

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**209500Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



IND 079690

**MEETING MINUTES**

Intra-Cellular Therapies, Inc.  
Attention: Kimberly E. Vanover, PhD  
Senior Vice President, Clinical Development  
430 East 29<sup>th</sup> Street  
Alexandria Center for Life Science, Suite 900  
New York, NY 10016

Dear Dr. Vanover:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ITI-007 (lumateperone).

We also refer to the meeting between representatives of your firm and the FDA on March 7, 2018. The purpose of the meeting was to discuss the format, timing, and clinical content of the proposed NDA for ITI-007.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Nam (Esther) Chun, Regulatory Project Manager at [nam.chun@fda.hhs.gov](mailto:nam.chun@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** March 7, 2018, 12:00PM to 1:30PM (EST)  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1313  
Silver Spring, Maryland 20903

**Application Number:** 079690  
**Product Name:** ITI-007 (lumateperone)  
**Indication:** Treatment of schizophrenia  
**Sponsor/Applicant Name:** Intra-Cellular Therapies, Inc.

**Meeting Chair:** Mitchell Mathis, MD  
**Meeting Recorder:** Nam (Esther) Chun, PharmD

**FDA ATTENDEES**

Mitchell Mathis, MD	Director, Division of Psychiatry Products (DPP)
Tiffany Farchione, MD	Deputy Director, DPP
Javier Muniz, MD	Clinical Team Leader, DPP
David Millis, MD	Clinical Reviewer, DPP
Praveen Balimane, PhD	Clinical Pharmacology Reviewer, OCP
Ikram Elayan, PhD	Pharmacology/Toxicology Supervisor, DPP
Violetta Klimek, PhD	Pharmacology/Toxicology Reviewer, DPP
Laura McGhee, PhD	Pharmacology/Toxicology Reviewer, DPP
Semhar Ogbagaber, PhD	Biometrics Reviewer, Division of Biometrics I (DBI)
Peiling Yang, PhD	Biometrics Team Leader, DBI
Jovita Randall-Thompson, PhD	Controlled Substance Staff
Dhananjay Marathe, PhD	QT-Interdisciplinary Review Team Lead, OCP
Nam (Esther) Chun, PharmD	Regulatory Project Manager, DPP

**SPONSOR ATTENDEES**

Kimberly Vanover, PhD	Senior Vice President, Clinical Development
Robert Davis, PhD	Senior Vice President and Chief Scientific Officer
Andrew Satlin, MD	Chief Medical Officer
Jelena Saillard, MS, MBA	Senior Director, Clinical Operations
Greg Hileman, PhD	Senior Director and Principal Regulatory Scientist

**1.0 BACKGROUND**

ITI-007 is an atypical antipsychotic agent under development for the treatment of schizophrenia. It acts as a pre-synaptic partial agonist at dopamine D<sub>2</sub> receptors, post-synaptic antagonist at D<sub>2</sub> receptors, antagonist at serotonin 5-HT<sub>2A</sub> receptors, inhibitor of the serotonin transporter, and phosphorylator of glutamatergic N-methyl-D-aspartate (NMDA) receptors. The Sponsor suggests that this pharmacologic profile allows the drug to have antipsychotic, antidepressant, and sleep-enhancing qualities, combined with a favorable side effect profile. The most frequent treatment-emergent adverse events (AEs) in previous studies have been headache, somnolence or sedation, and dizziness.

The Sponsor plans to submit data from the following three trials in support of an NDA application. For all trials, the primary efficacy endpoint is the change from baseline in the PANSS total score.

<b>Study</b>	<b>Treatment Groups</b>	<b>Efficacy Results</b>	<b>Safety Results</b>
ITI-007-005	<ul style="list-style-type: none"><li>• ITI-007 60 mg</li><li>• ITI-007 120 mg</li><li>• risperidone 4 mg</li><li>• placebo</li></ul>	The ITI-007 60 mg group and the risperidone 4 mg group separated from placebo. The ITI-007 120 mg group did not separate from placebo.	The incidence of neuromuscular and metabolic adverse events for the ITI-007 60 mg group was similar to that of the placebo group.
ITI-007-301	<ul style="list-style-type: none"><li>• ITI-007 40 mg</li><li>• ITI-007 60 mg</li><li>• placebo</li></ul>	Both the ITI-007 40 mg and the ITI-007 60 mg group separated from placebo. The separation was statistically significant for the 60 mg group.	The incidence of neuromuscular and metabolic adverse events for the ITI-007 60 mg group was similar to that of the placebo group.
ITI-007-302	<ul style="list-style-type: none"><li>• ITI-007 20 mg</li><li>• ITI-007 60 mg</li><li>• risperidone 4 mg</li><li>• placebo</li></ul>	Neither the ITI-007 20 mg group nor the ITI-007 60 mg group separated from placebo. The risperidone 4 mg group did separate from placebo.	The incidence of neuromuscular and metabolic adverse events for the two ITI-007 groups was similar to that of the placebo group.

The Sponsor submitted a letter requesting Preliminary Breakthrough Therapy Designation Request Advice on November 4, 2016. At that time, DPP had concerns about the plan for long-term human exposure due to neurotoxicities observed in the non-clinical studies in dogs. In a teleconference on November 15, 2016, we informed the Sponsor that we felt the BTDR request was premature and that we would not approve proposed research protocols that would involve human exposure to ITI-007 beyond a maximum six-week duration. Over the subsequent months, the Sponsor submitted additional non-clinical data indicating that the metabolic pathway for ITI-007 in dogs is distinctive from that in humans, and that the neurotoxicity observed in dogs is correlated with the formation of aniline metabolites that do not appear to be formed in humans. The data supports the hypothesis that the neurotoxicity observed in dogs is not relevant to humans. In a letter dated August 17, 2017, we informed the Sponsor that they had addressed our concerns sufficiently such that Study ITI-007-303, with exposure of human subjects to ITI-007

for a duration of up to one year, could be allowed to proceed provided that blood samples collected at each visit must be assessed for any circulating level of aniline metabolites, to ensure that aniline metabolites remain undetectable throughout the duration of the study.

In September 2017, the Sponsor submitted requests for both Breakthrough Therapy Designation and Fast Track Designation. On November 13, 2017, the BTDR was denied, and the FTDR was granted.

The Sponsor has requested a pre-NDA meeting. ITI-007 is an NME, and the NDA will be a 505(b)(1) submission. The objective of the meeting is to review and reach agreement with the Division on the format, timing, and clinical content of the proposed NDA.

FDA sent Preliminary Comments to Intra-Cellular Therapies on March 2, 2018.

## 2. DISCUSSION

### 2.1. Clinical/Statistical/Safety

***Question 1:*** The integrated summary of safety (ISS) will include analysis of different tiers of pooled safety data from all completed studies of ITI-007.

Data will be pooled in the following Tiers:

<b>Tier</b>	<b>Description</b>	<b>Datasets</b>
Tier 1	Three large, well-controlled efficacy studies in subjects with schizophrenia	ITI-007-005 ITI-007-301 ITI-007-302
Tier 2	All subjects with schizophrenia	ITI-007-002 Cohorts 4-9 ITI-007-005 ITI-007-006 ITI-007-008 ITI-007-009 Part 1 ITI-007-012 ITI-007-014 ITI-007-301 ITI-007-302 ITI-007-303 <sup>1</sup>
Tier 3	All subjects	All studies
Tier 4	Healthy volunteers	ITI-007-001 ITI-007-002 Cohorts 1-3 ITI-007-003 ITI-007-009 Part 2

		ITI-007-010 Group D ITI-007-011 Groups B and E ITI-007-013 ITI-007-016 ITI-007-200 Part A
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<sup>1</sup>The ITI-007-303 open-label safety study is being conducted in two parts. The first part, conducted under protocol Version 3.0, includes exposures up to 6-week treatment duration and these data will be pooled with data from other short-term treatment studies. The second part, conducted under protocol Version 4.0, includes exposures up to 1-year treatment duration and these data will be summarized in separate tables and described in the text of the ISS.

The data domains to be pooled across short-term treatment studies include disposition, demographics, exposure, concomitant medications, adverse events, laboratory data, vital signs, electrocardiogram data, and other safety endpoints. Safety analyses will be performed on the grouping of all studies, as well as on other groupings of studies based on similar study characteristics (e.g., normal volunteers vs patients, controlled vs uncontrolled). Safety analyses will examine possible effects of age, sex, race and other relevant characteristics on the safety of ITI-007.

The integrated summary of efficacy (ISE) will include analysis of pooled efficacy data from the two positive studies (Studies ITI-007-005 and ITI-007-301), as well as pooled efficacy data from all three controlled studies (Studies ITI-007-005, ITI-007-301, and ITI-007-302). Efficacy analyses will examine possible effects of age, sex, race, and other relevant characteristics on the efficacy of ITI-007.

The draft statistical analysis plans for the ISE and ISS are provided in Appendix B and Appendix C, respectively.

Does the FDA agree with the proposed plan for the pooling of data for the ISS and ISE as described in the meeting package and the draft ISS and ISE statistical analysis plans?

