility of results; results must be available prior to the baseline visit and must have returned to non-clinically significant range). Absolute value exclusions are listed in items 6b and 6c below:

a. Thyroid stimulating hormone (TSH) outside of the normal limits and clinically significant as determined by the investigator. Free thyroxine (T4) levels may be measured if TSH level is high. Patient will be excluded if Free T4 level is judged clinically significant by investigator;

b. 12-lead ECG (in a supine position at rest at screening or baseline visit; note: baseline ECG measures for determining inclusion into the study are based on the investigator/site read ECG data, though the database will reflect centrally read ECG data) mean of triplicate QTcF > 500 ms (independent from sex) and/or heart rate (HR) ≤50 beats per minute. Bundle branch blocks deemed clinically significant by investigator will be excluded. [Note: If it is the opinion of the investigator that a lower HR is physiological in a well-fit subject or due to stable concomitant medications, this will be reviewed and approved by the medical monitor on a case by case basis];

c. Alanine transaminase (ALT), aspartate transaminase (AST), or creatine phosphokinase values > 3 times the upper limit of normal (ULN);

d. Any other clinically significant abnormal laboratory result at the time of the screening as determined by the investigator;

7. Is a female of childbearing potential as determined by the investigator;
8. Has a history of neuroleptic malignant syndrome induced by any antipsychotic medication;
9. Has a history of human immunodeficiency virus (HIV) infection or demonstration of HIV antibodies;
10. Has a history of Hepatitis B or C infection AND evidence of active disease defined as elevated ALT, AST or bilirubin levels > 2 × ULN;
11. Has demonstrated Hepatitis B surface antigen or Hepatitis C antibodies at screening AND evidence of active disease defined as elevated ALT, AST or bilirubin levels > 2 × ULN;
12. Meets Diagnostic and Statistical Manual – 5th Edition (DSM-5) criteria for moderate to severe substance use disorder;
13. Has a positive urine drug or alcohol test at screening or evidence of either withdrawal from, or acute intoxication with cocaine, (meth) amphetamines, alcohol, barbiturates, or hallucinogens or similar compounds;

[redacted]

[redacted]

14. Has a likely allergy or sensitivity to ITI-007 or any psychoactive drug based on history;
15. Has used any of the following agents under the specified conditions:
    a. Lifetime exposure to ITI-007 [redacted] or, who has had exposure to any investigational product within 3 months of baseline visit or participated in the past 4 years in > 2 clinical studies of an investigational product with a central nervous system indication;
    b. Any strong or moderate CYP450 3A4 inhibitor or inducer within 7 days (or 5 half-lives, whichever is greater) prior to the baseline visit;
    c. Certain drugs with known psychotropic properties or any non-psychotropic drugs with known or potential significant central nervous system effects within 5 half-lives before the baseline visit unless noted below to be discontinued by the baseline with taper, if appropriate (see Section 5.8), including:
        i. Anxiolytics (except lorazepam as described in Table 5-7)
        ii. Sedative hypnotics
        iii. Central opioid agonists/antagonists including tramadol (Ultram). Except: following review by medical monitor for treatment of stable condition on case by case basis
        iv. Antipsychotics may be tapered and must be discontinued by the baseline visit
        v. Methotrexate
        vi. Any known 5-HT_{2A} receptor antagonist or inverse agonist including but not limited to mianserin, mirtazapine, nefazodone, cyproheptadine, pimavanserin, or fluvoxamine
        vii. Immunosuppressants
        viii. St. John's Wort must be discontinued by the baseline visit

        [Notes: Anticonvulsants, mood stabilizers, and antidepressants (such as SSRI or SNRI) may be allowed, but the dose should be stable for at least 3 months prior to screening and remain stable during trial participation, unless a shorter duration is reviewed and approved by the medical monitor. Dietary supplements, medical foods, or pharmaceuticals used specifically for the treatment of dementia,

agitation, or sleep, containing omega3 fatty acids, melatonin, kava kava, Vitamin B12, folate, or valerian root may be allowed, but the dose should be stable for at least 3 months prior to screening and remain stable during trial participation, unless a shorter duration is reviewed and approved by the medical monitor. Multivitamin as daily supplement is allowed. All stable psychotropic medications or supplements require review and approval by the medical monitor.];

16. Is unable to be safely discontinued from current above-mentioned psychotropic medications;
17. Is unable to swallow oral medication;
18. Is judged by the investigator to be inappropriate for the study;
19. Is an immediate family (i.e., spouse, parent, child, or sibling, whether biological or legally adopted) of the investigator, ITI or CROs conducting the study.

[redacted]

[redacted]

[redacted]

4.2 Withdrawal of Patients from the Study

In Part A, the planned overall duration of the study for each patient is up to up to 8 weeks (7 visits): a screening/baseline period of up to 2 weeks, an on-treatment period of 4 weeks, [redacted] there will be a follow-up period of approximately 2 weeks. The duration of the study is defined for each patient as the date signed written informed consent is provided through the last follow-up visit on Day 43 for patients who participate in Part A only.

[redacted]

4.2.1 Reasons for Withdrawal/Discontinuation

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

1. Does not meet the protocol inclusion criteria or meets the protocol exclusion criteria.
2. Noncompliance with the protocol.
3. A serious or intolerable AE that, in the investigator's opinion, requires withdrawal from the study.
4. Laboratory safety assessments that reveal clinically significant hematological or biochemical changes from baseline values, or baseline laboratory safety assessments that are returned after randomization in Part A [redacted]

5. Symptoms or an intercurrent illness not consistent with the protocol requirements or that justify withdrawal.
6. Lost to follow-up.
7. Other (e.g., pregnancy, development of contraindications of use of study drug).
8. The investigator or sponsor decide to discontinue the patient's participation in the study.

   [Note: Patients may be discontinued from study treatment, at the request of the Sponsor, if they experience adverse events that are unexpected based on previous ITI-007 clinical trials that might indicate an allergy or sensitivity to ITI-007 (e.g., rash or respiratory distress) and/or might indicate underlying neurological toxicity (e.g., any new instance of tremor, including treatment-emergent mild tremor, or worsening of existing tremor) and/or might indicate liver function impairment (e.g., elevated liver function tests such as AST or ALT), or for other reasons.]
9. The patient withdraws consent. If consent is withdrawn, the patient must be questioned by the investigator or study site staff whether the withdrawal is due to an AE, lack of efficacy, personal or family reasons, or whether the patient withdrew consent and refused all end-of-study procedures, including refusing to give a reason; these reasons must be documented in the electronic case report form (eCRF).

