Protocol Title:
Lumateperone for Schizophrenia

Version Date:
10/16/2019

Protocol Number:
7716

First Approval:
01/23/2019

Clinic:
Leiber Research Clinic

Expiration Date:
10/14/2020

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Lawrence Kegeles, MD
Joshua Kantrowitz, MD

Research Chief:
Daniel Javitt, MD, PHD

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting an annual continuation without modifications

Division & Personnel

Division

What Division/Department does the PI belong to?
Experimental Therapeutics
Within the division/department, what Center or group are you affiliated with, if any?
Lieber Clinic

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.
none

Application for Continuation of Research

Status

Current Status of Study:
Subject enrollment is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.

As of 8/22/19, five (5) participants have signed consent. Out of the 5, one subject withdrew consent immediately after consent/capacity evaluation and did not have any screening assessments completed. There are two participants currently on ITI-007 (lumateperone) and one participant who started ITI-007 but withdrew consent after several days due to perceived side effects that were unclearly described. The fifth subject is currently in screening with the intention to start ITI-007 mid-September.

The first subject started on ITI-007 has completed 5 months of treatment thus far, and is overall improved despite requiring a down titration to 40 mg for insomnia and a clinically determined prolonged taper of his pre-study antipsychotic. The 2nd participant currently on ITI-007 has done well through the first 3 weeks of treatment.

Funding

Have there been any changes in funding status since the prior approval?
No
Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?
Yes

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
No
Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?

Yes
Is the study covered by a certificate of confidentiality?
No

Overall Progress

Approved sample size
40 enrolled, 30 completed
Total number of participants enrolled to date
5
Number of participants who have completed the study to date
0
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
No
Comments / additional information

Sample Demographics

Specify population
schizophrenia/schizoaffective
Total number of participants enrolled from this population to date
5
Gender, Racial and Ethnic Breakdown

Male: 5
Female: 0

White: 3
Black: 0
Asian: 1
Other/Unknown: 1

Hispanic: 0
Non-Hispanic: 5

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
5
Number of participants currently enrolled
3
Did the investigator withdraw participants from the study?

No
Did participants decide to discontinue study involvement?
Yes
Circumstances of discontinuation:

One participant withdrew consent immediately after consent/capacity evaluation. No screening procedures were initiated.

One participant withdrew after several days of treatment with ITI-007 due to perceived side effects that were unclearly described.

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures
✓ Medication Trial
✓ Use of Investigational Drug or Device

Population

Indicate which of the following populations will be included in this research
✓ Adults over 50
✓ Individuals with Psychosis

Research Support/Funding

Will an existing internal account be used to support the project?
No
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract application is a pending review or a funding decision
Source of Funding

Industry
Sponsor
Intra-Cellular Therapies
Is the study investigator initiated?
Yes
Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
No

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
This protocol describes research conducted by the PI at other facilities/locations
No

Uploaded Protocol Summary Form

Upload Document

Select file to upload.
lumateperone PSF 10.7.19.pdf

Lay Summary of Proposed Research

Lay Summary of Proposed Research

An urgent need exists for new treatments of schizophrenia that are effective against a broad range of symptoms and free of limiting safety issues.ITI-007 (Lumateperonetosylate)is an experimental medication that affects brain proteins that is being developed as a schizophrenia treatment. ITI-007 appeared to work similarly to an FDA approved medication for schizophrenia (risperidone) in a recently published study (Lieberman et al 2016 : see attached). The purpose of this study is to offer open label ITI-007 treatment to patients who either poorly respond or poorly tolerate approved medications. A discussion about clozapine will occur during the consent process.

In this study, subjects will be started on ITI-007. Current antipsychotic medication will be slowly discontinued within the first 7 days of starting ITI-007, with some flexibility allowed if clinically indicated. No subjects will be left unmedicated because of this study.

Subjects will be seen weekly for the first 4 weeks, biweekly for the second month and then monthly for six months. Subjects will be monitored by clinical and safety rating scales, and will be required to show improvement after 3 months to remain in the study. Subjects not improving at this timewill be assessed for the risks/benefits of continuing.

Description of Subject Population

Sample #1

Specify subject population
schizophrenia/schizoaffective
Number of completers required to accomplish study aims
30
Projected number of subjects who will be enrolled to obtain required number of completers
40
Age range of subject population
18-60

Gender, Racial and Ethnic Breakdown
Based on the Epidemiologic Catchment Area Survey (Regier et al, Acta Psychiatr Scand 1993 attached), along with a more recent publication (Bresnahan et al, Int. J. Epidemiol, 2007 attached), we have revised our demographics section. The rates differ in other countries, but we have limited our response to the United States.
The demographics of schizophrenia in the United States are ~ 1% of the population of each ethnicity, with the exception of more men (ratio 1.4:1) and a 2 to 3 fold increased rate in African Americans. Of note, some studies suggest that people of African ancestry are just over diagnosed (Strakowski J Clin Psych 1993).
The literature supports that the demographics of schizophrenia in any specific area, such as New York City in general, and Washington Heights specifically should reflect the demographics of the area (see Reiger 1993). For example, Washington Heights has a large percentage of Hispanic people with schizophrenia because of the relatively large number of Hispanic people in Washington Heights. Thus we anticipate oversampling a Hispanic population relative to the US, and will increase outreach to other ethnicities if this happens.
The following is a gender and ethnic breakdown for the US population as of 2014, modified to reflect the demographics of schizophrenia (e.g. we increased the number of males to reflect a 1.4 to 1 ratio, and double the percentage of African Americans (13% of US->26%) and reduced the number of white's by 13% to make up the difference):
https://www.census.gov/quickfacts/table/PST045215/00.