***FDA Response to Question 1:*** *The proposed plan for pooling data for the ISS and ISE appears acceptable. Because of the exploratory nature of ISE, we have no objection to the draft ISE statistical analysis plan, but we may ask for additional exploratory analyses during the NDA review.*

*It is not clear if you also plan to include “study” as a factor in the model for ISE. If not, please include it as an additional exploratory meta-analysis wherever appropriate.*

***Discussion:*** *No further discussion.*

***Question 2:*** Five of the 18 ITI-007 clinical studies did not use SDTM and ADaM data format as the source for producing the tables and listings used in the clinical study reports. Specifically, Studies ITI-007-001 (Phase 1 single ascending dose study in healthy volunteers, N=40), ITI-007-002 (Phase 1 multiple ascending dose study with 5 days treatment duration in healthy volunteers,

N=24, and patients with schizophrenia, N=45), ITI-007-003 (Phase 1 single dose brain receptor occupancy study in healthy volunteers, N=16), and ITI-007-004 (Phase 2 single dose cross over study in patients with sleep maintenance insomnia, N=19) did not use SDTM and ADaM. Additionally, Study ITI-007-200 (Phase 1b/2 multiple ascending dose study with 7 days treatment duration in healthy volunteers, N=27, and patients with dementia, N=5) used SDTM, but not ADaM. We propose to submit datasets for these studies in legacy format. We will include annotated case report forms (aCRF), a define.pdf and will include a trial summary data set (TS) to allow confirmation that the study start was prior to 17 December 2016. For the remaining studies, including all adequate and well controlled studies which will be relied on to establish safety and efficacy, we will submit data in SDTM/ADaM format.

Does the agency agree to the proposed approach for submission of study data?

**FDA Response to Question 2:** *We have no objection, but the legacy data should be in the .xpt format.*

**Discussion:** *No further discussion.*

**Question 3:** Safety narratives have been prepared for serious adverse events and for non-serious adverse events leading to study medication discontinuation. These narratives are presented in the clinical study reports.

Does the FDA agree with the proposed approach to the presentation of safety narratives?

**FDA Response to Question 3:** *We agree with the proposed approach for the presentation of safety narratives.*

**Discussion:** *No further discussion.*

## 2.2. Regulatory

**Question 4:** To facilitate the Agency's review, and under the provision of the Fast Track Designation, ITI proposes a rolling NDA submission and seeks agreement on the schedule for submission.

The proposed timelines for a rolling NDA submission would include Modules 3 and 4 with supporting information from Module 2 and a partial submission of Module 5 to be submitted in April 2018. Module 1 and the remainder of Module 5, with supporting information from Module 2, will be submitted in mid-2018 to complete the NDA submission. The 1-year exposure data from the long term ITI-007-303 safety study is planned to be submitted in the 120-day safety update.

Consistent with the FDA Guidance for Industry: Premarketing Risk Assessment (March 2005), more than 2,000 individuals have been exposed to ITI-007 and will be included in the safety

assessments at the time of the completion of NDA submission. The long-term safety study ITI-007-303 will be ongoing at the time of the NDA submission and long-term safety data will be summarized in the ISS with datasets provided separately. Data from an anticipated 300 subjects exposed for a minimum of 6 months are expected to be available mid 2018 and will be submitted with Module 5 at that time, which will complete our rolling submission of the NDA. Data from an anticipated 100 subjects exposed for a minimum of 1 year are expected to be available late 2018 and will be included in the 120-day safety update.

<b>Module</b>	<b>Proposed Timing for Submission</b>
Module 1 – Administrative Information and Prescribing Information	<b>Mid 2018</b>
Module 2 – Common Technical Document Summaries	<b>April 2018</b> - Including Sections 2.2, 2.3, 2.3S, 2.3P, 2.3R, 2.4, and 2.6 in support of submission of Modules 3 and 4, and including Sections 2.5 and 2.7.1, 2.7.2, 2.7.3, 2.7.5, and 2.7.6 in support of clinical efficacy and clinical pharmacology in Module 5. <b>Mid 2018</b> – Section 2.7.4 in support of clinical safety in Module 5
Module 3 – Quality	<b>April 2018</b>
Module 4 – Nonclinical Study Reports	<b>April 2018</b>
Module 5 – Clinical Study Reports	<b>April 2018</b> – Clinical study reports and ISE <b>Mid 2018</b> – ISS with 6-month exposure data

- a. Does the FDA agree with the proposed approach for a rolling NDA submission and the proposed timelines for submission?
- b. Clinical study reports and the ISE will be completed and available for submission in April 2018. The 6-month exposure data will become available to complete the NDA submission mid 2018. Does the FDA agree with partial submission of Module 5, including clinical study reports and the ISE, in April 2018 and the completing of the submission of Module 5 with the 6-month exposure data for the ISS in mid 2018?
- c. According to FDA Guidance, for an NDA based on a small number of studies with similar design, it is possible that the Summary of Clinical Efficacy (SCE) could serve as the ISE. Does the FDA agree that the SCE can serve as the ISE for this NDA?

**FDA Response to Question 4:**

- a. *Generally, the Agency accepts for submission only a complete section of an NDA for rolling review and a section of an NDA should be submitted for review in a form adequate to have been included in a complete NDA submission. Therefore, we do not agree with your proposal to submit part of Modules 2 and 5 in April, 2018, and the remainder of those modules in mid-2018. Please refer to [Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics](#) for further information regarding rolling review.*

*In addition, please note that a user fee payment is required upon receipt of the first module submission as stated in section 736 of the FD&C Act, before we may commence review of any portion of an application.*

- b. No, we do not agree with your proposal. Please see our response to Question 4a.*
- c. We do not agree that the Summary of Clinical Efficacy could serve as the ISE. The three studies employed different designs. Each study tested a different set of ITI-007 doses. Two studies used risperidone as an active comparator, and one study did not. We request submission of an ISE as part of the NDA application.*

**Discussion:** *The Agency clarified that Modules 3, 4, and 5 should be submitted only when they are complete. The corresponding summaries for Module 2 should be submitted when the completed modules 3/4/5 are submitted.*

**Question 5:** A summary of the chemical, preclinical, and clinical data used to assess the abuse potential of ITI-007 is provided in Section 1.6.2.11. Based on these data, ITI has concluded that ITI-007 does not have abuse potential and should not be scheduled as a controlled substance. Currently no marketed drugs indicated for the treatment of schizophrenia are scheduled under the Controlled Substance Act, 1970.

Does the FDA agree that the package for the assessment of abuse potential for ITI-007 is complete to support NDA submission?

**FDA Response to Question 5:** *The studies you have conducted and described in your briefing package appear to comprise an adequate abuse potential assessment for our review under an NDA submission. However, ensure that your NDA submission addresses the following items and concerns:*

- 1. For the dependence study (Report RS1526) and self-administration study (Report RS1545) conducted in rats, and considering differences in metabolism of ITI-007 in rats and humans, justify the appropriateness of your selected doses and species selection for these studies. All preclinical abuse-related studies (i.e., dependence, drug discrimination, and self-administration studies) should have been performed using doses that produce PK measures comparable to the lowest to be marketed therapeutic dose and that also explore higher doses, i.e., that produce plasma levels that are multiples (2 to 3 times that) of highest therapeutic dose, as described in the [2017 Guidance for Industry: Assessment of Abuse Potential of Drugs](#).*
- 2. You should report all CNS- or abuse-related adverse events (AEs) from your clinical studies and provide detailed narratives for these AEs in accordance with recommendations in section V.B. of the 2017 Guidance mentioned above. Also, you should provide the list of*

*terms that prompt these reports (including abuse-related AE terms such as euphoria, impaired cognition, attention, mood, psychomotor effects, inappropriate affect, patient dropouts, overdoses, misuse, lost or unaccounted for medication, and unjustified dose increases). Where narratives are provided, they should include time of onset, and duration of the event, dose of drug taken, severity, and outcome. If available, pharmacokinetic values for each individual subject who experienced these AEs should be provided to understand if there is a temporal correlation between drug plasma levels, and AEs.*

3. *You should also report all possible cases of abuse (subjects taking the drug for non-therapeutic purposes, e.g., for psychoactive effects such as high or euphoria) occurring in your clinical trials. If collected by the investigator, information should include explanations from the subjects when there are drug accountability discrepancies. Towards this end:*
  - i. *Provide data in tabular form for all reports of abuse, overuse, lost/stolen/missing or unaccounted product that occurred in clinical trials. These data should include study number, and type of study, subject ID number, narratives, case description, and details.*
  - ii. *Provide narratives for cases where the patients drop out from studies for reasons that might be coded as “protocol violation”, “lack of efficacy” (to capture aberrant behavior in patients who drop out of the study supposedly due to lack of efficacy), “lost to follow up”, “non-compliance to study medication or procedures,” “over compliance” or for “other.” Case reports should be provided separately.*
  - iii. *Report any use of the investigational formulation by individuals other than the patients (family member, health care practitioner, etc.).*

**Discussion:** *No further discussion.*

**Question 6:** Based on the safety data of the pivotal Phase 2 and Phase 3 studies (Studies ITI-007-005, ITI-007-301, and ITI-007-302) and other clinical studies, ITI does not believe that a Risk Evaluation and Mitigation Strategy (REMS) is warranted. ITI proposes to use routine postmarketing pharmacovigilance and labeling to manage the identified and potential risks for ITI-007.