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

4.2.2 Handling of Withdrawals

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

Patients who discontinue study treatment or active participation in the study will no longer receive study drug. When a patient withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant screen of the eCRF. Whenever possible, all patients who discontinue study treatment or withdraw from the study prematurely will undergo all end-of-study assessments. Patients who fail to return for final assessments will

be contacted by the study site in an attempt to have them comply with the protocol. A minimum of 2 documented telephone calls should be made on different days over the course of 2 weeks. If the patient is unreachable by telephone, a registered letter should be sent to the patient requesting him or her to contact the study site.

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

4.2.3 Replacements

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

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

5 Study Treatments

5.1 Method of Assigning Patients to Treatment Groups

In Part A, patients who continue to meet all eligibility criteria at baseline (Visit 2) will be randomly assigned to one of the two treatment groups for a 4-week, double-blind on-treatment period. Patients will be randomly assigned to one of the following groups: 9 mg ITI-007 or matching placebo. The on-treatment period will be a total of 4 weeks.

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

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

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

[redacted]

5.2 Treatments Administered

In Part A, patients will be assigned to receive either 9 mg ITI-007 or placebo. [redacted]

[redacted]

5.3 Identity of Investigational Product

5.3.1 Investigational Product for Study Part A

In Part A, ITI-007 will be supplied as 4.5 mg over-encapsulated tablets (capsules)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

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

[redacted]

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

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

[redacted]

[redacted]

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging and Storage

[redacted]

[redacted]

5.4.2 Test Article Accountability

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

5.5 Overdose Management

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

[redacted]

5.5.2 Medication Errors

Dispensing study treatment to be taken by patients in an outpatient study increases risk for medication errors. All errors in medication dispensing or administration must be carefully documented. These errors may include, but are not limited to, providing the wrong dose (in Part A, not taking 2 capsules per dose or taking too many capsules per dose [redacted]

[redacted] losing medication, or administration at the wrong time of the day. Medication adherence will be emphasized at every visit. Written instructions will be provided to the patients with the treatment cards in order to minimize medication error. Additional adherence procedures may be implemented.

5.5.3 Treatment of Medication Errors

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

5.6 Blinding

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

[redacted]

5.6.1 Breaking the Blind

In Part A, a patient's treatment assignment will not be broken until the end of the study unless medical treatment of the patient depends on knowing the study treatment the patient received. In the event that the blind needs to be broken because of a medical emergency, the investigator may unblind an individual patient's treatment allocation. As soon as possible, the investigator should first contact the medical monitor to discuss the medical emergency and the reason for revealing the actual treatment received by that patient. The treatment assignment will be unblinded through IVRS/IWRS. Reasons for treatment unblinding must be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented.

[redacted]

[redacted] l clinical data have been entered into the database and all data queries have been resolved.

5.7 Treatment Compliance

Patient compliance will be assessed by counts of unused study drug at each visit during the double-blind on-treatment period for Part A [redacted] Table 6-1 [redacted]

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

[redacted]

5.8 Prior and Concomitant Therapy

Patients who are maintained on a stable dose of any allowed standard of care medications for at least 3 months prior to Day 1 (baseline) [unless a shorter duration is reviewed and approved by the medical monitor] and for the duration of study participation may be eligible for participation in this study. This includes stable doses of cholinesterase inhibitors and memantine.

Patients are required not to use the following during the study: alcohol, cannabis, any known 5-HT_{2A} receptor antagonist or inverse agonist, any strong or moderate cytochrome P450 3A4 inhibitor or inducer, any short-acting anxiolytic (except use of lorazepam described in Table 5-7 and Table 5-8 below), or certain drugs with known psychotropic properties or any non-psychotropic drugs with potential central nervous system effects, including:

i. Anxiolytics (except lorazepam as described in Table 5-7 and Table 5-8)
ii. Sedative hypnotics
iii. Central opioid agonists/antagonists including tramadol (Ultram). Except: following review by medical monitor for treatment of stable condition on case by case basis

iv. Antipsychotics should be tapered and must be discontinued by the baseline visit

v. Methotrexate

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

vii. Immunosuppressants

viii. St. John's Wort should be discontinued by the baseline visit

[Notes: Anticonvulsants, mood stabilizers, and antidepressants (such

[redacted]

[redacted]

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

[redacted]

Patients considered potentially eligible for participation will be required to discontinue prohibited psychotropic drugs for the duration of the study. Prior short-acting psychotropics can be washed off during the screening/baseline period if the wash off can be done safely so that the drug is out of the system within 5 half-lives by the baseline visit. Prior long acting psychotropic drugs including, but not limited to, fluoxetine, cariprazine, brexpiprazole, and aripiprazole may be excluded unless a washout was started during the course of normal patient care before the start of the screening period to ensure a wash off of at least 5-half-lives prior to the baseline visit. Wash off of prior medications should be reviewed by the medical monitor as part of eligibility review.

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

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

6 Study Assessments and Procedures

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

The schedules of events are presented in Table 6-1 [redacted]

Table 6-1 Part A Schedule of Events

Study Period	**Screening**	**Baseline**	**Double-Blind On-Treatment Period**				**Follow-up**
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7 or ET[1]**
Study Week	**-2**	**0**	**1**	**2**	**3**	**4**	**6**
Study Day	**Up to – 14[2]**	**1**	**8 (±1)**	**15 (±1)**	**22 (±1)**	**29 (±1)**	**43 (±2)**
	Clinic Visit	Clinic Visit	Phone contact	Clinic Visit	Phone contact	Clinic Visit	Clinic Visit
Informed Consent	Before Any Study-Specific Procedures are Conducted						
Review Patient/Caregiver Information Sheet	X						
Medical History incl. Demography and STOP-bang Questionnaire	X						
Modified Physical & Neurological Examination including Calculation of BMI (height and Modified Hachisnki Ischemia Scale at screening only)	X					X	X
12-lead ECG[3]	X	X				X	X
Vital Signs[4]	X	X		X		X	X
Hepatitis/HIV Testing	X						
Drug and Alcohol Screen	X	X					
Laboratory Assessments[5]	X					X	X
Dementia Diagnosis	X						
MMSE	X					X	
C-SSRS	X	X				X	X
CMAI-C[10]		X		X		X	
CGI-S of Agitation[10]	X	X		X		X	
CGI-S of Aggression[10]	X	X		X		X	
Caregiver Diary[6]	X	X		X		X	

Study Period	**Screening**	**Baseline**	**Double-Blind On-Treatment Period**				**Follow-up**
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7 or ET[1]**
Study Week	**-2**	**0**	**1**	**2**	**3**	**4**	**6**
Study Day	**Up to – 14[2]**	**1**	**8 (±1)**	**15 (±1)**	**22 (±1)**	**29 (±1)**	**43 (±2)**
	Clinic Visit	Clinic Visit	Phone contact	Clinic Visit	Phone contact	Clinic Visit	Clinic Visit
Day/Night Actigraphy[7]	X	X		X		X	
Review Inclusion/ Exclusion Criteria	X	X					
Eligibility Adjudication[8]	X						
NPI-C	X					X	
SAS & BARS & AIMS		X				X	
Blood Draw for Pharmacokinetic Assessments[9]		X				X	X
Blood Draw for Biomarker Assessments		X					
Randomization		X					
Medication Dispensed		X		X			
Unused Medication Returned				X		X	
Treatment Compliance Assessment				X		X	
AEs / SAEs	X	X	X	X	X	X	X
Prior/ Concom Med	X	X	X	X	X	X	X

[1] An attempt should be made to collect as many Day 43 assessments as possible upon early discontinuation / early termination from study treatment.

