

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**209500Orig1s000**

**OTHER REVIEW(S)**



## **RATIONALE**

The Division of Psychiatry Products (DPP) Review Team notified DPMH of their concern that infants exposed to lumateperone via breast milk may form anilines and thus be at risk for the toxicities observed in animal studies. Although aniline metabolites of lumateperone thought to be responsible for toxicities observed in dogs and rats were not present in (adult) humans at quantifiable levels, it is unknown whether infants exposed to lumateperone will exhibit comparable lumateperone metabolism and elimination pathways as adults. Because of the severity of the toxicities in animals and the lack of information on whether breastfed infants of lactating women taking lumateperone would be exposed to aniline metabolites, the Review Team concluded breastfeeding should be discontinued during treatment with lumateperone.

## **RECOMMENDATIONS**

DPMH recommends updating the postmarketing requirement (PMR) language for a lactation study, and the labeling language for subsection 8.2 *Lactation* of the lumateperone labeling, as shown below.

### **Revised PMR language for lactation study:**

Perform a lactation study (milk only) in lactating women who have received therapeutic doses of lumateperone using a validated assay to assess concentrations of lumateperone and its metabolites in breast milk.

### **Revised PLLR lactation labeling language:**

## **HIGHLIGHTS OF PRESCRIBING INFORMATION**

### **-----USE IN SPECIFIC POPULATIONS-----**

- Lactation: Breastfeeding not recommended. (8.2)

## **FULL PRESCRIBING INFORMATION**

### **8 USE IN SPECIFIC POPULATIONS**

#### **8.2 Lactation**

##### Risk Summary

There are no available data on the presence of lumateperone or its metabolites in human milk or animal milk, the effects on the breastfed infant, or the effects on milk production. Toxicity in animals has been linked to the formation of aniline metabolites of lumateperone [see *Nonclinical Toxicology (13.2)*]. Although aniline metabolites were not present in (adult) humans at quantifiable levels, it is unknown whether infants exposed to lumateperone will exhibit comparable lumateperone metabolism and elimination pathways as adults. In addition, there are published reports of sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) in breastfed infants exposed to antipsychotics. Based on findings of toxicity in animal studies and the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended during treatment with lumateperone.

## **17 PATIENT COUNSELING**

### Lactation

Advise females not to breastfeed during treatment with lumateperone [see *Use in Specific Populations (8.2)*]

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KRISTIE W BAISDEN  
12/20/2019 01:31:54 PM

TAMARA N JOHNSON  
12/20/2019 01:58:20 PM

**MEMORANDUM****DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE FOOD  
AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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DATE: December 9, 2019

TO: Tiffany R. Farchione, M.D.  
(Acting) Director  
Division of Psychiatry (DP)  
Office of Neuroscience  
Office of New Drugs

FROM: Sam H. Haidar, Ph.D., R.Ph.  
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Sean Kassim, Director  
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: EIR review covering inspection of (b) (4)  
[REDACTED]

**1. Inspection Summary**

The Office of Study Integrity and Surveillance (OSIS) inspected studies RITQ2, RITQ3, and RMYI-Part 2 at [REDACTED] (b) (4) on [REDACTED] (b) (4). Dr. Huixia Zhang (OCP) and ORA investigator CDR Stephanie Mangigian, in addition to Sam H. Haidar, OSIS, participated on the inspection.

We did not observe objectionable conditions and did not issue Form FDA 483 at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

**1.1. Recommendation**

Based on my review of the inspectional findings, I conclude that the IC201337 and IC201338 long term stability data are reliable.

**2. Inspected Studies**

**Project RITQ2- Title:** Quantitation of IC201337 and IC201338 in Human Plasma via HPLC with MS/MS Detection (Method Validation)

**Project RITQ3-Title:** Supplemental Data Report "Quantitation of IC201337 and IC201338 in Human Plasma via HPLC with MS/MS Detection" (Method Validation)

**Project RMYI-Part 2 (NDA 209500)**- Human plasma samples bioanalysis (IC201337 and IC201338) for Study ITI-007-017 using HPLC with MS/MS Detection.