Gender:
Male/female: 60/40%

Race:
White: 54%
Black 26%
Asian 5%
Other **15%**

Ethnicity:
Hispanic (all races) 17%
Non-hispanic: **83%**

Description of subject population
DSM-V diagnosis of schizophrenia or schizoaffective disorder who failed to show an adequate response in the level of psychotic symptoms to current antipsychotic or poorly tolerating current antipsychotic

Recruitment Procedures

Describe settings where recruitment will occur
Patients will be recruited from the Lieber Center under IRB protocol #6991.
Recruitment will also occur at the Washington Heights Community Service outpatient clinics.
All recruitment material will be approved by the local IRB prior to distribution.

Additionally, a description of this study will be posted on Columbia University Medical Center RecruitMe website. RecruitMe is a recruitment tool meant to connect those who what to participate in clinical trials to the researcher that are conducting them. Interested individuals will be contacted by study staff to deem if potentially eligible. If potentially eligible, a visit will be scheduled to have the participant sign consent and undergo screening procedures.

A description will also be listed on NAMI Metro's website: https://www.naminycmetro.org/get-involved/research-studies/

How and by whom will subjects be approached and/or recruited?

We will follow the IRB approved recruitment plan of IRB protocol #6991.
Study staff will visit the WHCS clinics to present the study to clinicians and patients, including distributing and posting the IRB flyer approved for this study.

Interested individuals who hear about this study from the RecruitMe or NAMI Metro websites will contract research staff listed on the postings to hear more about the study. If potentially eligible, interested individual will be scheduled for a consent and screening visit.

How will the study be advertised/publicized?

Word of mouth and advertisements. The trial will be listed on clinicaltrials.gov. The research study will also be listed on CUMC RecruitMe and NAMI Metro websites.

Do you have ads/recruitment material requiring review at this time?
Yes
Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number
NCT03817528

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement

Subjects may be recruited through the Lieber Clinic screening protocol-IRB #6991. Subjects will be permitted to participate in other projects that do not exclude experimental medications on a case by case basis.

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
No
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
6991
Describe Study Consent Procedures
Potential subjects from the WHCS clinics (Inwood and Audubon) may have their chart reviewed under IRB Protocol #6991 to see if he/she may be eligible for the current study. Please note that subjects will

still consent to the current protocol and undergo screening procedures of this protocol to be determined eligible for the study.
The chart review under IRB #6991 will allow our staff to identify subjects who MAY be eligible for the current study. As detailed in #6991, potentially eligible subjects will be contacted as described in the procedures outlined previously to hear about the study and decide if he/she is interested in participating.
Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Kantrowitz, Joshua, MD
Kegeles, Lawrence, MD
Type in the name(s) not found in the above list

Independent Assessment of Capacity

You have indicated that your study involves subjects who MAY LACK capacity to consent.
Does this study require an independent assessment of capacity?
Yes
Methods/procedures for capacity assessment
An independent psychiatrist will assess the subject's capacity to provide informed consent. If a subject has difficulty understanding all study elements during the consent process, the procedures will be explained again by a member of the research team. If there is still doubt about the subject's understanding of the key elements of the study and ability to provide informed consent, the subject will not be enrolled in the study.

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study
✓ Drug
Select the number of drugs used in this study
1

Drug #1

Name of the drug
Lumateperone tosylate (ITI-007)
Manufacturer and other information
Intracellular Therapies
Approval Status

IND is approved
IND#
141741
Who holds the IND/IND sponsor?
IND is held by PI/CU Investigator
Lieberman, Jeffrey, MD

Methods to Protect Confidentiality

Will the study be conducted under a certificate of confidentiality?
No

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.
We will not be compensating participants for the study, but we will provide reimbursement for study related expenses (e.g., travel, meals, etc) up to $50. You may be asked to provide receipts for reimbursement of expenses.

Uploads

Upload the entire grant application(s)
Upload copy(ies) of unbolded Consent Form(s)
ITI-007 -clean 8.21.19.pdf
Upload copy(ies) of bolded Consent Form(s)
Upload copy(ies) of recruitment materials/ads to be reviewed
Lumateperone Research Participant Post (for NAMI).pdf
Luma Columbia RecruitMe.pdf
ITI-007 flyer 5.16.19.pdf
Upload evidence of FDA IND approval(s)
Upload copy(ies) of the HIPAA form
7716_HIPPA_Authorization.pdf
Upload any additional documents that may be related to this study

Cover Page

Protocol Number: 7716 Version Date: 10/7/19

Protocol Title: ITI-007 (Lumateperone tosylate) for schizophrenia

Principal Investigator: Jeffrey A. Lieberman, M.D. contact PI)

Email: Jeffrey.Lieberman@nyspi.columbia.edu

Telephone: 646-774-5300

Office: PI Chair office Cell Phone: N/A

Lay Summary

This section is intended to provide a basic overview of the study including a description of its purpose, methods, and subject population. The summary should provide a concise overview of the study for non-scientific and scientific members of the IRB. Please avoid medical or technical terminology. In general, the abstract of a grant does not provide a suitable lay summary.

Please also paste of a copy of the Lay Summary into the PRISM PSF Form.

An urgent need exists for new treatments of schizophrenia that are effective against a broad range of symptoms and free of limiting safety issues. ITI-007 (Lumateperone tosylate) is an experimental medication that affects brain proteins that is being developed as a schizophrenia treatment. ITI-007 appeared to work similarly to an FDA approved medication for schizophrenia (risperidone) in a recently published study (Lieberman et al 2016 : see attached). The purpose of this study is to offer open label ITI-007 treatment to patients who either poorly respond or poorly tolerate approved medications. A discussion about clozapine will occur during the consent process.