[2] Extension to the screening period may be approved by the Sponsor or representative in extenuating circumstances related to the patient or caregiver.

[3] Each ECG assessment will comprise of triplicate 10 second epochs from 12-lead ECGs recorded 5 minutes apart. One triplicate ECG will be performed during screening, at baseline and on Days 29 and 43 (or Early Termination Visit). In all cases, ECGs are conducted before other assessments scheduled in the same time window; for example, when ECG, vital signs, and blood sample collection for PK measures are scheduled for the same time window, ECG measures should be conducted first, followed by vital signs and then blood sample collection.

[4] Vital sign assessments will include 3-positional blood pressure and pulse rate, respiratory rate, and oral temperature. The 3-positional blood pressure and pulse rate will be measured after 10 minutes in the supine position, 1 minute sitting, immediately after standing, and 3 minutes after standing. Pulse will be measured by counting pulse over 60 seconds. Height will be measured only at screening. Body weight will be measured during screening, at baseline and on Days 15 29 and 43 (or Early Termination Visit). Vital signs are always taken after conducting the ECGs, as applicable, and prior to any other assessments, including needle sticks for labs or PK samples, scheduled in the same time window.

[5] Clinical laboratory samples are to be taken after an overnight fast of at least 10 hours, after any scheduled ECG or vital signs have been recorded. Screening clinical laboratory may be fasting or non-fasting.

[6] Diaries will be dispensed at screening (Visit 1). Caregivers will be asked to fill out a daily diary during the screening/baseline period and throughout the study on-treatment period. The period between the screening visit (Visit 1) and the Baseline visit (Visit 2) will serve as baseline for the data collected in the diary and will serve to ascertain diary compliance before randomization. The diary will be reviewed by the investigator or approved clinical rater at the site to facilitate caregiver interviews and inform the clinical ratings.

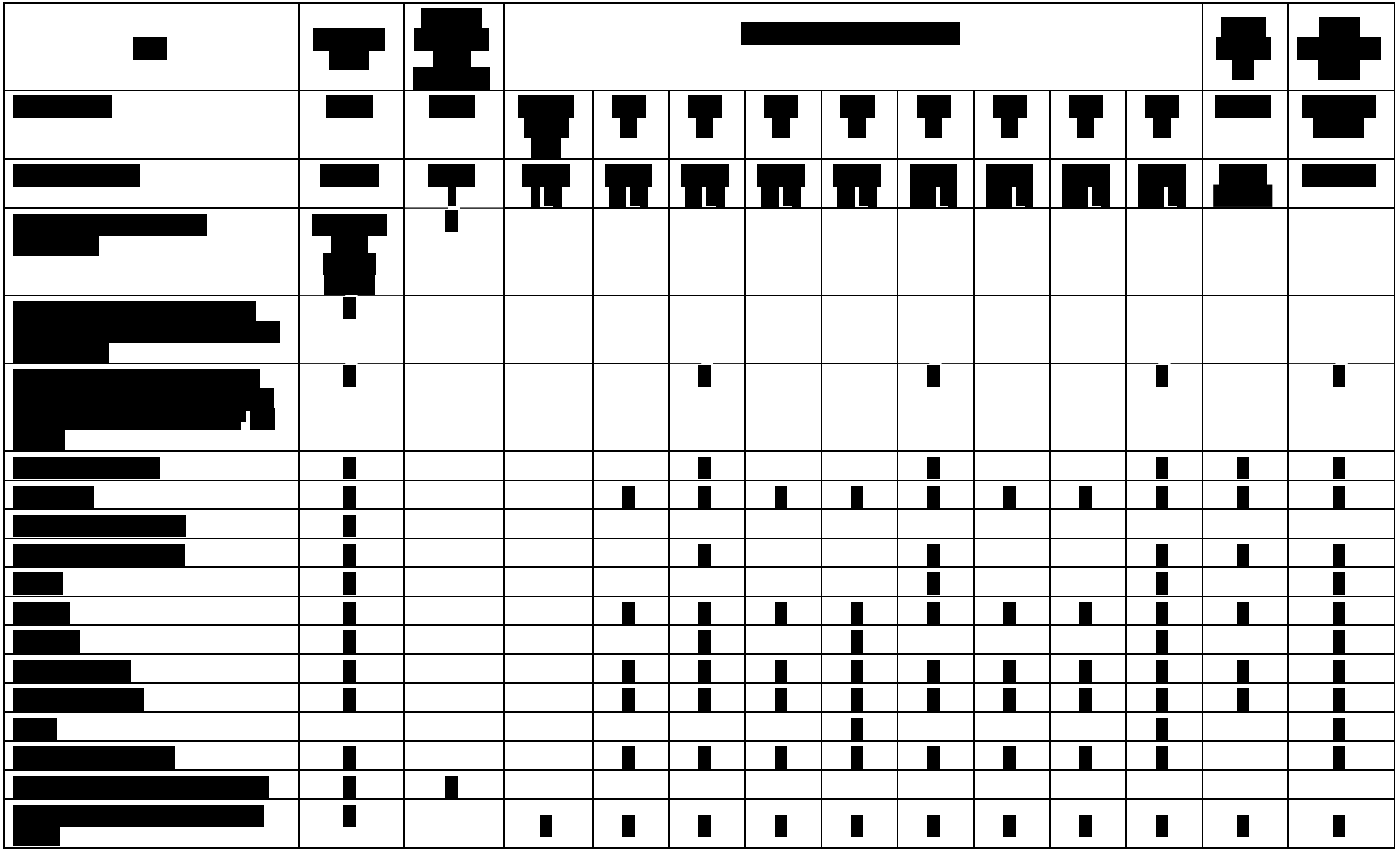
[7]Actigraphy units will be provided at screening (Visit 1) to patients and to caregivers who provide optional consent for the caregiver actigraphy data collection. Actigraphy units will be worn during the screening/baseline period and throughout the study on-treatment period; data will be downloaded from units at scheduled visits. The period between the screening visit (Visit 1) and the baseline visit (Visit 2) will serve as baseline for the data collected by actigraphy and will serve to ascertain actigraphy compliance before randomization.