### 3. Scope of Inspection

OSIS scientist Sam H Haidar, Ph.D., OCP clinical pharmacologist Huixia Zhang, Ph.D., and ORA investigator CDR Stephanie C. Mangigian audited the projects listed above at [REDACTED] (b) (4) on [REDACTED] (b) (4).

The previous FDA inspection of [REDACTED] (b) (4) was conducted by OSIS [REDACTED] (b) (4) and was classified as NAI. At the conclusion of the inspection, no deficiencies were observed, and no Form FDA 483 was issued.

The current inspection included examination of study records, facilities, laboratory equipment, method validation, sample analysis, and interviews with the firm's management and staff. In addition, Standard Operating Procedures (SOPs), employee training records, laboratory notebooks, freezer log books, and sample tracking records were examined in detail.

### 4. Inspectional Findings

At the conclusion of the inspection, we did not observe objectionable conditions and did not issue Form FDA 483 to [REDACTED] (b) (4)

#### 4.1 Specific concerns from OND

##### Project RMYI-Part 2:

The bioanalytical method validation for two compounds IC201337 and IC201338 was established in 2017 (original validation report RITQ2). On Oct 8, 2019, it appeared that the applicant conducted additional analysis of these stored samples and extended the long-term stability for IC201337 and IC201338 to 567 days (supplemental data report RITQ3). OCP requested inspection of the documentation for these long-term stability samples to ensure data quality and integrity of the reported results.

**OSIS Evaluation:**

For the two compounds IC201337 and IC201338, the inspection evaluated the original validation report RITQ2's stability data as well as the supplemental report RITQ3 with stability data of 567 days. The data for both projects are deemed acceptable. Additionally, a partial review, which included sample tracking, freezer logs, and certificates of analysis, was conducted of Project RMYI-Part 2, which involved the determination of IC201337 and IC201338 concentration in human plasma samples for study ITI-007-017. The analytical component was an exploratory study, and as such, did not follow GLP or current guidances according to the firm, nor was it subject to QA audit. It was, however, conducted according to (b) (4) SOPs.

**5. Conclusion**

After review of the inspectional findings, I conclude that the IC201337 and IC201338 RITQ2 and RITQ3 long term stability data are reliable.

**Final Classification:****NAI -**

(b) (4)

cc: OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/Taylor/Haidar/Mirza  
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/  
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au  
ORA/OMPTO/OBIMO/[ORABIMOE.Correspondence@fda.hhs.gov](mailto:ORABIMOE.Correspondence@fda.hhs.gov)

Draft: SHH 12/09/2019; 12/10/2019

Edit: SA 12/09/2019, 12/10/2019; SYK 12/10/2019

ECMS: <http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f8839027d3>

OSIS File #: (b) (4)

**FACTS:** (b) (4)

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SAM H HAIDAR  
12/10/2019 02:01:09 PM

STANLEY AU  
12/10/2019 04:13:38 PM

SEAN Y KASSIM  
12/11/2019 08:00:09 AM



# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 3, 2019

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.  
Clinical Analyst  
Division of Cardiovascular and Renal Products /CDER

To: Jasmeet (Mona) Kalsi  
DPP

Subject: QT-IRT Consult to NDA 209500

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo serves as a correction to a previous review that we placed in DARRTS on 2/11/2019. The previous review (IRT.review.nda209500(01feb19).pdf) contain an error in section 4.3.1 on page 6. It should read (addition, ~~deletion~~):

“For Day 15, the largest upper bounds of the 2-sided 90% CI for the mean difference between ITI-007 180 mg and placebo, and between ITI-007 60 mg and placebo were 19.8 ms and 8.9 ms, respectively.

For Day 51, the largest upper bounds of the 2-sided 90% CI for the mean difference between ITI-007 180 mg and placebo, and between ITI-007 60 mg and placebo were 12.0 ms and 5.3 ms, respectively.”