In this study, subjects will be started on ITI-007. Current antipsychotic medication will be slowly discontinued within the first 7 days of starting ITI-007, with some flexibility allowed if clinically indicated. No subjects will be left unmedicated because of this study.

Subjects will be seen weekly for the first 4 weeks, biweekly for the second month and then monthly for six months. Subjects will be monitored by clinical and safety rating scales, and will be required to show improvement after 3 months to remain in the study. Subjects not improving at this time will be assessed for the risks/benefits of continuing.

Background, Significance, and Rationale

In this section, provide a brief summary of the status quo of the relevant work field, and how the proposed study will advance knowledge. Specifically, identify the gaps in knowledge that your project is intended to fill. If no gaps exist that are obviously and directly related to your project, explain how your proposed research will contribute to the overall understanding of your field. Describe potential impacts of your project within your field of study and in a broader context. Provide a critical evaluation of existing knowledge. The literature review does not have to be exhaustive.

Schizophrenia is a severe, complex, chronic, and disabling psychiatric disorder with a lifetime prevalence of around 1%.

Numerous antipsychotics have been developed which all rely on the same underlying mechanism, namely interfering with dopamine receptors, and more specifically, dopamine D2 receptor antagonism. Therapies with phenothiazines, such as haloperidol and thiothixene, are effective but induce extra pyramidal symptoms (EPS) such as dystonia, muscle rigidity, tremor, and akathisia. Other medications, such as "atypical" or "second generation antipsychotics," may have less EPS, but are more prone to induce weight gain or metabolic side effects such as increased cholesterol or diabetes. Long-term effects, which develop after months to years of therapy, also include tardive dyskinesia. The adverse effects appear to be directly related to the dopamine D2 receptor blockade in the basal ganglia, whereas the antipsychotic effect of these compounds is dependent on reducing dopamine D2 mediated neurotransmission in the mesolimbic tracts (including the nucleus accumbens, stria terminalis, and the olfactory tubercle).

Clozapine is the most efficacious antipsychotic, yet is among the most prone to the aforementioned metabolic disturbances. It is also associated with an increased incidence of seizures and potentially lethal side effects of agranulocytosis and myocarditis. Consequently, there is tremendous unmet medical need for safer treatments that are more effective and have a broader spectrum of efficacy across multiple symptom domains.

ITI-007 (Lumateperone tosylate) is a new molecular entity with a unique pharmacologic profile that combines dose-related monoamine modulation with phosphorylation of intracellular signaling proteins (Lieberman et al 2016 : see attached). While it interacts with several targets that are common to some existing antipsychotics, its full actions are complex and unique (Snyder 2015). ITI-007 is a high-affinity serotonin 2A (5-HT2A) receptor antagonist with lower, but clinically relevant, affinity for other neurobiological targets, including D2 receptors. While 5-HT2A receptor antagonism in addition to D2 receptor antagonism has been the hallmark of atypical antipsychotics (Meltzer 1989), ITI-007 has a wider separation (sixtyfold) between its affinity for 5-HT2A receptors and D2 receptors than other antipsychotics, allowing full saturation of 5-HT2A receptors, even at modest levels of dopamine receptor occupancies (Snyder 2015). Moreover, unlike most other antipsychotics that are antagonists at D2 receptors both presynaptically and postsynaptically, and unlike aripiprazole and related compounds that are partial agonists at D2 receptors both presynaptically and postsynaptically, ITI-007 interacts with dopamine receptors in a unique way. At D2 receptors, ITI-007 is a presynaptic partial agonist and postsynaptic antagonist with functional mesolimbic/mesocortical selectivity (Snyder 2015). This allows for functional blockade of dopamine without increasing dopamine turnover and corresponds to antipsychotic efficacy without motor side effects (Snyder 2015). Above and beyond 5-HT2A and D2 receptor interactions, ITI-007 increases phosphorylation of mesolimbic GluN2B subunits of **N**-methyl-D-aspartate (NMDA) receptors (Snyder 2015). An increase in GluN2B increases synaptic NMDA activity via subcellular trafficking to plasma membranes (Goebel-Goody 2009). To the extent that a deficit in glutamatergic function contributes to schizophrenia symptoms (Laruelle 2005, Javitt 2007), indirect enhancement of glutamatergic NMDA function is predicted to reduce psychosis and improve cognitive function and negative symptoms. Although investigational therapeutics targeted solely at direct interaction with glutamate receptors or glycine transporters have not successfully translated into clear clinical benefit, it is recognized that the interaction between glutamate and dopamine modulation is important in schizophrenia (Schwartz 2012). At serotonin transporters, ITI-007 inhibits the serotonin transporter (Snyder 2015), an effect associated with many antidepressant drugs (13). ITI-007 lacks significant activity at many receptors (e.g., H1, muscarinic, serotonin 2C) that are associated with deleterious effects experienced with many other antipsychotics (i.e., clinically significant sleep induction, cognitive impairment, weight gain). Thus, by acting through serotonergic, dopaminergic, and glutamatergic signaling systems in a mechanistically and neuroanatomically selective

manner, ITI-007 represents a novel approach to the treatment of schizophrenia and other neuropsychiatric disorders.

In a recently published study (Lieberman 2016), ITI-007 was effective and safe for the treatment of schizophrenia and comparable with placebo with regard to safety.

This was a phase II randomized, double-blind, placebo-controlled, and active-controlled trial conducted at eight sites in the United States with randomization of 335 acutely psychotic adults with schizophrenia. ITI-007 (60 mg and 120 mg), placebo, and risperidone, included for assay sensitivity, were evaluated as monotherapy for 4 weeks.
The primary outcome measure was the Positive and Negative Syndrome Scale total score, with secondary analyses conducted on symptom subscales.