[8] Screening adjudication process to confirm eligibility will take place between screening and baseline and will be administered by remote, independent expert raters and/or medical monitor(s) who are approved for this role by the sponsor and with the adjudication conducted in conjunction with the sponsor. This includes the Qualitative Assessment of Biopsychosocial Conditions (Qual-ABC) to confirm subject suitability and caregiver appropriateness for participation in the study.

[9] Blood sample collection for pharmacokinetic analysis will be collected pre-dose at baseline (Visit 2) and on Study Days 29 (Visit 6) and on Day 43 at the final safety follow-up visit (Visit 7 or Early Termination Visit if a patient does not complete the on-treatment period) for determination of ITI-007 (IC200056 parent) and its metabolites (IC200131, IC200161, IC200565, IC201308, and IC201309) concentrations in plasma.

[10] CGI-S assessments should be completed by the same site rater on the same day after the NPI-C at screening and after the CMAI-C assessment at other visits.

[redacted]



6.1 Screening Assessments and Procedures

After obtaining written informed consent, the following assessments are to be performed within 2 weeks prior to baseline (Day 1), according to the schedule of events in Table 6-1 for Part A [redacted] assessments can be conducted on different days within the screening period.

6.1.1 Informed Consent

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

[redacted]

[redacted]

6.1.2 Medical History and Other Information

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

Medical history of sleep disorders are allowed, with the exception of rapid eye movement sleep disorder, but should be carefully documented, including but not limited to insomnia (sleep induction and/or sleep maintenance insomnia), sleep apnea (as determined by the STOP-bang questionnaire; Chung, 2008 for Part A) and periodic limb movements during sleep.

6.1.3 Modified Physical and Neurological Examination

A modified physical examination, including neurological and excluding genital/rectal examinations, will be performed. The examination should include evaluation of height (at screening only [m]); body weight (kg); appearance and skin; head and neck; eyes, ears, nose, and throat; chest and lungs; heart; abdomen; and extremities. Neurological examinations include an assessment of motor function, sensory function, reflexes, and gait. All physical and neurological examination findings must be documented in the patient's study chart and also recorded in the eCRF. The Modified Hachinski Ischemia Scale should be conducted at Screening Visit only. Physical and neurological examinations will be conducted according to the schedule of events in Table 6-1 [redacted]

6.1.4 Electrocardiogram Assessments

In Part A, each ECG assessment will be comprised of triplicate 10-second epochs from 12-lead ECGs recorded 5 minutes apart. Electrocardiogram parameters to be measured include HR, QRS, PR, QT, QTcF, and RR intervals.

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

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

assess cardiac function for the purposes of immediate safety concerns and baseline ECG measures for determining inclusion into the study are based on the investigator/site clinical judgement based on machine generated ECG data. ECG recordings will be made according to the schedule of events in Table 6-1.

[redacted]

[redacted]

[redacted]

6.1.5 Vital Sign Measurements

In Part A, vital sign assessments will include 3-positional blood pressure and pulse rate, respiratory rate, and oral temperature. The 3-positional blood pressure and pulse rate will be measured after 10 minutes in the supine position, 1-minute sitting, immediately after standing, and 3 minutes after standing. Pulse will be measured by counting pulse over 60 seconds. Height will be measured only at screening. Vital signs, including body weight will be measured at scheduled clinic visits according to the schedule of events in Table 6-1. Each patient's BMI will be calculated before Baseline to ensure that the patient meets the BMI inclusion criterion.

[redacted]

[redacted]

6.1.6 Hepatitis Screening

Blood samples will be collected at screening from all patients in order to perform hepatitis B surface antigen and hepatitis C antibody (immunoglobulin G) testing. Test results will be sent to the screening site and must be reviewed before the Baseline visit (Visit 2). Any patient with active disease as evidence by LFT elevation for hepatitis B or C will be excluded from participating in the study. Details regarding sample collection, processing, and shipping can be found in the study reference manual.

6.1.7 HIV Screening

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

6.1.8 Drug and Alcohol Screening

Urine drug (amphetamines, barbiturates, benzodiazepines, cannabinoids [THC], cocaine metabolites, methadone, opiates, phencyclidine, propoxyphene) and alcohol tests will be performed. Any patient with a positive urine drug or alcohol test at screening or evidence of either withdrawal from, or acute intoxication with cocaine, (meth) amphetamines, alcohol, barbiturates, or hallucinogens or similar compounds will be excluded from participating in the study.

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

When urine collection is not feasible to collect, missing urine drug screen data and risk for substance use will be reviewed as part of the screening adjudication process.

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

6.1.9 Laboratory Assessments

Laboratory assessments performed at screening are described in Section 6.5.

6.1.10 Dementia Diagnosis

The major clinical criterion for inclusion in the study is that the patient be diagnosed with probable AD according to the NIA-AA guidelines (McKhann, 2011; Appendix A). The NIA-AA guidelines will be used in this study at screening only to confirm the diagnosis of probable AD in patients evaluated for inclusion in the study. Diagnosis will be performed by the investigator or an expert site-based rater approved by the sponsor.

6.1.11 Mini Mental State Examination

The MMSE is a brief cognitive test assessing general cognitive function (Folstein, 1975) that has been employed in numerous clinical trials of Food and Drug Administration (FDA) products approved for the treatment of AD. The MMSE consists of 5 components: 1) orientation to time and place, 2) registration of 3 words, 3) attention and calculation, 4) recall of 3 words, and 5) language. The scores from each of the five components are summed to obtain the overall MMSE score. The score can range from 0 to 30, with lower scores indicating greater impairment in function. This will be used to assess severity at screening (Visit 1) and at the end of the study on-treatment period (Visit 6). The MMSE takes about 5 to 10 minutes to administer. The MMSE will be administered by the investigator or an expert site-based rater approved by the sponsor and results will be reviewed by an independent expert as a component of the systematic patient eligibility adjudication process for participation in Part A.

6.1.12 Columbia Suicide Severity Rating Scale

The C-SSRS is a questionnaire developed and validated by Kelly Posner and colleagues (2011) for the assessment of suicidal ideation and behavior. Several versions have been developed including the “Baseline” and “Screening” versions and a combined

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

The C-SSRS will be administered by the investigator or an expert site-based rater, as indicated in the Schedule of Events (Table 6-1 and Table 6-2).

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

6.1.13 Neuropsychiatric Inventory Clinician

The NPI-C is structured to allow clinician input to assessments of neuropsychiatric symptoms (Cummings, 1994). The NPI-C can be used to rate the presence of neuropsychiatric symptoms across many domains, as in the original NPI, as a standalone measure for specific symptom domains (e.g., dysphoria, agitation), or a combination of both (presence of neuropsychiatric symptoms across domains plus particular focus on one or more specific domains). Unlike the original NPI, the NPI-C allows the rater to obtain additional caregiver and patient information to inform the rating for *each* item within a domain. The NPI-C is completed following a caregiver interview (rating each item for frequency on a scale of 0 to 4, severity on a scale of 0 to 3, and distress on a scale of 0 to5), a patient interview (rating each item for frequency on a scale of 0 to 4) and a clinical assessment (rating each item for clinical impression of severity on a scale of 0 to 3). The NPI-C is validated looking back over the past 4 weeks. In the present study, the NPI-C will be used as a secondary endpoint, assessed at screening and endpoint, after 4 weeks of treatment. The score for each domain is the sum of clinical impression ratings for all items.