Thank you for requesting our input into the development of this product. If you have further question, please feel free to contact us via email at [cderdcrpqt@fda.hhs.gov](mailto:cderdcrpqt@fda.hhs.gov).

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FERDOUSE BEGUM  
12/03/2019 06:39:14 PM

DALONG HUANG  
12/03/2019 07:11:30 PM

CHRISTINE E GARNETT  
12/04/2019 07:25:10 AM

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** December 4, 2019

David Millis, M.D., Clinical Reviewer  
Division of Psychiatry Products (DPP)

Jasmeet Kalsi, PharmD, Regulatory Project Manager, (DPP)

Kimberly Updegraff, PharmD, MS, Associate Director for Labeling, (DPP)

**From:** Aline Moukhtara, RN, MPH, Team Leader  
Office of Prescription Drug Promotion (OPDP)

**Subject:** OPDP Labeling Comments for CAPLYTA (lumateperone) capsules, for oral use

**NDA:** 209500

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In response to DPP consult request dated October 16, 2018, OPDP has reviewed the proposed product labeling (PI) carton and container labeling for the original NDA submission for CAPLYTA (lumateperone) capsules, for oral use (Caplyta).

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPP (Kimberly Updegraff) on December 1, 2019, and are provided below.

OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on October 24, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Aline Moukhtara at (301) 796-2841 or [Aline.Moukhtara@fda.hhs.gov](mailto:Aline.Moukhtara@fda.hhs.gov).

25 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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ALINE M MOUKHTARA  
12/04/2019 09:24:05 PM



**RATIONALE**

DPMH concludes that there are no available human data to inform the safety of lumateperone use during lactation. Considering lumateperone is systemically absorbed and expected to be used by women of reproductive age, including lactating women, data are needed regarding the presence of lumateperone in human milk and any adverse effects on the breastfed infant.<sup>1</sup>

**RECOMMENDATION**

DPMH recommends issuing a postmarketing requirement (PMR) at the time of approval for lumateperone for the applicant perform a lactation study (milk only) in lactating women who have received therapeutic doses of lumateperone using a validated assay to assess concentrations of lumateperone in breast milk and the effects on the breastfed infant.

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<sup>1</sup> FDA Draft Guidance for Industry. Clinical Lactation Studies: Considerations for Study Design. May 2019.

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KRISTIE W BAISDEN  
11/14/2019 02:00:01 PM

TAMARA N JOHNSON  
11/15/2019 01:38:56 PM

## Ophthalmology Consult Review of NDA 209500

**Consult Request Date:** December 7, 2018  
**Review completed:** November 5, 2019

**Product name:** Lumateperone

**Applicant:** Intracellular Therapies, Inc.  
**Drug Class:** Atypical antipsychotic

**Division of Psychiatry Products Consult Request:**

Intra-Cellular Therapies has submitted NDA 209500 for lumateperone (ITI-007). This NME is an atypical antipsychotic agent for the treatment of schizophrenia. Study ITI-007-303, a one-year open-label trial of the long-term safety of lumateperone is ongoing. The Sponsor recently submitted new neurohistopathology results from the two-year rodent (rats and mice) carcinogenicity studies. These studies revealed retinal degeneration and pigmentation in rats. Retinal degeneration was considered test-article related based on increased incidence and severity relative to concurrent controls, and pigmentation was noted in multiple organ systems.

The Sponsor previously submitted an interim study report and interim data for subjects who have completed up to six months of treatment with lumateperone. The study protocol was approved before the new nonclinical neurohistopathology results were available. Ophthalmologic exams conducted in the open-label trial included funduscopic examination, intraocular pressure, slit-lamp examination, and examination of pupils, extraocular motility, and visual fields. Our initial review of the data does not reveal any obvious changes from baseline in the percentage of abnormal ophthalmologic exam results. DPP requests consultation from DTOP to assess whether there is an approach to analysis of the submitted ophthalmologic data that might reveal patterns of change that may be relevant in light of the newly-reported nonclinical neurohistopathologic findings. In addition, we request your future review of ophthalmologic exam results in the one-year exposure data, once that data is submitted in the upcoming 120-day safety update.