ITI-007 60 mg (p=0.017, effect size=0.4) and risperidone (p=0.013, effect size=0.4) demonstrated antipsychotic efficacy superiority over placebo on the primary end point. The results of secondary analyses reflected improvements in depressive symptoms by ITI-007 60 mg. ITI-007 120 mg did not separate from placebo, and had higher rates of adverse events. ITI-007 60 mg was well tolerated in this patient population, as evidenced by low discontinuation and adverse event rates, and were associated with a benign metabolic profile as evidenced by significantly lower levels of prolactin, fasting glucose, total cholesterol, and triglycerides than risperidone.

In not yet published studies, ITI-007 has been studied in 2 large, Phase 3 adequate, well-controlled studies in patients with exacerbated schizophrenia (Studies ITI-007-005, ITI-007-301, ITI-007-302). Efficacy of ITI-007 on the primary endpoint, with statistically significant greater reductions from baseline to study endpoint (Week 4) in PANSS total score compared to placebo, has been demonstrated in Study ITI-007-005 and Study ITI-007-301. In all 3 studies, progressive improvement across treatment days was seen in the PANSS total score from baseline to Week 4, with continued improvement from baseline seen between Weeks 4 and 6 in Study ITI-007-302. Supportive data from the Study ITI-007-301 provide evidence of pharmacological activity and clinical benefit from ITI-007 40 mg.

In conclusion, the mechanistically novel investigational drug ITI-007 was effective for the treatment of schizophrenia and comparable with placebo on safety measures in these trials. Secondary analyses indicated that ITI-007 improved schizophrenia symptoms and might have expanded therapeutic efficacy in comparison with current antipsychotic drugs.

The purpose of the present, open label study is to offer open label treatment to patients who either poorly respond or poorly tolerate approved medications. A discussion about clozapine will occur during the consent process. All this subjects will be made aware that clozapine may be the FDA approved treatment of choice for them.

In this open label study, subjects will be seen weekly for the first 4 weeks, biweekly for the second month and then monthly for total duration of six months. Subjects will be monitored by clinical and safety rating scales. Subjects will be required to show a CGI improvement scale of at least 3 after 3 months to remain in the study. Subjects not meeting this criteria will be assessed for the risks/benefits of continuing (see criteria for early discontinuation section for details).

Lieberman JA, Davis RE, Correll CU, Goff DC, Kane JM, Tamminga CA, Mates S, Vanover KE. ITI-007 for the Treatment of Schizophrenia: A 4-Week Randomized, Double-Blind, Controlled Trial. *Biological psychiatry* 2016; 79(12): 952-61.

Snyder GL, Vanover KE, Zhu H, Miller DB, O'Callaghan JP, Tomesch J, et al. (2015): Functional profile of a novel modulator of serotonin, dopamine, and glutamate neurotransmission. Psychopharmacology (Berl) 232:605–621.
Meltzer HY, Matsubara S, Lee JC (1989): Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin2 pKi values. J Pharmacol Exp Ther 251:238–246.
Goebel-Goody SM, Davies KD, Alvestad Linger RM, Freund RK, Browning MD (2009): Phospho-regulation of synaptic and extrasynaptic N-methyl-d-aspartate receptors in adult hippocampal slices. Neuroscience 158:1446–1459.
Laruelle M, Frankle WG, Narendran R, Kegeles LS, Abi-Dargham A (2005): Mechanism of action of antipsychotic drugs: From dopamine D(2) receptor antagonism to glutamate NMDA facilitation. Clin Ther 27 (suppl A):S16–S24.
Javitt DC (2007): Glutamate and schizophrenia: Phencyclidine, N-methyl-D-aspartate receptors, and dopamine-glutamate interactions. Int Rev Neurobiol 78:69–108.
Schwartz TL, Sachdeva S, Stahl SM (2012): Glutamate neurocircuitry: Theoretical underpinnings in schizophrenia. Front Pharmacol 3:195.
Meyer JH (2007): Imaging the serotonin transporter during major depressive disorder and antidepressant treatment. J Psychiatry Neurosci 32:86–102.

Specific Aims and Hypotheses

Concisely state the objectives of the study and the hypothesis or primary research question(s) being examined. There should be one hypothesis for every major study procedure or intervention. For pilot studies, it is important not to overstate the study's objectives. If there are no study hypotheses, describe broad study goals/aims.

To assess safety and efficacy of open label ITI-007 40-60 mg in patients who either poorly respond or poorly tolerate approved medications.

Inclusion/Exclusion Criteria

This section details your study sample(s) and addresses the requirement for risk minimization.
You may choose to divide your sample by population (healthy controls vs. subjects) or by procedure (subjects who will have an MRI) and then define different sets of criteria for each.

For each sample, create or insert a table to describe detailed criteria for study inclusion and exclusion and the method you will use to ascertain each criterion. The method of ascertainment may describe tests, scales and instruments. When relevant, indicate the level of training of the person who will make the assessment (e.g. clinical interview by a psychiatrist).

Inclusion/Exclusion Criteria needs to be numbered and listed in outline form (see Table template below).