The NPI-C will be assessed at screening and again after four weeks of treatment according to the schedule of events in Table 6-1 for Part A [redacted]

6.1.14 Clinical Global Impression scale for Severity of Illness

The CGI scale for Severity of Illness (Guy, 1976) is a standardized assessment tool that the clinician can use to rate the overall severity of illness and efficacy of medication. CGI-S of Agitation and CGI-S of Aggression will be used in this study at screening and baseline (as a criterion for inclusion or exclusion) and throughout the study as a measure of efficacy (Table 6-1 and Table 6-2). Scores on the CGI-S range from 1 (not ill at all) to 7 (among the most extremely ill). A CGI-S assessment will be completed by the investigator or another ITI-approved expert site-based rater, the same person who completes the CMAI-C assessment, following and informed by the CMAI-C and all other available clinical information at all visits except screening. At screening, the CGI-S assessments will be completed following and informed by the NPI-C and all other available clinical information.

6.1.15 Caregiver Daily Diary [redacted]

Caregivers will be asked to record the frequency of patient agitation and aggressive behaviors on a daily basis in order to inform the caregiver's input to the clinician at the study visits. A formal structure for the diary will be provided in order to collect daily reports in a systematic and consistent way across caregivers. Caregivers and clinicians will review the daily diary together at the study visits. The intent is to reduce the reliance on caregiver memory of frequency of events that occurred over the past two weeks by recording events daily.

Diaries will be dispensed at screening (Visit 1). Caregivers will be asked to fill out a daily diary during the screening/baseline period and throughout the study on-treatment period. The period between the screening visit (Visit 1) and the baseline visit (Visit 2) will serve as baseline for the data collected in the diary and will serve to ascertain diary compliance before randomization. The diary will be reviewed by the investigator or approved clinical rater at the site to facilitate caregiver interviews and inform the clinical ratings (Table 6-1).

6.1.16 Actigraphy [redacted]

Actigraphy is a non-invasive method of monitoring human rest/activity cycles. A small actigraph unit, also called an actimetry sensor or actigraphy device, is worn for a week or more to measure gross motor activity. The unit is usually, in a wrist-watch-like package, worn on the wrist. The movements the actigraph unit undergoes are continually recorded and some units also measure physiological measures (e.g., HR) and environmental measures

(e.g., light exposure). The data can be later read to a computer and analyzed offline; in some brands of sensors the data is transmitted and analyzed in real time. Actigraphy will be measured for the patient and the primary caregiver, by way of separate, optional consent of the primary caregiver. The actigraph unit will be secured in place at the initial screening visit (Visit 1) and worn throughout the on-treatment period (through Visit 6); data will be downloaded from the unit at scheduled visits. The period between the screening visit (Visit 1) and the baseline visit (Visit 2) will serve as baseline for the data collected by actigraphy and will serve to ascertain actigraphy compliance before randomization. If wearing the actigraph unit is not tolerated and is removed by the patient, the data will not be collected after the second attempt of securing the device in place; such data will be handled as missing data as described in the statistical analysis plan. Re-securing of the actigraph unit will not be repeatedly attempted so as not to further agitate the patient or increase the burden to the caregiver.

6.1.17 Eligibility Adjudication [redacted]

Eligibility of potential patients will be confirmed through a formal adjudication process, in which screening data obtained to evaluate patient diagnosis, severity of illness, medical appropriateness for participation in the clinical study, and appropriateness of the designated caregiver for participation in the clinical study. Adjudication of patient eligibility will be administered by remote, independent expert raters and/or medical monitor(s) who are approved for this role by the sponsor and adjudication will be conducted in conjunction with the sponsor. Further information regarding the screening adjudication can be found in the study reference manual.

6.2 Efficacy Assessments and Procedures

6.2.1 CMAI-C

The purpose of the CMAI is to measure the frequency of agitated behaviors (Cohen-Mansfield, 1989). The CMAI has been validated in measuring behavior over the past 2 weeks. Recall of frequency is a reasonably objective, quantifiable and reliable measure. In the present study, recall of frequency of agitated behavior will be supported by a structured clinical interview performed by the clinician and the use of a daily caregiver diary that will be referred to before and during the course of the standardized interview. Frequent individual agitation behavior is troubling for the patient and disruptive to the caregiver; physically aggressive behavior is particularly troublesome for the patient and

distressful to the caregiver. The Community version (CMAI-C; 37 items rated 1-7 for frequency) (Cohen-Mansfield, 1991; Cohen-Mansfield, 1995) will be utilized in the present study. The 37 CMAI-C items are specifically worded to ensure the rater's standardization, consistency and specific shared understanding in the interview of the community-based non-professional primary caregiver for each specific agitation behavior item. Items that do not apply to the patient are skipped. The 1 to 7 scoring range of the CMAI-C offers significantly finer granularity than other versions that utilize a 1 to 5 scoring range with regards to the taxonomy of specific agitated behaviors, while maintaining the objectivity of the frequency-based rating of each item.

The CMAI-C Factor Composite score (Appendix C) includes key symptom items from the CMAI-C that have been demonstrated to reliably cluster in meaningful symptom domains associated with agitation and aggression according to factor analyses (Rabinowitz, 2005).

The CMAI-C is the primary efficacy measure which will be administered in its full validated form (but only a subset of items will be included in the primary efficacy analysis, Appendix C) and will be assessed according to the schedule of events in Table 6-1 for Part A [redacted]

6.2.2 Clinical Global Impressions

The CGI-S of Agitation and CGI-S of Aggression (Section 6.1.14) will be a clinical efficacy assessment by the investigator of each patient's severity of illness. The CGI-S assessments will be measured after 2 and 4 weeks of treatment according to the schedule of events in Table 6-1 for Part A [redacted]

6.2.3 Neuropsychiatric Inventory Clinician

The NPI-C (Section 6.1.13) will be assessed at screening and again after four weeks of treatment according to the schedule of events in Table 6-1 for Part A [redacted]

6.2.4 Caregiver Daily Diary (Part A only)

The caregiver daily diary will be administered as described in Section 6.1.15.

[redacted]

6.3 Safety and Tolerability Assessments

All patients who receive study drug will be evaluated for safety (Table 6-1 and Table 6-2).