**Reviewed:** 120-Day Safety Update with the interim study report of Study ITI-007-303.

## Ophthalmic Examinations

**Submission Table 2.7.4-63: Summary of Ophthalmic Examinations (Safety Set)**

Ophthalmic Assessment	120-Day Update 1-Year Interim Analysis					
	ITI-007 60 mg					
	Baseline	Day 75	Day 150	Day 225	Day 300	Day 368
<b>Funduscopy examination</b>						
Number of patients with assessment, n	387	374	314	263	174	18
Patients with abnormal finding, m (%)	61 (16%)	61 (16%)	61 (19%)	53 (20%)	32 (18%)	1 (6%)
Patients with clinically significant abnormal findings, q	8	10	5	7	4	0
<b>Visual acuity</b>						
Number of patients with assessment, n	388	376	314	263	174	18
Patients with abnormal finding, m (%)	86 (22%)	81 (21%)	52 (17%)	49 (19%)	31 (18%)	3 (17%)
Patients with clinically significant abnormal findings, q	7	7	5	7	3	0
<b>Slit-Lamp examination</b>						
Number of patients with assessment, n	388	376	314	263	174	18
Patients with abnormal finding, m (%)	119 (31%)	130 (35%)	115 (37%)	94 (36%)	67 (38%)	10 (56%)
Patients with clinically significant abnormal findings, q	3	5	5	6	5	0
<b>Confrontation visual fields</b>						
Number of patients with assessment, n	388	376	314	263	174	18
Patients with abnormal finding, m (%)	13 (3%)	17 (4%)	14 (4%)	17 (6%)	9 (5%)	1 (6%)
Patients with clinically significant abnormal findings, q	2	3	2	2	1	0

Note: Subjects may be counted more than once across visits but are counted only once within a specified visit.

m = number of subjects with an abnormal assessment at the specified visit; n = number of subjects with a baseline and a postbaseline assessment at the specified visit; q = number of subjects with an abnormal examination that was assessed as clinically

**Consult Reviewer's Comments:** The ophthalmic assessment is not adequate to assess the potential effect of lumateperone on the retina for the following reasons:

1. Less than 5% of patients have had their one year exam and less than 45% have had a 10 month exam. Almost 20% did not have a 5 month exam.
2. Confrontation visual fields are not an accurate method for assessing retinal function.
3. Optical coherence tomography examinations at baseline and with follow-up of at least one year following initiation of treatment are needed to assess the potential effects of lumateperone on the retina.
4. The submitted funduscopy examinations included inconsistencies in the findings such as:
  - a. Patient (b) (6), a 56-year old man with a normal baseline eye exam had macular degeneration reported in his left eye on Day 225, but not on day 262.
  - b. Patient (b) (6), a 36-year old woman was reported to have lattice retinal degeneration in both eyes at baseline and on Day 148; but, was reported as having a normal funduscopy exam on Days 78, 225 and 302.
  - c. Patient (b) (6), a 54-year old woman with peripheral retinal scarring in the left eye and an epiretinal membrane in the right eye at baseline, Day 75, and Day 148, but a normal fundus exam at Day 230 and Day 307.
  - d. Patient (b) (6), a 53-year old man with Congenital retinal pigment epithelial hypertrophy (CHRPE) in the left eye at baseline; but, reported as normal on Days 78 and 148.
  - e. Patient (b) (6), a 37-year old man with esotropia at baseline, but not at Days 78, 150, or 225.
  - f. Patient (b) (6), a 56-year old man with a scar in the temporal region of the right retina noted on baseline, but listed as normal on Days 90, 157, or 225.
  - g. Patient (b) (6), a 45-year old man was reported to have a chorioretinal scar in his right retina at baseline, but was listed as normal on days 78, and 148.
  - h. Patient (b) (6), a 58-year old man with severe glaucoma on fundus exam, but with normal pressures in each eye.