Does the FDA agree that ITI-007 for the treatment of schizophrenia, with a routine postmarketing pharmacovigilance process in place, adequately assesses potential patient risks for this patient population and an additional REMS program is not required?

**FDA Response to Question 6:** *On face, we agree. However, this will be a matter of review.*

***Discussion:*** *The Agency noted that the data to be submitted for assessment of abuse potential, as described in Question 5, will be part of our review to assess whether a REMS will be required.*

***Question 7:*** On 20 September 2017, ITI made a request for a waiver of the need to conduct a Thorough QT (TQT) study. On 9 January 2018, ITI submitted additional information to the Division based on data from clinical studies ITI-007-005, ITI-007-301, and ITI-007-302. ITI submitted this information in response to email correspondence from the Division dated 30 November 2017. A summary of these data are provided in Section 1.6.2.12. The status of the TQT waiver may be resolved by the time of this pre-NDA meeting.

If a waiver is not granted, does the FDA agree that ITI may submit any additional data it is required to develop, to evaluate QT effects, in the 120-day safety update to the NDA?

***FDA Response to Question 7:*** *We do not agree that the submitted data is sufficient for us to grant a TQT waiver. We also do not agree with using the 120-day safety update to the NDA to submit the QT safety data that we will need to review to assess the NDA application as ready for filing.*

*The adequacy of a study to act as a substitute for a TQT study depends on whether the highest studied dose provides at least a 2-fold exposure margin over the highest clinically relevant exposure. None of the three clinical studies (ITI-007-005, ITI-007-301, and ITI-007-302) in which ECGs were collected following highest oral dosing of up to 120 mg q day of ITI-007 satisfy this exposure margin requirement. Furthermore, the exposures studied in these trials do not cover the highest clinically relevant exposures (three-fold higher exposures corresponding to strong CYP3A4 inhibition in drug-drug interaction with itraconazole) for the potential therapeutic dose of 60 mg q day. The Sponsor observed 91 data points from 69 patients with exposures greater than three-fold higher than the mean exposures for the potential therapeutic dose of 60 mg. However, we consider the exposure margin in the context of mean exposures, and not individual exposures. We will require completion of a TQT study in order to consider the NDA application complete and suitable for filing.*

***Discussion:*** *The Sponsor is planning to complete a TQT study and asked to clarify our preferred timing for submission of the study results. Our expectation is for submission of the TQT results as part of the NDA filing.*

***Question 8:*** The proposed table of contents of the ITI-007 electronic Common Technical Document (eCTD) is provided as Appendix A, including all nonclinical and clinical reports as well as datasets to be submitted with the NDA.

Does the FDA agree that the overall proposed table of contents and organization of the NDA to be submitted in eCTD format are acceptable?

***FDA Response to Question 8:*** *The format for the proposed table of contents appears acceptable.*

**Discussion:** *No further discussion.*

**Additional Clinical Pharmacology Comments**

- *Please confirm that the final “to-be-marketed” formulation was used in all the pivotal efficacy/safety studies as well as the key clinical pharmacology studies (i.e., food-effect study, strength proportionality study etc.)*

[REDACTED] (b) (4)

The to-be-marketed formulations for [REDACTED] (b) (4) 42 mg capsules (equivalent to [REDACTED] (b) (4) 60 mg of the tosylate salt, [REDACTED] (b) (4)) are the same as the formulations used for pivotal efficacy/safety studies and key clinical pharmacology studies except for capsule colors and imprinting (ref. IND 79,690 SN0091).

- *Please clarify if the planned strengths are all compositionally proportional. Otherwise, you may need to conduct an in vivo strength proportionality/equivalency study.*

ITI-RESPONSE:

[REDACTED] (b) (4)

- *We recommend the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be consistent with FDA Guidance for Industry, “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” (available at <https://go.usa.gov/xn4qB>). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.*
- *Keeping in mind the Advice Letter issued during the development stage (based on the potential role of metabolite(s) towards toxicity in a non-clinical species), please plan to submit a concise but comprehensive package supporting all the data/evidence/hypothesis that the toxicity is limited to the non-clinical species and not prevalent in the clinic. Please present this detailed analysis/justification (including, but not limited to- the species difference in biotransformation, comprehensive comparative metabolite exposures e.g., anilines, across species, tables listing the key drug-related moieties in plasma and urine across species, and all other relevant information etc.) in the Clinical pharmacology section of the NDA submission.*

**Additional Nonclinical Comments**

*We would like to reiterate that you need to perform a careful evaluation of the brain from rats sacrificed at the end of the rat carcinogenicity study for any possible neurotoxicity. If any drug-related neurotoxicity findings are seen, you need to determine whether these findings are related to the lysosomal accumulation of the drug seen in rats and dogs in different organs including the brain or they are caused by other mechanisms.*

*In addition, you need to assess the relevance of the lysosomal accumulation of drug-related material seen in different organs in animals to humans.*

*Carcinogenicity study reports; 2-year rat and mouse studies, must be finalized and the pathology reports signed by the pathologist at the time of the NDA submission..*

**Discussion:** *No further discussion.*

**Additional Biometrics Comments**

*When you submit the NDA, please include as part of the original submission for the three controlled efficacy studies (-005, -301, -302):*

- (a) All raw as well as derived variables in .xpt format*
- (b) SAS programs that produced all efficacy results that are intended for inclusion in the labeling*
- (c) SAS programs by which the derived variables were produced from the raw variables*
- (d) A listing of all interactions with the Agency pertaining to this IND/NDA including serial numbers and submission dates of the protocols, SAPs, amendments, and any relevant meetings*
- (e) Minutes of DSMB meetings, if applicable.*

**Discussion:** *No further discussion.*

**Additional Clinical Discussion**

*The Agency expressed concern regarding the inconsistent efficacy results across trials and how these might be conveyed in labeling. In particular, the 120 mg dose did not separate from placebo in the 005 study; the 40 mg dose did not separate from placebo on the primary endpoint*

*in the 301 study; and neither the 20 mg nor the 60 mg dose separated from placebo, while the risperidone group did separate from placebo, in the 302 study.*

*The Agency encouraged the Sponsor to submit any additional analyses that may help explain the lack of efficacy of the 60 mg dose compared to risperidone in the 302 study, and the apparent lesser efficacy of the 120 mg dose compared to the 60 mg dose in the 005 study. In addition, any analyses that reveal particularly good efficacy in specific subpopulations of patients would help support the NDA application. If presenting histograms displaying the patients who achieved a particular level of response (e.g., points improvement on the primary endpoint), you should ensure that the bars are independent with individual patients only represented in one bar (i.e., 1 to 2 points/3 to 4 points/etc. rather than >1/>2/>3/etc.). The Sponsor noted that they also plan to look at concentration effects as they have sparse PK in all three studies.*

### **3. Other**

#### **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

As stated in our January 2, 2018 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at  
<https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>.

#### **PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email [Pedsdrugs@fda.hhs.gov](mailto:Pedsdrugs@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

## **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

## **SUBMISSION FORMAT REQUIREMENTS**

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. As of **May 5, 2017**, the following submission types: **NDA**, **ANDA**, and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

### **ABUSE POTENTIAL ASSESSMENT**

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>

### **MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

### **OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS**

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

#### **I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

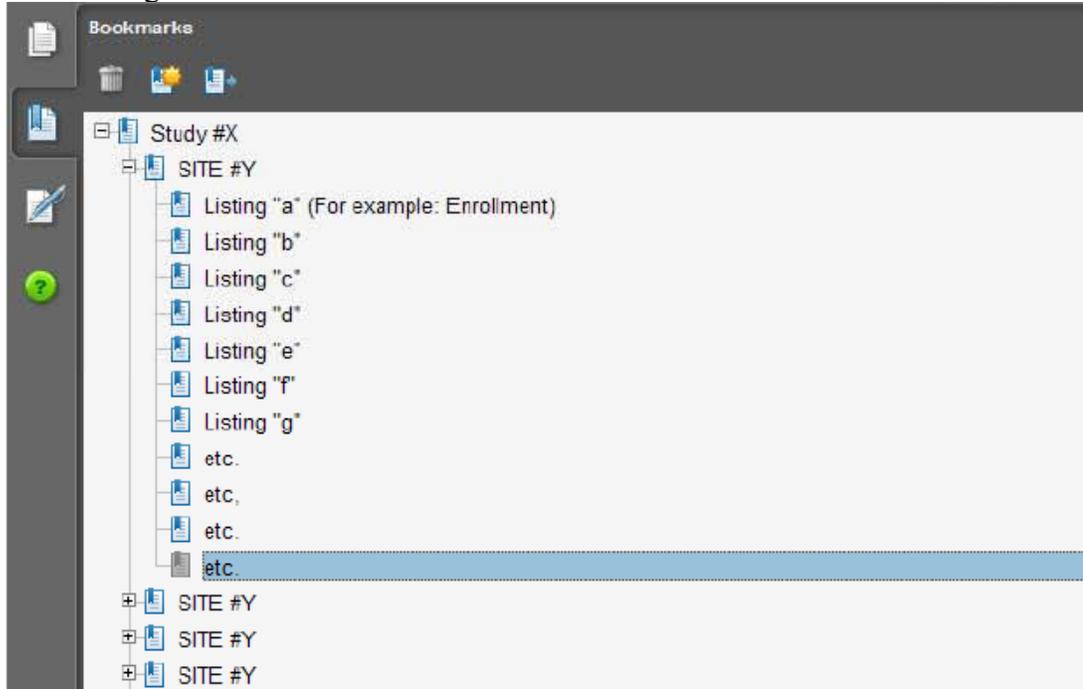
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
  - a. Site number
  - b. Principal investigator
  - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
  - a. Number of subjects screened at each site