6.3.1 Adverse Events

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

6.3.1.1 Definition of Adverse Event

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

The AE may be:

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

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

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

TEAEs will be defined as any AEs, regardless of the relationship to study drug, that occur or worsen in intensity after the first dose of study drug and on or before the last date of study drug.

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

6.3.1.2 Definition of Serious Adverse Event

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

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

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

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

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

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

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

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

6.3.1.3 Nonserious Adverse Event

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

6.3.1.4 Definition of Relationship to Study Drug

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

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

Table 6-3 Causality Categories

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

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

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

6.3.1.5 Definition of Intensity

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

Table 6-4 Intensity Categories

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

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

6.3.1.6 Period of Observation for Adverse Events

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

If the investigator detects an SAE in a study patient after the end of the period of observation and considers the event possibly related to prior study treatment, he or she should contact the sponsor to determine how the AE should be documented and reported.

6.3.1.7 Documenting, Reporting, and Eliciting Adverse Events

All AEs reported or observed during the study will be collected and recorded on the AE page of the eCRF for each patient from the date the ICF was signed until the end of study procedures are completed.

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

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

6.3.1.8 Notification About Serious or Unexpected Adverse Events

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

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

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

- Study number

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

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

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

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

6.3.1.9 Exceptions

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

6.3.1.10 Follow-Up of Adverse Events

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

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

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

6.3.2 Safety Assessments

Safety assessments scheduled through the course of the study (Table 6-1 and Table 6-2) will include suicidality assessment by the C-SSRS, cognitive status assessment by the MMSE, movement disorder assessment by the AIMS, BARS and SAS, vital sign measurements, ECG evaluations, and physical and neurological examination.

6.3.2.1 C-SSRS

The C-SSRS will be completed at visits according to the schedule of events (Table 6-1 [redacted] Details of the C-SSRS are presented in Section 6.1.12.

6.3.2.2 MMSE

The MMSE will be completed at screening and after 4 weeks of treatment according to the schedule of events (Table 6-1 and Table 6-2). Details of the MMSE are presented in Section 6.1.11.

6.3.2.3 Abnormal Involuntary Movement Scale

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

abnormal movements. The patient's awareness of and distress caused by the abnormal movements are also noted. The AIMS is to be completed at baseline and as specified in the schedule of events (Table 6-1 and Table 6-2).

6.3.2.4 Barnes Akathisia Rating Scale

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

6.3.2.5 Simpson-Angus Scale

The SAS is a measure of extrapyramidal side effects (Simpson, 1970). Ten items including rating gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head rotation, glabella tap, tremor, and salivation are rated on a scale from 0 (normal) to 4 (extreme in severity). The SAS should be conducted by the investigator or an expert site-based rater in a room where the patient can walk a sufficient distance to allow a natural pace (e.g., 15 paces). Each side of the body should be examined. In the case of patients with more advanced dementia, certain items may be difficult or almost impossible to rate such as arm and leg drop; in the event that an item cannot be assessed in an individual patient, the reason should be noted and the item will be counted as missing data. The SAS is to be completed at baseline and as specified in the schedule of events (Table 6-1 and Table 6-2).

6.3.2.6 Vital Sign Measurements

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

6.3.2.7 ECG Assessments

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

6.3.2.8 Modified Physical and Neurological Examination

The modified physical and neurological examinations will be conducted at screening and as scheduled (Table 6-1[redacted]). Details of the physical and neurological examinations are presented in Section 6.1.3.

6.4 Safety Monitoring Committee

No safety monitoring committee will be used for the study.

6.5 Laboratory Analyses

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

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

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

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

The following clinical analytes will be determined:

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

Clinical chemistry: albumin; alkaline phosphatase; blood urea nitrogen; gamma-glutamyl transferase; calcium; creatinine; glucose; insulin; HbA_{1c} (Part A at screening and Day 29 [redacted], if applicable, at screening and on Study Days 25, 100, 175, and 189); cholesterol (high-density lipoprotein and low-density lipoprotein [LDL] [calculated] and homogenous LDL will be reported, and homogenous LDL will be reflexed if a patient's triglycerides are >400); triglycerides; phosphate; potassium; prolactin; ALT; AST; lactate dehydrogenase; sodium; chloride; bilirubin (total, direct); total protein; serum B12/folate (at screening only); uric acid; creatine phosphokinase; and thyroid panel (at screening only, thyroid-stimulating hormone will be assayed and if the result is abnormal, the free thyroxine and free triiodothyronine will be assayed).

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

Laboratory assessments will be conducted according to the schedule of events (Table 6-1 and Table 6-2).

[redacted]

Further details regarding sample collections, processing and specific testing can be found in the study reference manual.

[redacted]

6.8 Pregnancy

In this study only females of nonchildbearing potential will be enrolled. In an unlikely event if the pregnancy occurs, pregnancy is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive

medication. Any pregnancy of a study participant or partner of a study participant that occurs during study participation must be reported using a clinical study pregnancy form. To ensure patient safety, each pregnancy must be reported to ITI within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the patient was discontinued from the study. Pregnancy complications and elective terminations for medical reasons should not be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

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

7 Statistical and Analytical Plan

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

Blinded (Part A) [redacted] data reviews will be conducted prior to unblinding the patients' treatment assignments (Part A) [redacted] The reviews will assess the accuracy and completeness of the study database, patient evaluability, and appropriateness of the planned statistical methods. An unblinded review of the Part A interim data will be conducted by the DMC, based on the interim analysis plan.

7.1 Analysis Endpoints

7.1.1 Primary Efficacy Endpoints – Part A

The multiple primary efficacy endpoint(s) of Part A are the change from baseline to Day 29 in the CMAI-C three Factor scores related to aggressive behavior, non-aggressive agitated behavior, and verbally agitated behavior.

7.1.2 Secondary [redacted] Efficacy Endpoints [redacted]

7.1.2.1 Key Secondary Efficacy Endpoint – Part A

The key secondary efficacy endpoint for Part A is the change from baseline to Day 29 in the CGI-S of illness (e.g., CGI-S of Agitation and/or CGI-S of Aggression).

[redacted]

[redacted]

[redacted]

7.2 Sample Size Calculations

In Part A, approximately 292 patients (if no sample size adjustment is made after the interim analysis) will be randomly assigned in a 1:1 ratio to 1 of the 2 treatment groups. A sample size of 292 patients will provide approximately 264 patients assuming an approximately 9% discontinuation rate before the first post baseline assessment of the primary efficacy outcome measure (CMAI-C). 132 patients per treatment group will provide approximately 90% power, assuming an effect size of 0.4 at a two-sided significance level of 5%.

The power calculations for the primary and key secondary efficacy endpoints were performed using the R software.