**Ophthalmology Consult Summary/Recommendation:**

Based on the lateness of the nonclinical ocular findings during development, adequate ophthalmic examinations were not included in the initial development plan for lumateperone. It is therefore recommended that:

1. All participants in any ongoing or future studies of lumateperone with a duration of 3 months or longer receive ophthalmologic exams. These ophthalmologic exams should include best corrected distance visual acuity, threshold visual field exams and Optical Coherence Tomography (OCT) at baseline and at the end-of-study for any study of 3 to 6 months duration, or at not less than 4 months intervals for any study longer than 6 months.
2. A clinical study with ophthalmic examinations is recommended to be conducted in at least 60 patients being treated with lumateperone for at least 12 months duration. These ophthalmologic exams should include best corrected distance visual acuity, threshold visual field exams and Optical Coherence Tomography (OCT) at baseline, month 4, month 8, and month 12 (and every 4 months if the trial continues past 12 months).

Wiley A. Chambers, M.D.,  
Supervisory Medical Officer, Ophthalmology

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/s/  
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WILEY A CHAMBERS  
11/05/2019 08:08:18 AM

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**MEMORANDUM**  
**REVIEW OF REVISED LABELS AND LABELING**  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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Date of This Memorandum: October 28, 2019  
Requesting Office or Division: Division of Psychiatry Products (DPP)  
Application Type and Number: NDA 209500  
Product Name and Strength: Caplyta (lumateperone) capsules, (b) (4) 42 mg  
Applicant/Sponsor Name: Intra-Cellular Therapies, Inc.  
OSE RCM #: 2018-2109-1  
DMEPA Safety Evaluator: Loretta Holmes, BSN, PharmD  
DMEPA Team Leader: Sevan Kolejian, PharmD, MBA

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## 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised blister labels and carton labeling received on October 1, 2019 and October 24, 2019 for Caplyta. The Division of Psychiatry Products (DPP) requested that we review the revised blister labels and carton labeling for Caplyta (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous labels and labeling review<sup>a</sup> and via email communication<sup>b</sup>.

## 2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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<sup>a</sup> Holmes L. Labels and Labeling Review for Caplyta (NDA 209500). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 May 23. RCM No.: 2018-2109.

<sup>b</sup> Kalsi, J. FDA Communication: "NDA 209500 Container/Carton Comment" Message to Michael Olchaskey. Silver Spring (MD): FDA, CDER, OND, DPP (US); 2019 Oct 18.

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LORETTA HOLMES  
10/28/2019 03:58:42 PM

SEVAN H KOLEJIAN  
10/29/2019 05:02:56 PM

## Consultative Review

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**Subject:** Consultative Review of NDA 209500

**From:** Rainer Paine, MD, PhD (Reviewer)  
Teresa Buracchio, MD (Team Leader)  
Division of Neurology Products (DNP), CDER

**Through:** Eric Bastings, MD (Deputy Director)  
Division of Neurology Products, CDER

**To:** Jasmeet (Mona) Kalsi, PharmD  
Regulatory Project Manager  
Division of Psychiatry Products

**Material Reviewed:** NDA 209500 submission and other reference documents.

**Date Received:** 3/13/2019

**Date Reviewed:** 7/16/2019

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### **EXECUTIVE SUMMARY**

#### **Background**

This is a consultative review of NDA 209500 for the drug lumateperone for the treatment of schizophrenia.

Significant concern regarding peripheral neuropathy was not present at the time the pivotal clinical study for lumateperone (Study 303) was designed, so no specific monitoring beyond general physical exams and adverse event reporting was used for its detection.

However, nonclinical studies later showed that oral administration of lumateperone was associated with adverse effects in the CNS and the peripheral nervous system (PNS) of dogs and rats. Administration of lumateperone in dogs was associated with neuronal degeneration and necrosis in the sub-chronic toxicology study and axonal degeneration and inflammatory changes (perivascular cuffing) in the chronic toxicology study. These findings increased with increasing dose and duration of exposure. In rats, there was a dose-related increase in the incidence and severity of axonal degeneration in the sciatic nerve following administration of lumateperone in the chronic toxicology and carcinogenicity studies. Axonal degeneration of the dorsal funiculus in the spinal cord was also observed following administration of lumateperone in the rat carcinogenicity study.