CRITERION	METHOD OF ASCERTAINMENT
Inclusion:	
1. Age between 18-60	Self-report
2. DSM-V diagnosis of schizophrenia or schizoaffective disorder	SCID

3. Has capacity to provide informed consent	Physician evaluation
4. Medically stable for study participation	Medical history, physical examination and screening laboratory parameters, information from clinical team, review of medical record.
5. Judged clinically not to be at significant suicide or violence risk.	The Columbia Suicide Severity Rating Scale (C-SSRS); clinical interview
6. Inadequate response or tolerability to previous antipsychotic therapy, as defined by at least one of the following: prior clozapine failure, a PANSS >80 despite at least six weeks of current antipsychotic therapy, a CGI-I of 4 or greater after at least two six week trials of antipsychotics (retrospective assessment) or failure to tolerate an adequate dose of at least **two** antipsychotics (as defined by the PDR).	PANSS, CGI, medical history, including a discussion of the risks/benefits of clozapine

CRITERION	METHOD OF ASCERTAINMENT
Exclusion:	
1. Substance abuse within last 90 days	Physician evaluation/Urine toxicology screen
2. ECG abnormality that is clinically significant, known personal or family history of prolonged QTc (>500)	ECG reviewed by study cardiologist
3. Pregnancy, lactation, or lack of use of effective birth control	Instructions to study subject, pregnancy tests as per protocol and review of the medical record.
4. Presence or positive history of significant unstable medical or neurological illness (including any history of seizure disorder, dementia, traumatic brain injury, untreated syphilis, hepatitis B/C, renal insufficiency or mental retardation), history of HIV, neuroleptic malignant syndrome, serotonin syndrome or retinal degeneration or retinal pigmentation/deposits	Medical history, Ophthalmologic exam
5. Clinically significant abnormal laboratory tests, positive for hepatitis B or C or LFT's > 2x ULN, use of strong CYP3A4 inhibitors or inducers (appendix A).	Screening labs

6. History or presence of concomitant major psychiatric illness.	SCID
7. Use of other antipsychotic medications at baseline.	Physician evaluation
8. Use of another investigational medication in the previous 4 weeks.	Physician evaluation

Study Procedures

Provide a clear, concise narrative of study procedures with special attention to the subjects' involvement. Detail the overall study timeline and location of study procedures, list all interventions, assessments and interviews, estimate the duration of each procedure, provide dosing schedules, identify study personnel involved in each procedure, and provide credentials for relevant personnel. For complicated study designs, we strongly encourage attaching tables, flow-charts, and study algorithms.

Screening

Subjects must give written informed consent to participate prior to the initiation of any study procedure.

"Screening" is defined as the pre-study assessments to determine subject eligibility for entry into the study, made within 30 days of the first treatment visit. If screening examinations show any disqualifying abnormality, the subject will be excluded from participation in the study. In the case of laboratory abnormalities, the examination may be repeated up to one time. If the investigator wishes to include a subject with a laboratory value outside normal range, a comment (stating that these lab values are not clinically significant) must appear on the CRF.

Subjects will have a clinical interview to confirm that they have an eligible psychiatric diagnosis, a physical of the eyes, nose, ears, mouth, heart, lungs, abdomen, and nervous system, temperature, blood pressure, pulse, and breathing rate, height, weight, electrocardiogram, laboratory safety tests including hematology: hemoglobin, hematocrit, RBC count, RBC with differential counts and percentages, platelet count, activated partial thromboplastin time, prothrombin time (expressed as INR); Biochemistry: lipid panel, prolactin, CPK, magnesium, phosphorus, thyroid panel, amylase, lipase, sodium, potassium, total protein, albumin, total bilirubin, AST, ALT, alkaline phosphatase, gamma-GT, troponin, cholesterol, creatinine, BUN(urea-N), glucose, and uric acid; urinalysis: pH, glucose, protein, bilirubin, urobilinogen, nitrite, leukocytes and erythrocytes. A midstream urine sample (approx. 30 mL) will be obtained in order to avoid contamination and allow a proper assessment; drug screen for any substances of abuse (e.g., amphetamines, cocaine, morphines, marijuana) hepatitis screen: for hepatitis B surface antigen (HBsAg) hepatitis C will be based on HCV antibodies, serum pregnancy test: βHCG results will be collected for all women. Subjects will be asked medical/health history and will be assessed for any incidental medical symptoms or medical complaints such as headache; dizziness; nausea; sleepiness; visual, hearing, taste, or smell changes; urinary symptoms; chest, limb, back, joint, or abdominal pain; rashes; itching; and shortness of breath.

A discussion about clozapine will occur during the consent process, and the reasons for not beginning clozapine will be documented in the chart. All this subjects will be made aware that clozapine may be the FDA approved treatment of choice for them.

d. Study Procedures

Treatment period

In this open label study, subjects will be seen weekly for the first 4 weeks, biweekly for the second month and then monthly for total study duration of six months. Subjects will be monitored by clinical and safety rating scales (PANSS, side effects checklist, CGI severity and improvement, AIMS, BARS and SAS and C-SSRS: Biweekly for the 1st six weeks and then monthly), and will be required to show a CGI improvement scale of less than 4 after 3 months to remain in the study. Subjects not meeting this criteria will be assessed for the risks/benefits of continuing (see criteria for early discontinuation section).

Clinical labs (blood draws), Vitals, neurological exam, and ECG will be done Biweekly for the 1st six weeks and then monthly. Urine pregnancy tests will be done at screening, prior to 1st dose and then monthly.

Each visit is expected to take 1 to 2 hours.

Unscheduled clinical evaluations may occur at any time if deemed appropriate by the Investigator in order to follow up on safety and/or adherence or discontinue patient participation. An unscheduled assessment may be performed to evaluate for the presence of other antipsychotic drug(s).

Dosing: Patients will be instructed to take ITI-007 60 mg once daily in the evening (QPM). To improve tolerability, patients may be instructed to take the study treatment with food. Subjects may be up or down titrated within a range of 40 to 60 mg for efficacy or adverse effects. Any patient not tolerating the study treatment should be discontinued and started on standard of care medication. Study treatment may be discontinued at any time at the discretion of the Investigator or upon withdrawal of consent by the patient.