- b. Number of subjects randomized at each site
  - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
- a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
  - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
  - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

## **II. Request for Subject Level Data Listings by Site**

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
  - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
  - b. Subject listing for treatment assignment (randomization)
  - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
  - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)

- j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



### III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf> ) for the structure and format of this data set.

**Attachment 1**  
**Technical Instructions:**  
**Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

<b>DSI Pre-NDA Request Item<sup>1</sup></b>	<b>STF File Tag</b>	<b>Used For</b>	<b>Allowable File Formats</b>
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

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<sup>1</sup> Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1  
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page  
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

## **DATA STANDARDS FOR STUDIES**

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team ([cdcr-edata@fda.hhs.gov](mailto:cdcr-edata@fda.hhs.gov)) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for

in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

#### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

*There were no issues requiring further discussion.*

#### **5.0 ACTION ITEMS**

*No action items were identified during the meeting.*

#### **6.0 ATTACHMENTS AND HANDOUTS**

From: Kimberly Vanover [mailto:kvanover@intracellulartherapies.com]  
Sent: Monday, March 05, 2018 5:07 PM  
To: Chun, Nam ( Esther) <Nam.Chun@fda.hhs.gov>  
Subject: Re: IND 79,690 SN0119 Type B Meeting Request

Dear Dr. Chun,

Thank you for the preliminary comments.

We confirm that we would like to focus the discussion at the meeting on Questions 4 and 7.

Accordingly, we will revise our attendee list to a subset of those previously proposed. Our attendees will include:

Kimberly Vanover, PhD, Senior Vice President, Clinical Development

Robert Davis, PhD, Senior Vice President and Chief Scientific Officer  
Andrew Satlin, MD, Executive Vice President and Chief Medical Officer  
Jelena Saillard, MS, MBA, Senior Director, Clinical Operations  
Greg Hileman, PhD, Senior Director and Principal Regulatory Scientist

We note that you provided Additional Clinical Pharmacology Comments with requests for additional information. We provide that below.

“Please confirm that the final “to-be-marketed” formulation was used in all the pivotal efficacy/safety studies as well as the key clinical pharmacology studies (i.e., food-effect study, strength proportionality study etc.)”

ITI RESPONSE: [REDACTED] (b) (4)

The to-be-marketed formulations for [REDACTED] (b) (4) 42 mg capsules (equivalent [REDACTED] (b) (4) 60 mg of the tosylate salt, respectively) are the same as the formulations used for pivotal efficacy/safety studies and key clinical pharmacology studies except for capsule colors and imprinting (ref. IND 79,690 SN0091).

“Please clarify if the planned strengths are all compositionally proportional. Otherwise, you may need to conduct an in vivo strength proportionality/equivalency study.”

ITI-RESPONSE: [REDACTED] (b) (4)

Kind regards,  
Kim

Kimberly E. Vanover, Ph.D.  
SVP, Clinical Development  
Intra-Cellular Therapies, Inc.  
[kvanover@intracellulartherapies.com](mailto:kvanover@intracellulartherapies.com)  
917-279-2966  
Confidential

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MITCHELL V Mathis  
04/05/2018



IND 79690

**MEETING MINUTES**

Intra-Cellular Therapies, Inc. (ITI)  
Attention: Kimberly E. Vanover, Ph.D.  
Vice President, Clinical Development  
3960 Broadway, 6<sup>th</sup> Floor  
New York, NY 10032

Dear Dr. Vanover:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ITI-007, IC200056 (tosylate).

We also refer to the meeting between representatives of your firm and the FDA on June 23, 2014. The purpose of the meeting was to discuss Phase 3 clinical trial design for schizophrenia.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please email Simran Parihar, PharmD, Regulatory Health Project Manager, at [simran.parihar@fda.hhs.gov](mailto:simran.parihar@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Mitchell Mathis, M.D.  
CAPT, USPHS  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** End of Phase 2

**Meeting Date and Time:** Monday, June 23, 2014 at 9:30 AM – 11:00 AM (ET)  
**Meeting Location:** White Oak Building 22, Conference Room #1309

**Application Number:** IND 79690  
**Product Name:** ITI-007, IC200056 (tosylate)  
**Indication:** Treatment of Schizophrenia  
**Sponsor/Applicant Name:** Intra-Cellular Therapies, Inc. (ITI)

**FDA ATTENDEES**

Ellis Unger, MD	Deputy Director of Office of Drug Evaluation I (OND)
Mitchell Mathis, MD	Director, Division of Psychiatry Products (DPP)
Silvana Borges, MD	Acting Clinical Team Leader
Cara Alfaro, PharmD	Clinical Reviewer
Linda Fossom, PhD	Pharmacology/Toxicology Supervisor
Violetta Klimek, PhD	Pharmacology/Toxicology Reviewer
Hao Zhu, PhD	Clinical Pharmacology Team Leader
Praveen Balimane, PhD	Clinical Pharmacology Reviewer
Peiling Yang, PhD	Statistical Team Leader
Thomas Birkner, PhD	Statistical Reviewer
Martin Rusinowitz, MD	Controlled Substance Staff Reviewer
Simran Parihar, PharmD	Regulatory Health Project Manager, DPP

**SPONSOR ATTENDEES**

Kimberly Vanover, PhD	Vice President, Clinical Development, ITI
Sharon Mates, PhD	Chairman, President and Chief Executive Officer, ITI
(b) (4)	(Consultant)
(b) (4)	(Consultant)
(b) (4)	(Consultant)
Jelena Saillard	Director, Clinical Operations, ITI

**1.0 BACKGROUND**

Intra-Cellular Therapies is developing ITI-007 for the treatment of schizophrenia. ITI-007 is a 5-HT<sub>2A</sub> receptor antagonist, post-synaptic D<sub>2</sub> antagonist, pre-synaptic partial D<sub>2</sub> agonist and serotonin reuptake inhibitor. According to the sponsor, based on a completed PET study in human subjects, ITI-007 fully occupies cortical 5HT<sub>2A</sub> receptors at  $\geq 10$  mg and occupies 39%

of striatal D2 receptors at 40 mg (highest dose administered). The sponsor estimates that 60 mg will achieve ~50% D2 receptor occupancy. ITI-007 has two major circulating metabolites (IC200161, IC200131) with significant pharmacologic activity.

The Sponsor has completed one Phase 2 study. Study ITI-007-005 was a randomized, double-blind, placebo- and active-controlled trial in subjects with acutely exacerbated schizophrenia. A total of 335 subjects were randomized (1:1:1:1) to ITI-007 60 mg/day, ITI-007 120 mg/day, risperidone 4 mg/day or placebo. The duration of the double-blind phase of the study was 4 weeks and the primary efficacy endpoint was the mean change in total PANSS score from baseline to day 28. Approximately 74% of subjects completed this study. ITI-007 60 mg showed superiority over placebo (LS mean difference -5.8,  $p = 0.017$ ) on the primary endpoint; ITI-007 120 mg did not (LS mean difference -0.9,  $p = 0.708$ ). Risperidone 4 mg also showed superiority over vs. placebo (LS mean difference -6.0,  $p = 0.013$ ). The Sponsor states that there were no SAEs during this trial and, for the ITI-007 treatment groups, no increases in prolactin, glucose, insulin, total cholesterol, LDL or triglycerides and no extrapyramidal symptoms. According to the sponsor, the most common adverse events in the ITI-007 treatment arms were sedation/somnolence, dry mouth, dizziness, nausea and diarrhea.

In this End of Phase 2 meeting, the sponsor is seeking the Division's advice on the following:

- Phase 3 clinical plan in schizophrenia
- Clinical pharmacology and drug-drug interaction plan
- Nonclinical development plan

## 2. DISCUSSION

### 2.1. Clinical Efficacy & Safety

**Question 1:** Does the Agency agree that the primary endpoint of change from baseline on the total PANSS at the end of a 4-week treatment period is appropriate for both Phase 3 clinical trials?