[redacted]

7.3 Analysis Sets

In Part A the following analysis sets will be used in the statistical analyses:

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

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

Full Analysis Set (FAS): The Full Analysis Set (FAS) will contain all randomized patients who received at least one dose of study drug and who had a valid (pre-dose) baseline and at least one valid post baseline measurement of CMAI-C. All analyses using the FAS will group patients according to the randomized treatment, regardless of the treatment received during the course of the study. FAS will be used in the analysis of the primary, key secondary and exploratory efficacy endpoints.

Per-protocol Set (PPS): The PPS is defined as all randomized patients who completed the study on-treatment period and did not have any major protocol deviations. The major protocol deviation criteria will be specified in the SAP and finalized as part of the blinded data review prior to the final database lock. All analyses using the PPS will group patients according to the randomized treatment.

Safety Analysis Set: The Safety Analysis Set is defined as all patients who received at least 1 dose of study drug. All analyses using the safety set will group patients according to the treatment actually received.

PK Set: The PK Set will contain of all patients who received at least one dose of study drug, had a baseline measurement and at least one post baseline measurement of CMAI-C, and had at least one PK sample collected and analyzed. Analyses using the PK Set will group patients according to the treatment actually received.

[redacted]

7.4 Description of Subgroups to be Analyzed

Subgroup analyses for efficacy and safety variables may be conducted as deemed appropriate and will be detailed in the SAP.

7.5 Statistical Analysis Methodology

Categorical variables will be presented using the number and percentage of patients in each category. Unless otherwise stated, the calculation of percentage will be based on the number of patients in the analysis set of interest. Unless otherwise specified, descriptive statistics of continuous variables (e.g., age, height, weight) will consist of the number of patients (n), mean, standard deviation, median, minimum, and maximum. Source data for summary tables and statistical analyses will be presented as patient data listings.

Unless stated otherwise, statistical tests will be performed at a two-sided 5% significance level, leading to two-sided 95% confidence intervals (CIs). A Holm-based parallel gatekeeping procedure and adaptive design will be implemented to adjust for multiplicity resulting from the analysis of multiple endpoints (primary and key secondary efficacy endpoints, where each includes multiple endpoints) and multiple looks at the data (interim and final). No adjustment for multiplicity will be made for exploratory efficacy endpoints (Part A), safety variables (Part A [redacted] unless otherwise stated in the SAP.

All investigative sites with fewer than 6 ITT patients will be pooled as follows: The largest site with fewer than 6 ITT patients will be pooled with the smallest site with fewer than 6 ITT patients. If this results in a pooled site still having fewer than 6 ITT patients, this site will be pooled together with the next smallest investigative site, if one exists; otherwise, no further pooling is needed. Sites with the same number of ITT 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 ITT patients. If the primary efficacy analysis model, described in section 7.5.2, presents convergence issues due to the too small number of patients per site, the same site pooling algorithm will be applied again, but this time pooling sites with fewer than 12 ITT patients. 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.

All statistical analysis will be performed using SAS® software Version 9.2 or higher. Additional details regarding the statistical analysis methodology will be provided in the SAP.

7.5.1 Patient Disposition, Analysis of Demographics and Other Baseline Characteristics

Patient disposition and withdrawals will be summarized by visit and by treatment group (Part A), when applicable. The incidence of patients who were screened, screen failed, randomized, completed or discontinued treatment and completed or discontinued study, including the corresponding reasons for early withdrawal, will be presented overall, by Part, and by treatment group (Part A). Time to discontinuation due to all reasons, AEs, lack of efficacy, or due to any reason of special interest will be summarized by Part, evaluated using the Kaplan-Meier method and will be compare between the ITI-007 9 mg the placebo groups (Part A) using the Log-rank test.

Demographic and baseline characteristics, including efficacy parameters and safety assessments, will be summarized by part and by treatment group (Part A). No formal statistical testing will be carried out for comparing demographic or other baseline characteristics between treatment groups (Part A).

7.5.2 Analysis of Primary and Key Secondary Efficacy Endpoints – Part A

Part A of the study is designed to evaluate the efficacy profile of ITI-007 9 mg based on the following primary and key secondary endpoints:

- Primary Endpoint(s) – Change from baseline to Day 29 in the CMAI-C three Factor scores related to aggressive behavior, non-aggressive agitated behavior, and/or verbally agitated behavior.
- Key Secondary Endpoint(s) – Change from baseline to Day 29 in the CGI-S of Agitation and/or CGI-S of Aggression.

A multiplicity adjustment based on a parallel gatekeeping procedure will be applied at the interim and final analyses to control the overall Type I error rate (familywise error rate) in the strong sense across the primary and key secondary endpoints at alpha=0.05 (two-sided). The primary efficacy endpoints (Primary Family) will serve as a parallel gatekeeper for the key secondary efficacy endpoints (Secondary Family) in the sense that the treatment effect on the

key secondary efficacy endpoints will be evaluated if and only if the treatment effect on at least one primary efficacy endpoint is significant. A stepwise multiple testing procedure that applies a truncated Holm test will be applied to the primary efficacy endpoints and a regular Holm test will be applied to the key secondary efficacy endpoints. Details of this gatekeeping procedure will be provided in the statistical analysis plan.

Each of the primary efficacy endpoints will be evaluated using a mixed model repeated measures (MMRM) analysis. The model will include the change from baseline of CMAI-C score to each pre-specified time points (Weeks 2 and 4) as the response variable, and treatment (ITI-007 9 mg and placebo), site (or pooled site), visit, corresponding baseline CMAI-C score, the stratification variable, defined by the MMSE score at screening, and interaction terms for baseline CMAI-C score-by-visit, and treatment-by-visit as fixed effects and the patient term will be included in the model as a random effect. Model parameters will be estimated using restricted maximum likelihood. An unstructured covariance matrix will be used to model the correlation among repeated measurements within patient. The Kenward-Roger's correction will be used to estimate the denominator degrees of freedom in the model. Least-squares means (LSMs) and the corresponding standard errors will be presented by treatment group and visit. Contrast estimates (LSMs) for between-treatment group comparisons (ITI-007 9 mg vs. placebo) and the corresponding standard errors, effect sizes, and p-values will also be presented. In the event the convergence cannot be attained with the unstructured correlation matrix, the following alternative structures will be attempted in the specified order: heterogeneous Toeplitz structure (TOEPH), heterogeneous autoregressive(1) (ARH(1)), heterogeneous compound symmetry (CSH), No Diagonal Factor Analytic (FA0(q), with q equal to the number of time points), Toeplitz structure (TOEP), autoregressive(1) (AR(1)), and compound symmetry (CS).

The key secondary efficacy endpoint(s), change from baseline to Day 29 in the CGI-S of Agitation and/or CGI-S of Aggression, will be analyzed similarly to the primary efficacy endpoint(s), using an MMRM method similar to the one specified for the analysis of the primary efficacy endpoint(s) while substituting CMAI-C score related variables in the model with the corresponding CGI-S related variables, such as baseline score and baseline score-by-visit interaction.