Ophthalmologic exam: Patients will receive an ophthalmologic exam by an ophthalmologist (for retinal degeneration or pigmentation/deposits) at baseline and at the conclusion of the study (6 months). The exam will include a standard evaluation, and an optical coherence tomography (OCT) and visual field exams

Concomitant Medications:
There is no washout or medication free period required for this study.

Subjects will not be permitted to remain on pre-study antipsychotics in this study. All pre-study antipsychotics will be discontinued by the study physician as clinically indicated (e.g. taper/abrupt discontinuation). Current antipsychotic medication will be down-tapered within the first 7 days of this treatment Period, with some flexibility allowed if clinically indicated. Subjects will be started on ITI-007 during the cross taper period, and no subjects will be left unmedicated because of this study.

All other medications, including other psychotropics, will be continued as clinically indicated. Subjects receiving serotonin modulating medications and benzodiazepines (and other sedating medications) will be monitored for excessive sedation at every visit with the side effect checklist.

Coordination with outside providers:

All subjects not receiving care at the Lieber Schizophrenia clinic will be asked to sign a release to contact their current community psychiatrist or therapist prior to enrollment. The community psychiatrist or therapist will be updated on the status of the subject prior to enrollment, at the beginning and end of each treatment period and upon study completion.

The outside provider will be provided with the 24 hour contact for the study physician. These updates will be documented in the study chart.

End of Participation

Care at termination of the study will transfer back to their previous providers.

If ITI-007 becomes commercially available during this study, the trial may be discontinued.

If subjects are hurt by the study their medical care will be provided, but their insurance will be billed for the care. Any relevant health information revealed during the study will be shared with the subject or their health care provider at the subject's request.

Criteria for Early Discontinuation

Define criteria that will be used to exit or drop subjects from the study. Indicate the time points when such criteria will be applied, and describe the rating instruments, parameters, and thresholds that will lead to a decision to terminate a subject's participation. In addition, explain procedures for managing subjects who are dropped from the protocol.

For treatment studies: To minimize risks to subjects, operationalized drop-out criteria should be defined so that subjects who worsen, or in some cases, fail to improve, are removed from the study and offered standard care. The threshold for drop-out should consider the level of risk associated with non-improvement for the specific disorder, the availability of alternatives, and the typical required duration of treatment. For example, emergence of suicidal intent, or psychosis, should prompt immediate clinical evaluation and withdrawal from the study.

After three months, we will conduct a clinical evaluation that considers both schizophrenia symptoms (CGI-I) and side effects and tolerability of the medication.

For symptom improvement, we will require a CGI-I of at least 3. We considered requiring a CGI of at least 2, but with the revised stricter I/C criteria, we feel that even a CGI of 3 is clinically meaningful. For subjects without a CGI-I of at least 3, they will be assessed for the risks/benefits of continuing. Medication tolerability and patient preference for continuing will be evaluated at this time, and subjects could remain in the study after 3 months with a CGI of 4 with improved tolerability. Subjects with a CGI-I of >4 will be removed.

Regardless of CGI status, all subjects will be verbally re-consented at three months, with a capacity assessment by an independent psychiatrist, and this evaluation will include a discussion of clozapine.

Stopping Rules

The study *stopping criteria* are well defined and are listed below:

A subject will not receive any further doses of the study drug should any of the following events occur:

- Any serious adverse event. If drug relationship can be ruled out (e.g., hospitalization due to traumatic injury), no decisions will be taken for the study as a whole.

- Liver function tests values above the following limits:

  - ALT or AST above 3xULN
  - Alkaline phosphatase or total bilirubin above 1.5Xuln

- Prothrombin time expressed as INR >1.3

- An increase of creatinine of more than 35% from the individual baseline value.

- Decrease in Hemoglobin by more than 2 mg/dL.

- QTc (Fridericia) longer than 500 msec or increasing by more than 60 msec from the individual baseline value confirmed by a second ECG after at least 5 minutes rest.

- Changes by more than 40 mm Hg in systolic blood pressure, by more than 20 mm Hg in diastolic blood pressure or blood pressure equal or above 180 mm Hg systolic or 110 mm Hg diastolic. Values should be confirmed by a second measurement after at least 5 minutes rest.

- Symptomatic orthostatic hypotension. Values should be confirmed by a second measurement after at least 5 minutes rest.

- Any other physical examination finding, change in vital signs, adverse event, or laboratory abnormality that in the opinion of the Investigator would cause an excessive risk if the subject continued the study.

A subject will be discontinued from the study and not receive any further dose of study medication if a CGI-improvement (CGI-I) score of 6 or 7 or a C-SSRS of 4 or 5 at anytime.

Blood and other Biological Samples

Describe how the sample will be used and indicate, when relevant, the amount of the sample. The IRB wants to know that the sample is sufficient for the purposes of the study, but that sampling is limited to what is minimally necessary.

If you've indicated that you intend to store a sample for future use, indicate where the sample will be stored, how long the sample will be stored, and to what purposes the sample will eventually be put. Check the IRB website at http://irb.nyspi.org/irbdnn/Policies/GeneticResearch/tabid/96/Default.aspx for specific guidance and additional information about future use of DNA samples.

Approximately 200 mL of blood (equal to 13.5 tablespoons) will be drawn during the entire study on different days, no more than one tablespoon at a time.

Assessment Instruments

List all assessment instruments, indicate who will administer them, and provide an estimate the duration of each. The IRB wants to know that assessments instruments are appropriate measures for the purposes of the study and are no more burdensome than is necessary. The IRB will consider the burden of assessment instruments (in terms of time, sensitivity of material, etc.) in the risk/benefit analysis. Please attach copies or otherwise provide all non-standard instruments.