**FDA Response to Question 1:**

*The mean change from baseline to endpoint for the PANSS total score is an acceptable primary efficacy endpoint. However, we note that no antipsychotic agents have been approved based on the demonstration of efficacy and safety from 4-week trials only. Inclusion of a pivotal trial of at least 6 weeks duration provides an additional 2 weeks of placebo-controlled data which is helpful in evaluating not only ITI-007 efficacy but also its safety profile. We would probably accept one 4-week and one 6-week trial to support the efficacy and safety of ITI-007 in the treatment of schizophrenia in your Phase 3 development program.*

**Discussion at Meeting:** *The Sponsor stated that the Phase 2 study demonstrated statistically significant separation of ITI-007 from placebo beginning at week 2 and maintained to week 4 (study endpoint). Based on these data, as well as the Division's acceptance of 4 week trials*

*for other antipsychotics, the Sponsor wishes to include two 4-week trials in their Phase 3 program. The Division reiterated comments provided in the preliminary response. Additionally, the Division would take a more conservative approach and request at least one 6-week trial for a first-in-class new molecular entity. The additional 2 weeks (4 vs. 6 week trial) would provide placebo-controlled efficacy and safety data for ITI-007.*

**Question 2:** Does the Agency agree that the planned statistical approach is appropriate for Phase 3 clinical trials?

**FDA Response to Question 2:**

*We generally have no objection to the use of MMRM and the fixed-sequence multiple testing procedure as the primary efficacy analysis. You will also need to pre-specify some sensible sensitivity analyses to explore the impact of possible deviations from the Missing at Random (MAR) assumption. We consider the proposed ANCOVA LOCF analysis as secondary/supportive analysis, and not as a sensitivity analysis, because it requires stronger assumptions (Missing completely at Random) compared to the proposed primary analysis (MMRM, which requires MAR).*

**Discussion at Meeting:** *The sponsor asked for some suggestions regarding acceptable sensitivity analyses. We indicated that we have no particular analysis in mind. In general, analyses that can reasonably handle the potential situation when the missingness mechanism is Not Missing at Random (NMAR) would be acceptable, but the details would need to be pre-specified.*

**Question 3:** Does the Agency agree that risperidone is appropriate to use as the active control in one Phase 3 clinical trial and that 4 mg of risperidone once daily is an appropriate dose for that study? Does the Agency agree that the other Phase 3 clinical trial does not require an active control?

**FDA Response to Question 3:**

*Risperidone 4 mg/day is an acceptable active control for study ITI-007-302. However, we strongly recommend inclusion of an active control in all pivotal trials to aid in the interpretation of the study results.*

**Discussion at Meeting:** *The Sponsor indicated that one of the reasons they did not include an active control in one of the Phase 3 trials was that subjects may have an expectation bias for improvement in clinical symptoms since they have a greater chance of receiving a potentially effective drug (two doses ITI-007, risperidone) than placebo. While this may be true, if an active control is not included in the study, interpretation of the study results will be more difficult. Inclusion of an active control is recommended for assay sensitivity. However, inclusion of an active control is not a requirement.*

**Question 4:** Does the Agency agree that the proposed doses of 40 mg and 60 mg ITI-007 are appropriate for evaluation in the Phase 3 clinical trials?

**FDA Response to Question 4:**

*Your plan to include 40 mg and 60 mg of ITI-007 in the two Phase 3 trials is less than optimal to fully explore the effective dose ranges. It is important to establish the full dose-response relationship of the drug to appropriately label the product with respect to both safety and efficacy. Please consider selecting a wider range of doses to capture both the minimal effective dose as well as maximal effective dose (without significant side-effects). Please perform dose-response (exposure-response) analysis to select the appropriate doses in Phase 3 trials.*

**Discussion at Meeting:** *The Division stressed the importance of including different doses in the Phase 3 trials to characterize the full dose-response. Though we note that the 120 mg dose did not separate from placebo in the Phase 2 trial, the current Phase 3 protocol proposals do not include any doses of ITI-007 between 60 and 120 mg. The sponsors were requested to perform dose-response analysis and integrate that with the receptor-occupancy for the various pharmacological pathway(s) to help select a broader range of doses in the Phase 3 studies.*

**Question 5:** Does the Agency agree with this proposed approach to monitoring safety in the ITI-007 Phase 3 program?

**FDA Response to Question 5:** *On face, the overall safety monitoring plan for the Phase 3 program appears acceptable. For the Phase 2 study, we note that the majority of discontinuations were due to “withdrew consent”. Please make every effort to determine more accurately the reason for subject discontinuation for this category.*

**Discussion at Meeting:** *The Division noted that the discontinuation category “withdrew consent” is not a meaningful category and usually includes discontinuations that should be categorized as “adverse reactions” or “lack of efficacy”. The Sponsor should consider other categories that would more accurately capture the reasons for discontinuation. Discontinuation categories should also be included in the training of clinical investigators. At a minimum, case report forms should include a comment line if “withdrew consent” remains as a category as this would allow the Division to determine whether the discontinuation was accurately categorized.*

**Question 6:** Does the Agency agree with this proposed approach to hypothesis testing to demonstrate superiority of the safety parameters of ITI-007 over risperidone in the Phase 3 program?

**FDA Response to Question 6:**

*We remind you that clinical data with respect to adverse events (e.g. hyperglycemia, dyslipidemia, weight, prolactin) is usually included in product labeling. If ITI-007 is similar to placebo with respect to these adverse events, this information would appear in labeling.*

*If you intend to demonstrate superiority on a target adverse event, at least two clinical trials with risperidone as the active control would be required as evidence to support a claim. If*

*two or more studies show superiority of ITI-007 compared to the active control with respect to the pre-specified adverse event of interest (i.e. you are testing a hypothesis for that adverse event), the inclusion of such information in labeling could be considered. We would look very closely, however, at the fairness of the comparison, e.g., the relative doses at which the drugs are being compared. For example, it would not be acceptable to select an unnecessarily high dose of risperidone to compare to a minimally effective dose of your drug. We would also examine the duration of the clinical trial, a 4-week trial may not be of sufficient duration to adequately evaluate adverse events of interest. It would be most convincing if all doses of your drug were shown superior to a modest dose of risperidone with respect to the adverse event of interest. If you intend to include a claim regarding a specific adverse event (e.g. weight gain) in labeling, you would need to prospectively define and reach an agreement on this endpoint and the analysis plan. This endpoint would also need to be incorporated in a strong control of studywise type I error rate. For inclusion in labeling, we could also require a separate study to evaluate the ITI-007 effects on the target adverse event.*

**Discussion at Meeting:** *The Division reiterated that the safety data, especially metabolic parameters including hyperglycemia, dyslipidemia, and weight gain, would be included in the relevant sections of product labeling. If ITI-007 had similar effects to placebo on those parameters, this would be evident in labeling.*

*The Division stated that since we do not have a precedent for this type of safety claim, the bar to demonstrate superiority would be set rather high. For safety outcomes to be considered as key secondary endpoints, a multiple testing procedure would be required by considering both efficacy and safety endpoints as a single family. Two clinical trials would be required to demonstrate superiority of ITI-007 to risperidone, risperidone would have to separate from placebo on the efficacy endpoint and all doses of ITI-007 that had demonstrated efficacy would have to be superior to risperidone on the a priori parameters of interest. It is unlikely that the Division would accept numerical changes in laboratory parameters for a superiority claim – differences would have to be clinically meaningful (e.g. categorical shifts). It is also unlikely that the Division would accept a long list of safety variables as key secondary endpoints – the Sponsor is advised to choose one safety parameter or construct a composite of the parameters of interest. The sponsor should pre-specify similar sensitivity analyses to deal with missing data as for the efficacy endpoint. If the Sponsor wishes to pursue a superiority claim, it is advised that they obtain advice from the Division as the protocols are being developed.*

**Question 7:** Does the Agency agree with the proposed step-wise approach for assessing cardiovascular risk including assessment of the potential for QTc interval prolongation in the Phase 3 program and drug-drug interaction studies?

**FDA Response to Question 7:**

*Currently the agency requires a thorough QTC study to be performed for all new molecular entities during development to fully characterize its cardiovascular risk.*

*We appreciate your efforts to more stringently assess the cardiovascular risk in the future Phase 3 clinical studies. Further, we suggest 12-lead ECG monitoring should be done on days- 1, 8, and 28 at pre-dose as well as Tmax for parent as well as all the metabolites in appreciable amounts in circulation (IC200161, IC200131, IC200565 etc.), not just 3-6 hr post-dose as suggested.*

**Discussion at Meeting:** *No further discussion.*

**Question 8:** *Does the Agency agree that the currently available 3-month GLP toxicity studies in rats and dogs sufficiently qualify ITI-007 for treatment beyond a 3-month duration in the clinical studies up to 1 year?*

**FDA Response to Question 8:**

*No, we do not agree. In general, 3-month general toxicity studies in two animal species would support clinical studies up to 3 months in duration at appropriate doses and longer animal studies would be needed to support clinical studies longer than 3 months.*

*However, we are concerned by the histopathology findings of neuronal degeneration, neuronal necrosis and pigmentation in the brain and spinal cord in your 3-month dog toxicology study, but not seen (at lower doses) in your 1-month dog study. In the report for that study, the Pathologist recommended further characterization of those brain findings; however, we are not aware of any follow-up on this issue. Based upon the human PK data you provided, in response to our request, it appears that there is no margin of safety for your proposed clinical doses (40 and 60 mg) for those findings in the 3-month dog study. For significant histopathological findings in the brain, we would limit clinical dosing so that systemic exposures (Cmax and AUC) do not exceed 1/10<sup>th</sup> the exposures at the NOEL in the most sensitive animal species (dog in this case).*