The human clinical studies were completed before the Agency received these nonclinical results. Across all lumateperone clinical studies in patients with schizophrenia, 1217 received at least one dose of lumateperone: 1097 received lumateperone for at least 7 days, 880 for at least 28 days, and 330 for at least 42 days. 55 patients with a year or more of lumateperone exposure were included in the 120-day safety update, with an additional 52 patients having  $\geq$  350 days of exposure.

A search of the adverse event database for the term “neuropathy” yielded one patient with onset of diabetic peripheral neuropathy several years prior to the patient’s entry into the study. A search of the physical exam database revealed eleven patients with treatment-emergent abnormal neurological exams. There was no discernable pattern in the types of abnormalities reported. A search of the concomitant medications database for “neuropathy” or “peripheral neuropathy” as the indication for new prescriptions initiated during the study found no new prescriptions for which either term appeared as the indication.

The Applicant asserts that aniline metabolites, which do not appear to be formed in humans, are responsible for the toxicities observed in the CNS of dogs. An Advisory Committee meeting is scheduled for July 31, 2019.

The consult request asks DNP to comment on the best way to monitor for neuropathy in future studies of lumateperone.

### **Conclusions and Recommendations:**

Given the time- and dose-dependent neuronal toxicity observed in nonclinical studies, we recommend adding nerve conduction studies (NCS) to the safety monitoring of future studies of lumateperone, in addition to comprehensive neurological examinations.

Baseline and follow-up NCS testing would be preferable to monitoring only by neurological exam because it might detect subclinical changes, such as declining action potential amplitude or conduction velocity, that would not become symptomatic until after a longer treatment course. Changes in NCS measurements relative to baseline could detect a developing neuropathy prior to symptom onset.

The earlier in the course of the toxic process that NCS studies are performed, the smaller the slowing and amplitude loss, relative to baseline studies, would likely be. Note that there can be a “coasting” phenomenon, with weeks of worsening of the sensory symptoms after stopping some drugs, such as pyridoxine, taxanes, and platins.

A trend of declining amplitudes or conduction velocities across multiple tested nerves or subjects would warrant removing a subject or stopping a study, respectively. A unilateral change for a given nerve could be attributed to a focal process, such as a nerve entrapment. Bilateral changes would argue strongly for a systemic process, such as a drug adverse effect.

In general, NCS studies should include both sensory and motor nerve assessments. If patients, such as children, are unable to tolerate motor nerve conduction studies, an alternative could be to include painless motor function assessments such as hand dynamometry and timed walking or standing up from chair (Get up and go) tests. These functional assessments could be done first in the protocol. The potentially painful motor nerve study could be scheduled last so that at least some useful data might be obtained if subjects do not tolerate the motor nerve study.

Although there are approximate general normal ranges, each EMG/NCS laboratory has its own internally validated normal ranges due to variations in equipment and operators. Although EMG technicians can carry out most procedures, a neurologist is needed to interpret the results. In order to increase assessment accuracy, the same clinical neurophysiologists should do the repeated examinations of a given patient.

Quantitative sensory testing (QST) can also be considered for monitoring large- and small-fiber sensory modalities. However, QST is highly dependent on the full cooperation of the patient and may be falsely abnormal if the patient is biased toward an abnormal result or is cognitively impaired. QST lacks the objectivity of NCSs. Reproducibility studies on the placebo-controlled group should be included.

The Neuropathy Impairment Score (NIS) plus 7 nerve tests (NIS+7) could be considered as an endpoint for monitoring peripheral neuronal toxicity. The NIS or NIS+7 has been used in clinical trials for diabetic sensorimotor polyneuropathy, monoclonal gammopathy of undetermined significance neuropathy, chronic inflammatory demyelinating polyradiculopathy, and transthyretin-type familial amyloid polyneuropathy (ATTR-FAP).