CGI-S/CGI-S: 5 minutes

SCID: 1 hour

PANSS: 30 minutes

C-SSRS ratings:10 minutes

BARS: 5 minutes

SAS: 5 minutes

AIMS 5 minutes

Research Related Delay to Treatment

Research involving participants who are in need of treatment invariably involves delay to care, and this delay is associated with risk. Scheduling of procedures must be carefully organized to minimize delay. Other delay must involve only that minimally necessary to accomplish the aims of the research while respecting subject well- being and safety. Describe the delay, by virtue of research participation in this study, before a participant can receive treatment of known efficacy or standard care routinely offered in the community.

This is an investigational product that is not a proven effective treatment, and if you complete the full study, it will be at least six months before a subject will receive FDA approved treatment. Patients will be considered for removal if there is no benefit after 3 months.

Clinical Treatment Alternatives

Describe what other treatment or assessment options are available to subjects who do not participate in research.

Subjects have the option to be on other available antipsychotic medications outside the study. The consent process will include a discussion of clozapine.

Risks/Discomforts/Inconveniences

"Risk" is a broad term used to convey the potential for harm, burden, and inconvenience related to research participation. Use this section to provide a comprehensive description of foreseeable physical, psychological, social, interpersonal, and economic risks introduced by the research. Include the source of the information. Consider both the probability and magnitude of harm and its impact. Describe the foreseeable harms associated with the research (untoward effects of a medication) and those related to delay to individualized treatment. Include data from the literature, and local data, if available, on risk rates and subject experiences with research procedures. Describe procedures in place to minimize risk. In general, please create a numbered list of risks/categories of risk, and in general put the list in the order of significance or level of risk, the most significant risks first followed by others.

In addition to specific risks of ITI-007, subjects may worsen from discontinuing their baseline antipsychotics.

Safety and Efficacy in Humans

ITI-007 is an experimental drug which is not approved by the FDA. In research studies already conducted with ITI-007 in the U.S. and in other countries, over 1,500 people have received ITI-007. This includes approximately 700 people at a dose of at least 60 mg in ongoing studies and approximately 100 people at 120 mg.

People have not been exposed to ITI-007 for longer than 42 days in completed studies. A one-year study is ongoing but not complete.

The most frequent side effects observed with ITI-007 administered up to 42 days include:

- Headache
- Tiredness or sleepiness
- Dizziness or lightheadedness

Summary of side effects:

Oral doses up to and including 140 mg once daily for 5 days, up to and including 120 mg administered once daily for 28 days, and up to and including 60 mg once daily for 6 weeks have been administered to patients with schizophrenia. Doses of 9 mg once daily for 7 days have been administered to patients with dementia. ITI-007 has been well tolerated in across this broad range of doses.

A total of 1431 subjects have been exposed to ITI-007 in the completed clinical trials; 763 of these 1431 subjects (53.3%) have experienced at least 1 TEAE. The most commonly reported TEAEs (reported in ≥5% of subjects) have been headache, somnolence, sedation, nausea, dry mouth, and dizziness (Table).

Table: Treatment-Emergent Adverse Events Reported in 5% or More of Subjects in Completed Clinical Studies

MedDRA Preferred Term	Subjects Exposed to ITI-007 (N=1431)
	n (%))
At least 1 treatment-emergent adverse event	763 (53.3)
Headache	201 (14.0)
Somnolence	165 (11.5)
Sedation	83 (5.8)
Nausea	81 (5.7)
Dry mouth	79 (5.5)
Dizziness	72 (5.0)

MedDRA, Medical Dictionary for Regulatory Activities.

Additional adverse events that have been reported in ≥2% of subjects include constipation (3.5%), diarrhea (3.4%), blood CPK increased (3.1%), insomnia (2.5%), dyspepsia (2.4%), vomiting (2.2%), and orthostatic hypotension (2.0%).

Most TEAEs have been non-serious and have not led to discontinuation of ITI-007. Of the 1431 subjects who have been exposed to ITI-007 in completed clinical trials of patient populations, 57 subjects (4.0%) have discontinued treatment with ITI-007 because of adverse events. Adverse events that resulted in discontinuation from the study were considered related to ITI-007 in only 2.2% (31 of 1431) of the subjects.

No deaths have occurred during the clinical studies. Nonfatal SAEs have been reported in 1.7% (25 of 1431) of subjects after administration of ITI-007. Only 1 SAE (single episode of convulsion) in a patient with schizophrenia was considered related to ITI-007, for an overall frequency of drug-related SAEs of 0.1%. The patient who experienced the convulsion had preexisting risk factors for seizures and was inappropriately randomized into the study (i.e., protocol violation) based upon an incomplete medical history and inaccurate self-reports of convulsions by the patient at screening.

Overdose

Previous clinical trials have not evaluated ITI-007 at doses greater than a single dose of 40 mg or a multiple dose of 30 mg administered once daily for 7 days in healthy volunteers or greater than a multiple dose of 140 mg in patients with schizophrenia. In case of an overdose that exceeds the previously studied doses, the patient should be closely monitored in a hospital setting with sufficient attention to the symptoms and the clinical course. Supportive measures may include gastric lavage and respiratory and cardiovascular support as needed.

Drug Abuse and Dependency

No formal studies have been conducted to assess the drug abuse or dependency potential of ITI-007 in humans. However, available data from clinical trials do not suggest that ITI-007 has the potential for drug abuse or dependency. Additionally, nonclinical data have indicated that neither ITI-007 nor ITI-131 (IC200131) produces tolerance or sensitization in male rats during repeated administration or a syndrome of behavioral and/or physical dependence on abrupt withdrawal (Study# RS1526). Neither ITI-007 nor ITI-131 (IC200131) was self-administered by rats, suggesting that ITI-007 and IC200131 are highly unlikely to be abused in a recreational manner by humans (Study# RS1545).