*You will need to better characterize those pigmentation and neural changes, including neuronal changes and any associated glial response in dog brain and spinal cord, and discuss the relevance of these findings for human subjects.*

*If you cannot justify the lack of relevance of dog finding for humans, you will need to limit clinical doses (as described above) and submit final study reports of your 6-month rat and 9-month dog toxicology studies with adequate dosing prior to initiation of clinical trials of longer than one-month duration.*

**Discussion at Meeting:** *The sponsor postulated that the neuropathological findings in the 90-day study in dogs are spurious/artifactual and they proposed investigational strategies to support this interpretation (see the attached slide, which was provided at the meeting). The sponsor committed to submitting the results of these investigations to the IND as soon as possible.*

*The Division expressed safety concerns regarding the whole body tremors/seizures/convulsions observed in dogs which may be associated with the neuronal pathology as well as the duration of treatment with ITI-007. The sponsor agreed to characterize the red pigmentation occurring in*

*multiple organs (including brain) and to determine whether the drug and/or its metabolites are accumulating in those organs with repeated drug treatment.*

*The Division agreed that the proposed 6-week clinical trial could proceed, using clinical doses that were considered appropriate based upon the 4-week repeated-dose general toxicology studies. However, submission (and our review) of the chronic animal studies (6-month rat and 9-month dog) may be needed prior to initiation of additional clinical trials, depending upon whether the sponsor can justify lack of clinical relevance for the histopathological findings in dogs.*

## **2.2. Clinical Pharmacology**

**Question 9:** Does the Agency agree with the proposed clinical pharmacology development plan to support Phase 3 clinical trials and registration?

### **FDA Response to Question 9:**

*The agency is generally in agreement with the proposed clinical pharmacology development plan. However, we would recommend the sponsor to consider the following:*

- *Drug-interaction study for assessing the effect of a strong CYP3A4 inhibitor should be performed using either clarithromycin or itraconazole and not ketoconazole. Please consult the recent FDA guidance against using ketoconazole due to serious potential side effects: <http://www.fda.gov/Drugs/DrugSafety/ucm371017.htm>*
- *Characterize the parent as well as major metabolites (IC200161, IC200131, IC200565 etc.) for their inhibition potential towards CYP's, Phase 2 enzymes and transporters.*
- *Characterize the parent as well as major metabolites (IC200161, IC200131, IC200565 etc.) for their induction potential towards major CYP's using human hepatocytes*
- *Conduct a follow up in vivo metabolism or transporter- DDI study (as a perpetrator or victim) based on any positive in vitro data.*
- *Conduct an alcohol dose-dumping (in vitro) study with the drug product.*

*Also, the final study protocols should be submitted to the agency for feed-back regarding doses, study design, etc. prior to the conduct of the study.*

**Discussion at Meeting:** *The sponsors stated that they have not yet finalized the formulation to be marketed and the two Phase 3 trials will utilize 2 different formulations. Therefore, the Division instructed them to conduct "PK bridging" studies with the final "to be marketed" formulation later. Additionally, food effect study at the highest marketed strength will be required with the final formulation.*

*Post meeting comment: Based on sponsor's statement that the final formulation will be an IR formulation, an in vitro alcohol dose-dumping study will not be necessary.*

## **2.3. Pharmacology/Toxicology**

**Question 10:** Does the Agency agree with the proposed nonclinical development plan to support Phase 3 clinical trials and product registration?

**FDA Response to Question 10:**

*On face, we agree that your proposed nonclinical studies: 1) Fertility and early embryonic development in rats; 2) Embryofetal development in rats and rabbits will support your Phase 3 clinical development; and additional studies 3) Peri-postnatal development study in rats and 4) Carcinogenicity studies in mice and rats would support NDA filing. However, it is also possible that additional studies may be needed based on the results of your planned studies (see Question 8).*

**Discussion at Meeting:** *No further discussion.*

## 2.4. Control Substance Staff

**Question 11:** Does the Agency agree that no specific abuse liability studies for ITI-007 are required?

**FDA Response to Question 11:**

*No, we do not agree. The Sponsor asserts that ITI-007 lacks affinity for receptors known to mediate abuse potential, such as dopamine transporters, opiate receptors and  $\gamma$ -aminobutyric acid receptors. This profile needs to be further described in detail and studied, along with a full panel of abuse drug targets, with more data than that which is provided in the meeting package.*

*It appears that the drug's properties as a 5-HT<sub>2a</sub> receptor antagonist as well as a D<sub>2</sub> receptor post-synaptic antagonist, along with relatively few adverse side effects suggestive of abuse, speak against abuse potential. However, we cannot provide additional comments until full protocols and study reports (including primary data) are available for review.*

*Upon further review a decision will be made regarding the need for animal behavior pharmacology studies and human abuse liability studies*

**Discussion at Meeting:** *No further discussion.*

## 2.5. Other Comments

*When the final protocols for the Phase 3 clinical trials are submitted, we will provide additional comments. The following pertain to the draft protocols included in the briefing package:*

*According to the Study Events Schedule, informed consent is obtained during the screening period (day -7 to day -2). However, according to exclusion criterion #9, subjects cannot be receiving antipsychotic medications "within the screening period through to study day -1".*

*Please clarify when the medication washout period begins and whether the washout begins prior to obtaining informed consent.*

*Please clarify the duration of the washout period with consideration of the long half-life of some psychotropics (e.g. fluoxetine, aripiprazole).*

**Discussion at Meeting:** *No further discussion.*

### **3.0 PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

### **4.0 DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

## **5.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS**

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

## **6.0 ABUSE POTENTIAL ASSESSMENT**

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

## **7.0 ATTACHMENTS AND HANDOUTS**

Sponsor’s version of the meeting minutes and response to Question 8 (see above)

FDA EOP2 Meeting

June 23, 2014

Sponsor Minutes

Meeting Type: Type B  
Meeting Category: End of Phase 2  
Meeting Date and Time: Monday, June 23, 2014 start 9:30am to 10:35am (ET)  
Meeting Location: White Oak Building 22, Conference Room #1309  
Application Number: IND 79690  
Product Name: ITI-007, IC200056 (tosylate)  
Indication: Treatment of Schizophrenia  
Sponsor/Applicant Name: Intra-Cellular Therapies, Inc. (ITI)

**FDA Attendees:**

Ellis Unger, MD Deputy Director of Office of Drug Evaluation I (OND)  
Mitchell Mathis, MD Director, Division of Psychiatry Products (DPP)  
Slivana Borger, MD Acting Clinical Team Leader  
Cara Alfaro, PharmD Clinical Reviewer  
Linda Fossom, PhD Pharmacology/Toxicology Supervisor  
Violetta Klimek, PhD Pharmacology/Toxicology Reviewer  
David Claffey, PhD CMC Team Leader  
Hao Zhu, PhD Clinical Pharmacology Team Leader  
Praveen Balimane, PhD Clinical Pharmacology Reviewer  
Peiling Yang, PhD Statistical Team Leader  
Thomas Birkner, PhD Statistical Reviewer

Martin Rusinowitz, MD Controlled Substance Staff Reviewer

Simran Parihar, PhD Regulatory Health Project Manager, DPP

**Intra-Cellular Therapies, Inc. Attendees:**

Kimberly Vanover, PhD Vice President, Clinical Development, ITI

Sharon Mates, PhD Chairman, President and Chief Executive Officer, ITI (via phone)

(b) (4) (Consultant)

(b) (4) (Consultant)

(b) (4) (Consultant)

Jelena Saillard Director, Clinical Operations, ITI

Brief introductions were followed by (b) (4) indicating to the Division that ITI would present additional perspective regarding the questions in the same order as in the FDA preliminary responses, and that there were no further comments for questions # 10 and 11.

**Question 1**

Clinical Question: Does the Agency agree that the primary endpoint of change from baseline on the total PANSS at the end of a 4-week treatment period is appropriate for both Phase 3 clinical trials?

FDA Preliminary Response:

The mean change from baseline to endpoint for the PANSS total score is an acceptable primary efficacy endpoint. However, we note that no antipsychotic agents have been approved based on the demonstration of efficacy and safety from 4-week trials only. Inclusion of a pivotal trial of at least 6 weeks duration provides an additional 2 weeks of placebo-controlled data which is helpful in evaluating not only ITI-007 efficacy but also its safety profile. We would probably accept one 4-week and one 6-week trial to support the efficacy and safety of ITI-007 in the treatment of schizophrenia in your Phase 3 development program.

Meeting Discussion:

ITI provided additional perspective and explanation relative to the observation of statistically significant efficacy with separation from placebo by 60 mg ITI-007 as early as 2-weeks in the Phase 2 trial and the maintenance of efficacy through weeks 3 and 4. Additionally, ITI stressed the importance of the ability to achieve an efficacious antipsychotic dose of ITI-007 upon first administration without a slow dose titration. ITI expressed concerns relative to the increased early discontinuation and unnecessary

exposure to placebo in acutely exacerbated patients, by extending the study duration from 4 to 6-weeks in Phase 3. The company expressed that ITI-007 safety would be better demonstrated in the planned longer duration Phase 3 exposure trials that would be conducted to support the overall safety database.