The primary and key secondary efficacy analyses described above will also be conducted on the PPS as a supportive analysis.

Additional exploratory analyses of the primary and key secondary efficacy endpoints may be conducted if deemed necessary and will be detailed in the SAP.

7.5.3 Sensitivity Analyses of Primary Efficacy Endpoint – Part A

The purpose of sensitivity analyses is to to explore the robustness of the MMRM results for the primary efficacy analysis under a different assumption on the mechanism of missing data. The MMRM method assumes a Missing At Random (MAR) mechanism for missing data. That is, the probability that measurements are missing depends on the set of observed measurements, but is unrelated to the specific unobserved missing values that, in principle, should have been obtained. Sensitivity analyses for this study will be based on different assumptions on the mechanism of missing data.

A pattern-mixture model (PMM) using a placebo-based multiple imputation (MI) method assumes a Missing Not At Random (MNAR) mechanism for the missing data. Applying PMM using a placebo-based MI assumes that patients who discontinue early from the ITI-007 treatment will follow the trajectory of outcomes similar to the one in the placebo group, after discontinuation of the ITI-007 treatment, taking into account observed measurements prior to discontinuation. Patients who discontinue early from the placebo group will be assumed to have unobserved outcomes similar to the observed ones in placebo patients who remain on study. This strategy is conservative with respect to the experimental treatment because it minimizes the difference between treatment and placebo groups.

A responder analysis will be conducted to support the evidence of the existence of a treatment effect. Patients who discontinue early from the study treatment will be considered as failures and will be classified as non-responders.

Details on implementing the sensitivity analyses will be provided in the SAP.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.5.8 Interim Analyses – Part A

One interim analysis (IA) is planned during Part A of the study after 140 patients have completed the 28-day On-Treatment Period or confirmed to have discontinued study after at least one post-baseline assessment of the primary efficacy outcome measure (CMAI-C). The IA will be conducted such that the ongoing study integrity is maintained, and will be reviewed by an independent Data Monitoring Committee (DMC).

The interim analysis will be used to reassess the assumptions of variability and effect size. The interim data may be used for a decision to terminate the study due to superior efficacy or futility or to adjust the sample size, at the discretion of the Sponsor.

The statistical details of the Part A interim analysis will be provided in the SAP. The operational details of the interim analysis will be provided in the DMC Charter.

An additional interim analysis will report on the completion of Part A of the study, with the final analysis including data from both Parts A and B.

7.6 Data Quality Assurance

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

7.6.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as

part of the case histories. These source documents may include records of screening assessments such as the clinical scales (Table 6-1), laboratory reports, and ECG strips.

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

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

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

8 Ethics

8.1 Independent Ethics Committee or Institutional Review Board

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

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

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

8.2 Ethical Conduct of the Study

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

8.3 Patient Information and Consent

A written informed consent in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50 shall be obtained from each patient before entering the study or performing any unusual or nonroutine procedure that involves risk to the patient. An informed consent template may be provided by the sponsor to study sites. If any institution-specific modifications to study-related procedures are proposed or made by the study site, the consent should be reviewed by the sponsor, its designee, or both before IRB submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB for

review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form.

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

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

9 Investigator's Obligations

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

9.1 Confidentiality

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

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

9.2 Financial Disclosure and Obligations

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

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

9.3 Investigator Documentation

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

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

9.4 Study Conduct

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

9.5 Adherence to Protocol

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

9.6 Adverse Events and Study Report Requirements

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

9.7 Investigator's Final Report

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

9.8 Records Retention

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

9.9 Publications

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

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

10 Study Management

10.1 Monitoring

10.1.1 External Data Monitoring Committee

See Section 7.5.8 for details on DMC for the interim analysis.

10.1.2 Monitoring of the Study

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

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

10.1.3 Inspection of Records

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

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

10.2 Management of Protocol Amendments and Deviations

10.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the sponsor or its

designee. Amendments to the protocol must be submitted in writing to the investigator's IRB for approval before patients can be enrolled into an amended protocol.

10.2.2 Protocol Deviations

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

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the patient or investigator that results in a significant, additional risk to the patient. Significant deviations can include nonadherence to inclusion or exclusion criteria, enrollment of the patient without prior sponsor approval, or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the patient being withdrawn from the study (Section 4.2).

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

10.3 Study Termination

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

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

10.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by

the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Upon completion of the clinical study report, the study results will be posted on publicly available clinical trial registers, as required by the applicable regulatory requirement(s).

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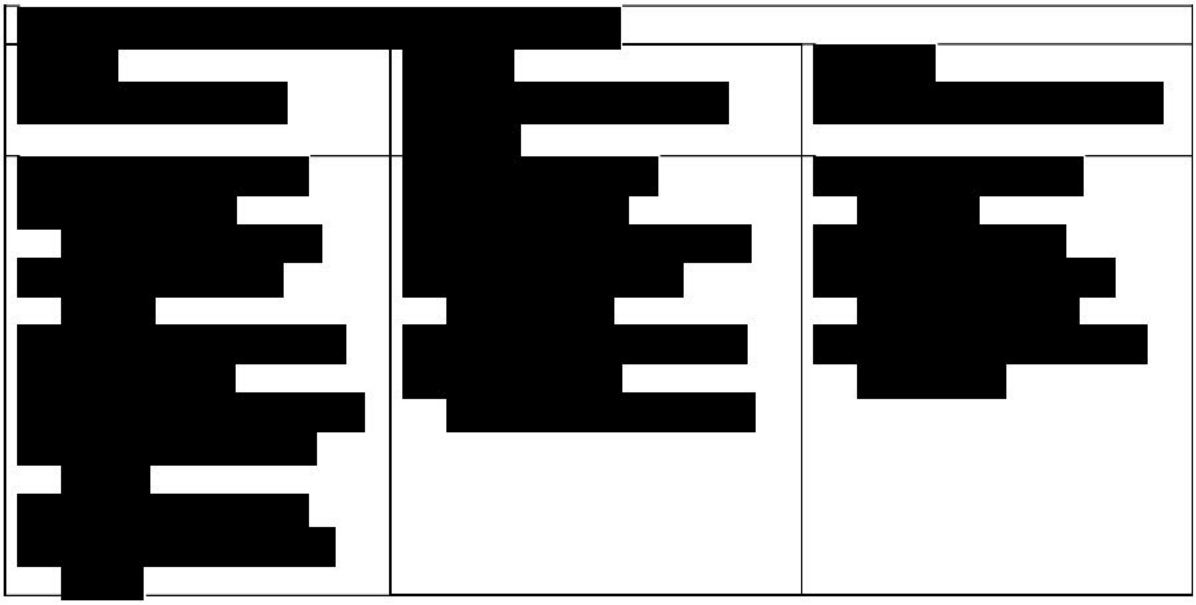

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