Other Potentially Clinically Relevant Information

Side effects in Canine studies:

Toxicology studies of up to 6 months treatment duration have been conducted in rats and up to9 months in dogs. The available preclinical data for ITI-007 indicate that early symptoms are decreased activity in rats and decreased activity and changes in demeanor in dogs. These behavioral disturbances are reversible without intervention and wane with increasing time after administration of ITI-007, usually within 4 to 6 h. Adverse central nervous system histopathology that included axonal degeneration and perivascular cuffing occurred only in dogs after long-term repeated administration at high levels of exposure; these findings may not be relevant to humans given the striking differences in metabolism between dogs and humans. The major pathway of metabolism of ITI-007 in dogs in oxidation, whereas in humans it is direct glucuronidation and a combination of ketone reduction and glucuronidation. Nonclinical findings must be interpreted considering the quantitative differences in metabolism among species, particularly between dogs and humans. Nonetheless, in dogs, premonitory clinical signs of decreased activity, motor impairment, and tremor occurred early in administration and at lower doses than any adverse CNS histopathology; therefore, it is recommended that administration beyond 6 weeks treatment duration of ITI-007 be stopped upon signs of motor impairment or tremor.

Rodent studies

Based on neurohistopathology findings in the rodent (rats and mice) 104-Week Oral Gavage Carcinogenicity Studies with ITI-007 studies (see page 71-73 in the IB), the FDA has requested that the study be limited to six months and that study participants must receive an ophthalmologic exam (for retinal degeneration or pigmentation/deposits) at baseline and at the conclusion of the study (6 months). These neurohistopathology findings included sciatic nerve degeneration or edema, axonal degeneration in the spinal cord, infiltrates of pigmented macrophages (liver, lung, and brain), and retinal degeneration at doses (>10 mg/kg/day) more than double both the NOAEL level (5 mg/kg/day) and the equivalent human doses. None of these issues were noted in human studies.

Genetics: ITI-007 showed potential to be toxic to genetic material (genes or DNA). When tested in two different animal studies, ITI-007 did not cause toxicity to genes and was well tolerated. Please see section 4.3.6 of the IB for full details.

Reproductive safety: Although a safety margin has been established in reproductive toxicity studies, at this time in the development process, ITI-007 should not be administered to pregnant and lactating females.

Female subjects in this study must uses a highly effective methods of birth control:
Methods of birth control considered to be effective include contraceptive implants, injectables, oral contraceptive pills, double barrier methods (condom with spermicide or a diaphragm with spermicide), some intrauterine devices (IUD), sexual abstinence, vasectomized partner. Subjects will be instructed to use a combination of at least two contraceptive methods with your partner during the study to ensure you do not become pregnant while taking the study medication and up to 3 months after the last dose of the study medication.

The study medication may be passed in breast milk from mother to infant. Subjects will be instructed to not breast-feed while taking part in the study for at least 3 months post study.
Male subjects with a partner that is of childbearing age must use contraception during the study and up to 3 months after the last dose of the study.

CPK: In previous clinical studies with ITI-007 there have been instances of increased blood CPK levels. However, patients with increased blood CPK levels have been noted in all treatment groups, including placebo, during the screening period, study treatment period, and stabilization period. In most instances, these levels decreased while patients remained on study treatment. Patients were asymptomatic and, when tested, CPK elevations were associated with the skeletal muscle (CPK-MM) and not with the cardiac muscle (CPK-MB) isoform. Although these increases in CPK levels were notable, they are not uncommon in this patient population and do not appear associated with clinical signs and symptoms. Similar events have been described for other antipsychotic medications.

Dosing: Although administration with food is not necessary for safety, the frequency of adverse events decreased with administration of ITI-007 as a formulated capsule with food. Administering the formulated capsule with food lowers the maximal plasma concentrations of ITI-007 without changing the area under the curve, thereby maintaining overall exposure and improving tolerability.

Methods to Protect Confidentiality

Describe the data management plan and the methods you will employ to protect subject privacy and the confidentiality of research data. The section should detail how information will be collected, recorded, coded, stored, transmitted, and as applicable, shared with other investigators so as to minimize risks related to breach of confidentiality. Confirm that identifiers are removed, to the extent possible, from research data, and explain if there are links between subject identity and research data, or if the data is anonymous. Also, indicate where the data is stored, who is responsible for its safekeeping, and who has access to subject identity and codes, if any, which cross-link research data and subject identity. Confirm that identifiable data is not collected, stored, or transmitted by mail, fax, on removable drives, laptops, or via the internet without proper protections, e.g. encryption.

Describe methods to protect confidentiality
Blood and urine samples, behavioral assessments, and all other clinical/neuropsychological data will be obtained from the subjects for specific research purposes. Data will include self-report information, observer records, and physiological and behavioral information collected during test sessions. Each subject is assigned a unique ID and all data related to that subject is entered at the site by the site data entry personnel.
Study information will be collected at NYSPI, and entered into a secure electronic database stored at NYSPI.

Direct Benefits to Subjects

Describe only benefits to individual subjects that are likely to accrue during the study itself. Do not include subject compensation or treatment to be provided at the end of the study, as these do not figure into the IRB's risk benefit considerations. Do not describe diagnostic and evaluation components unless subjects receive clinical feedback. Do not describe the anticipated scientific benefits of the research. Some studies offer no direct benefit to subjects.

Participation in this study may or may not help with your symptoms.

References

See main protocol