The Division explained its perspective that it considers ITI-007 to be a first-in-class new chemical entity (NCE) and as such, the Division tends to take a more conservative approach than if it were a 3<sup>rd</sup> drug in a class. The Phase 3 program is the last chance to gather placebo-controlled safety data and inclusion of a pivotal trial of at least 6 weeks treatment duration provides an additional 2 weeks of placebo-controlled safety data. They have not approved any antipsychotic on the basis of two 4-week pivotal trials and would be setting a precedence by allowing one 4-week and one 6-week pivotal trial for ITI-007.

## **Question 2**

Clinical Efficacy Question: Does the Agency agree that the planned statistical approach is appropriate for Phase 3 clinical trials?

FDA Preliminary Response:

We generally have no objection to the use of MMRM and the fixed-sequence multiple testing procedure as the primary efficacy analysis. You will also need to pre-specify some sensible sensitivity analyses to explore the impact of possible deviations from the Missing at Random (MAR) assumption. We consider the proposed ANCOVA LOCF analysis as secondary/supportive analysis, and not as a sensitivity analysis, because it requires stronger assumptions (Missing completely at Random) compared to the proposed primary analysis (MMRM, which requires MAR).

Meeting Discussion:

ITI stated that they will plan to use the MMRM for the primary efficacy analysis. ITI requested the Division to clarify what sensitivity analysis would be preferred.

The Division suggested multiple imputation or a pattern mixture model with less stringent assumptions than 'missing completely at random', but emphasized that ITI should propose a sensible statistical analysis plan for performing a prespecified analysis for handling missing data, as a sensitivity analysis to the primary MMRM analysis, and an associated drop-out pattern analysis.

## **Question 3**

Clinical Efficacy Question: Does the Agency agree that risperidone is appropriate to use as the active control in one Phase 3 clinical trial and that 4 mg of risperidone once daily is an appropriate dose for that study? Does the Agency agree that the other Phase 3 clinical trial does not require an active control?

FDA Preliminary Response:

Risperidone 4 mg/day is an acceptable active control for study ITI-007-302. However, we strongly recommend inclusion of an active control in all pivotal trials to aid in the interpretation of the study results.

Meeting Discussion:

ITI stated that it appreciates the benefits of including a positive control to aid in interpretation of data and discussed the benefit of reducing the placebo response with fewer active treatment arms with respect to signal detection. ITI proposed to use an active control in one Phase 3 trial and to reduce the number of arms in the other Phase 3 trial.

The Division strongly recommended inclusion of an active control in all pivotal trials to differentiate between a negative study and a failed study. However, the Division noted that it is not a requirement to include an active control in all Phase 3 trials. The Division stated that it is the Sponsor's risk, as it would not be possible to assess if it is a negative or a failed trial in the absence of an active control. The Division suggested that ITI should make a case for the inclusion or exclusion of an active control in the Phase 3 clinical protocols.

#### **Question 4**

Clinical Efficacy Question: Does the Agency agree that the proposed doses of 40 mg and 60 mg ITI-007 are appropriate for evaluation in the Phase 3 clinical trials?

FDA Preliminary Response:

Your plan to include 40 mg and 60 mg of ITI-007 in the two Phase 3 trials is less than optimal to fully explore the effective dose ranges. It is important to establish the full dose-response relationship of the drug to appropriately label the product with respect to both safety and efficacy. Please consider selecting a wider range of doses to capture both the minimal effective dose as well as maximal effective dose (without significant side-effects). Please perform dose-response (exposure-response) analysis to select the appropriate doses in Phase 3 trials.

Meeting Discussion:

ITI discussed its exploration of the high dose range in the ITI-007-005 Phase 2 clinical trial, with the inclusion of 120 mg ITI-007. While this dose was safe, it failed to separate from placebo. It was noted that approximately a third of the patients in 120 mg group reported somnolence/sedation and it is possible this may have interfered with the remote video-interviews used for central ratings of the primary endpoint. ITI emphasized that a clear efficacy signal was achieved with 60 mg ITI-007 with less sedation than reported in the 4 mg risperidone treated subjects or in the 120 mg ITI-007 treated subjects. As such ITI proposed to move forward with the active dose of 60 mg ITI-007 and include one lower dose in the Phase 3 program in order to more fully explore the effective dose range. Based on the ITI-007-003 PET study in healthy volunteers, ITI measured approximately 40% peak striatal D2 occupancy

at 40 mg ITI-007; ITI projected about 50% striatal D2 occupancy for 60 mg and about 70% for 120 mg. ITI proposed to stay in the 40 – 50% striatal D2 receptor occupancy range that is more clozapine-like than other atypical antipsychotics and as such, proposed to evaluate doses of 40 mg and 60 mg in the Phase 3 program.

The Division emphasized the benefit of evaluating a wider range of doses to capture both the minimal effective dose as well as maximal effective dose (without significant side-effects), as these data are important for writing the label. They noted that replication is not required at every dose for approval. The Division suggested that ITI may include different doses in different trials, and may even choose to evaluate 60 mg and a lower dose in one trial and evaluate 60 mg and a higher dose in a second trial. The Division requested that ITI submit the full rationale for dose selection with the Phase 3 clinical protocols.

### **Question 5**

Clinical Safety Question: Does the Agency agree with this proposed approach to monitoring safety in the ITI-007 Phase 3 program?

FDA Preliminary Response:

On face, the overall safety monitoring plan for the Phase 3 program appears acceptable. For the Phase 2 study, we note that the majority of discontinuations were due to “withdrew consent”. Please make every effort to determine more accurately the reason for subject discontinuation for this category.

Meeting Discussion:

ITI informed the Division that all efforts would be made to accurately capture the reason for subject discontinuations in the Phase 3 program.

The Division emphasized the importance of accurately determining the reason for subject discontinuation. They suggested inclusion of a comments line or section in addition to a check-box for capturing the reason for early discontinuation in the case report form. They may be able to provide additional specific suggestions on how best to capture this information. When ITI submits the Phase 3 clinical protocol, it should be made clear that this section is addressing the Division’s comments and is based on the Division’s suggestions on how to accomplish this.

[Post-meeting note: Additional comments for withdrawal of consent are available in the ITI-007 Phase 2 data set, but these were not listed formally in the Tables, Listings and Figures. ITI will include the reasons for early discontinuation in the final Clinical Study Report that will be submitted to the IND.]

### **Question 6**

Clinical Safety Question: Does the Agency agree with this proposed approach to hypothesis testing to demonstrate superiority of the safety parameters of ITI-007 over risperidone in the Phase 3 program?

#### FDA Preliminary Response:

We remind you that clinical data with respect to adverse events (e.g. hyperglycemia, dyslipidemia, weight, prolactin) is usually included in product labeling. If ITI-007 is similar to placebo with respect to these adverse events, this information would appear in labeling. If you intend to demonstrate superiority on a target adverse event, at least two clinical trials with risperidone as the active control would be required as evidence to support a claim. If two or more studies show superiority of ITI-007 compared to the active control with respect to the pre-specified adverse event of interest (i.e. you are testing a hypothesis for that adverse event), the inclusion of such information in labeling could be considered. We would look very closely, however, at the fairness of the comparison, e.g., the relative doses at which the drugs are being compared. For example, it would not be acceptable to select an unnecessarily high dose of risperidone to compare to a minimally effective dose of your drug. We would also examine the duration of the clinical trial, a 4-week trial may not be of sufficient duration to adequately evaluate adverse events of interest. It would be most convincing if all doses of your drug were shown superior to a modest dose of risperidone with respect to the adverse event of interest. If you intend to include a claim regarding a specific adverse event (e.g. weight gain) in labeling, you would need to prospectively define and reach an agreement on this endpoint and the analysis plan. This endpoint would also need to be incorporated in a strong control of studywise type I error rate. For inclusion in labeling, we could also require a separate study to evaluate the ITI-007 effects on the target adverse event.

#### Meeting Discussion:

ITI discussed that the safety parameters from the ITI-007-005 Phase 2 trial showed no difference from placebo in the prospective analysis and showed statistically significant improvement over risperidone in a post-hoc analysis. ITI requested the Division to please clarify whether it will accept a separate hypothesis sequence testing for safety from the hypothesis testing for efficacy.

The Division emphasized that there is no precedence for safety comparisons with antipsychotic drugs. They stated that ITI would need to demonstrate first that a dose of ITI-007 is efficacious, then determine whether that efficacious dose has a safety advantage, though the efficacy and safety hypothesis testing could be conducted as separate sequences in terms of type I error control. The Division discussed the difficulty in achieving significance with serial testing of 5 or 6 adverse events and suggested that a composite safety endpoint could be considered. It was noted that the Division would have to review and agree to any safety comparison plan and any composite safety endpoint prospectively. The Division also discussed the importance for any safety endpoint (e.g., clinical lab value) to be both statistically significant and clinically meaningful (i.e., be at a level that would require treatment). The Division reminded ITI that with no difference from placebo, ITI will get data in the label without prospectively defining the comparisons to an active control. If ITI decides to pursue the prospective comparisons to an active control to seek a claim, the Division strongly recommended that ITI consult with the Division

regarding the details of the specific plan. The Division suggested that ITI should indicate this clearly in the Cover Letter with the submission and request Division feedback.

#### **Question 7**

Clinical Safety Question: Does the Agency agree with the proposed step-wise approach for assessing cardiovascular risk including assessment of the potential for QTc interval prolongation in the Phase 3 program and drug-drug interaction studies?

FDA Preliminary Response:

Currently the agency requires a thorough QTC study to be performed for all new molecular entities during development to fully characterize its cardiovascular risk. We appreciate your efforts to more stringently assess the cardiovascular risk in the future Phase 3 clinical studies. Further, we suggest 12-lead ECG monitoring should be done on days- 1, 8, and 28 at pre-dose as well as Tmax for parent as well as all the metabolites in appreciable amounts in circulation (IC200161, IC200131, IC200565 etc.), not just 3-6 hr post-dose as suggested.

Meeting Discussion:

ITI stated that this feedback will be taken into consideration for the Phase 3 program and that it plans to seek a separate meeting with the Division to discuss further when additional ECG data have been gathered.

#### **Question 8**

Clinical Safety Question: Does the Agency agree that the currently available 3-month GLP toxicity studies in rats and dogs sufficiently qualify ITI-007 for treatment beyond a 3-month duration in the clinical studies up to 1 year?

FDA Preliminary Response:

No, we do not agree. In general, 3-month general toxicity studies in two animal species would support clinical studies up to 3 months in duration at appropriate doses and longer animal studies would be needed to support clinical studies longer than 3 months.

However, we are concerned by the histopathology findings of neuronal degeneration, neuronal necrosis and pigmentation in the brain and spinal cord in your 3-month dog toxicology study, but not seen (at lower doses) in your 1-month dog study. In the report for that study, the Pathologist recommended further characterization of those brain findings; however, we are not aware of any follow-up on this issue. Based upon the human PK data you provided, in response to our request, it appears that there is no margin of safety for your proposed clinical doses (40 and 60 mg) for those findings in the 3-month dog study. For significant histopathological findings in the brain, we would limit clinical dosing so that systemic exposures (Cmax and AUC) do not exceed 1/10th the exposures at the NOEL in the most sensitive animal species (dog in this case).

You will need to better characterize those pigmentation and neural changes, including neuronal changes

and any associated glial response in dog brain and spinal cord, and discuss the relevance of these findings for human subjects.

If you cannot justify the lack of relevance of dog finding for humans, you will need to limit clinical doses (as described above) and submit final study reports of your 6-month rat and 9-month dog toxicology studies with adequate dosing prior to initiation of clinical trials of longer than one-month duration.

Meeting Discussion:

ITI presented a slide [attached] in support of the neuropathological observations in the dog 90 day study being spurious/artifactual findings. Additionally, the slide provided a summary of early, clear, reversible and predictive clinical signals associated with exaggerated pharmacology related to excessive dopamine receptor antagonism that are not observed in humans. Based on these data, ITI believes that ITI-007 can be safety advanced into Phase 3 clinical trials.

The Division declared that they are allowing ITI to proceed with Phase 3 clinical trials of 4-week and 6-week treatment duration based on the currently available nonclinical data. ITI will provide additional nonclinical data before submitting an open label clinical trial protocol to support longer treatment duration.

#### **Question 9**

Clinical Pharmacology Question: Does the Agency agree with the proposed clinical pharmacology development plan to support Phase 3 clinical trials and registration?

FDA Preliminary Response:

The agency is generally in agreement with the proposed clinical pharmacology development plan. However, we would recommend the sponsor to consider the following:

Drug-interaction study for assessing the effect of a strong CYP3A4 inhibitor should be performed using either clarithromycin or itraconazole and not ketoconazole. Please consult the recent FDA guidance against using ketoconazole due to serious potential side effects:

<http://www.fda.gov/Drugs/DrugSafety/ucm371017.htm>

Characterize the parent as well as major metabolites (IC200161, IC200131, IC200565 etc.) for their inhibition potential towards CYP's, Phase 2 enzymes and transporters.

Characterize the parent as well as major metabolites (IC200161, IC200131, IC200565 etc.) for their induction potential towards major CYP's using human hepatocytes.

Conduct a follow up in vivo metabolism or transporter- DDI study (as a perpetrator or victim) based on any positive in vitro data.

Conduct an alcohol dose-dumping (in vitro) study with the drug product.

Also, the final study protocols should be submitted to the agency for feed-back regarding doses, study design, etc. prior to the conduct of the study.

Meeting Discussion:

ITI requested the Division to clarify if the protocols should be submitted for just the clinical studies or all the in vitro studies listed.

The Division clarified that only clinical protocols should be submitted. The Division referred ITI to the FDA guidance for the in vitro studies. It was also clarified that a bridging study should be conducted if the market formulation is different than the formulation used in Phase 3 trials.

#### **Question 10**

Pharm/Tox Question #1: Does the Agency agree with the proposed nonclinical development plan to support Phase 3 clinical trials and product registration?

FDA Preliminary Response:

On face, we agree that your proposed nonclinical studies: 1) Fertility and early embryonic development in rats; 2) Embryofetal development in rats and rabbits will support your Phase 3 clinical development; and additional studies 3) Peri-postnatal development study in rats and 4) Carcinogenicity studies in mice and rats would support NDA filing. However, it is also possible that additional studies may be needed based on the results of your planned studies (see Question 8).

Meeting Discussion: None.

#### **Question 11**

Pharm/Tox Question #2: Does the Agency agree that no specific abuse liability studies for ITI-007 are required?

FDA Preliminary Response:

No, we do not agree. The Sponsor asserts that ITI-007 lacks affinity for receptors known to mediate abuse potential, such as dopamine transporters, opiate receptors and  $\gamma$ -aminobutyric acid receptors. This profile needs to be further described in detail and studied, along with a full panel of abuse drug targets, with more data than that which is provided in the meeting package.

It appears that the drug's properties as a 5-HT<sub>2a</sub> receptor antagonist as well as a D<sub>2</sub> receptor post-synaptic antagonist, along with relatively few adverse side effects suggestive of abuse, speak against abuse potential. However, we cannot provide additional comments until full protocols and study reports

(including primary data) are available for review. Upon further review a decision will be made regarding the need for animal behavior pharmacology studies and human abuse liability studies.

Meeting Discussion: None.

**Action Items:**

1. ITI will propose a statistical analysis plan for performing a pre-specified analysis for handling missing data as a sensitivity analysis to the primary MMRM analysis for the Phase 3 clinical trials and perform an associated dropout pattern analysis.
2. ITI will provide the rationale for including or excluding an active control in the Phase 3 clinical protocols.
3. ITI will submit the full rationale for dose selection with the Phase 3 clinical protocols.
4. ITI will make all efforts to capture reasons for early discontinuation in the Phase 3 program by clearly addressing in the Phase 3 clinical protocols how early discontinuations will be characterized including a section for additional comments in regards to withdrawal of consent in the case report forms; ITI will note in the protocol that this is in response to the Division's comments.
5. ITI will seek detailed feedback from the Division on a specific analysis plan related to the superiority safety claims in comparison to an active control, if ITI intends to proceed with seeking this claim in the label. ITI will provide the additional analysis of the dog 3-month toxicity data and further characterization of the observed pigmentation.
6. The Division agreed that ITI can conduct clinical trials of 4 and 6 week treatment duration in Phase 3 based on the existing nonclinical data.
7. ITI will provide the clinical pharmacology drug-drug interaction protocols to the Division for feed-back regarding doses, study design, etc. prior to the conduct of these drug-drug interaction studies.
8. ITI intends to seek a separate meeting with the Division to discuss plans for assessing cardiovascular risk including assessment of the potential for QTc interval prolongation after additional ECG data have been gathered.
9. ITI will submit a PSP to the IND within 60-days from the EOP2 Meeting date, i.e. August 23<sup>rd</sup> 2014.

Slide Attached

# Response to question 8

- ITI believes that the neuropathological observations in the dog 90 day study are spurious/artifactual findings.
  - Independent blinded review of this dog study by a neuropathology expert determined that there were no neuropathological changes.
    - The full report from this independent review has not been made available to ITI.
    - All efforts will be made to obtain the full report and submit to the IND.
  - ITI will conduct additional analyses of these data as the Division suggested and will conduct a second blinded review by a different independent expert. These results will be submitted to the IND as soon as possible.
- ITI believes that ITI-007 can be safely advanced into Phase III clinical trials because:
  - Early and clear predictive clinical signals (e.g. tremors) have been observed in dogs. For example, tremors are:
    - Rapid in onset,
    - Appear only at high plasma concentrations,
    - Clearly dose related,
    - Predictive of later/more-severe clinical signs.
    - Upon cessation of drug treatment, all clinical signs reverse.
  - Tremors have not been seen at any of the doses tested in humans, up to 140 mg, which is greater than 2 times the highest proposed dose for the Phase III trials.

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MITCHELL V Mathis  
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