## References:

Ghavanini AA, Kimpinski K.

Revisiting the evidence for neuropathy caused by pyridoxine deficiency and excess.  
J Clin Neuromuscul Dis. 2014 Sep;16(1):25-31

Chong PST, Cros DP

Technology Literature Review: Quantitative Sensory Testing  
Muscle Nerve 29: 734–747, 2004

Cohen JA, Mowchun J, Grudem J

Peripheral Nerve and Muscle Disease  
Oxford University Press, 2009

Berk JL, et al.

Repurposing Diflunisal for Familial Amyloid Polyneuropathy A Randomized Clinical Trial  
JAMA. 2013 Dec 25;310(24):2658-67.

Dyck PJ, Davies JL, LitchyWJ, O'Brien PC.  
Longitudinal assessment of diabetic polyneuropathy using a composite score in the  
Rochester Diabetic Neuropathy Study cohort.  
Neurology. 1997;49(1):229-239.

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/s/

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RAINER PAINE  
08/21/2019 04:28:48 PM

TERESA J BURACCHIO  
08/26/2019 08:55:11 AM

## Clinical Inspection Summary

<b>Date</b>	7/30/2019
<b>From</b>	Cara Alfaro, Pharm.D., Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
<b>To</b>	Jasmeet (Mona) Kalsi, Pharm.D., Regulatory Project Manager David Millis, M.D., Medical Officer Division of Psychiatry Products
<b>NDA #</b>	209500
<b>Applicant</b>	Intra-Cellular Therapies, Inc.
<b>Drug</b>	Lumateperone
<b>NME</b>	Yes
<b>Proposed Indication</b>	Treatment of schizophrenia
<b>Consultation Request Date</b>	11/29/2018
<b>Summary Goal Date</b>	7/19/2019, extended to 7/30/2019
<b>Action Goal Date</b>	9/27/2019
<b>PDUFA Date</b>	9/27/2019

### I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Glass, Aukstuolis, Tran-Johnson, and Garcia as well as the sponsor, Intra-Cellular Therapies, were inspected in support of this NDA. Although inspectional observations were noted at the clinical investigator sites and the sponsor's site, they are unlikely to have a significant impact on the overall study results. Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

The clinical investigator and sponsor inspections covered Protocols ITI-007-005 and ITI-007-301. Inspectional observations noted at the clinical investigator sites included lack of documentation of assessment of potential adverse events reported during central (remote) PANSS interviews, obtaining blood draws for genetic testing in subjects declining participation in this optional procedure, and under-reporting of adverse events. The most significant under-reported adverse event was one subject experiencing "orthostatic hypotension" and "syncope," with only "orthostatic hypotension" being reported to the sponsor. It is recommended that the review division consider including the additional case of syncope in the sponsor's proposed labeling.

The most significant inspectional observation noted at the sponsor site related to the sponsor's reporting of protocol deviations. In the NDA submission as well as in subsequent submissions provided by the sponsor in response to information requests, inadequate information was included to evaluate the impact of protocol deviations related to restricted concomitant

medications (i.e., lorazepam) on the primary efficacy endpoint (i.e., the change in PANSS total score). In addition, some protocol deviations related to these restricted concomitant medications were not included at all. It was determined that Site #106, enrolling in Study ITI-007-301, was noncompliant regarding lorazepam dosing in the study (i.e., the total dose and proximity of dosing to the PANSS evaluations) in at least 28 of 31 (90%) enrolled subjects. We recommend that the review division conduct a sensitivity analysis with regard to this clinical site.

In addition, in the NDA submission, the sponsor disclosed that 11 subjects enrolled in Protocol ITI-007-005 were “forced randomized” and received a different investigational product than assigned per the randomization schedule due to inadequate investigational product at some sites. Review of the randomization schedule provided during the sponsor inspection identified 4 additional subjects who received a different investigational product than assigned. We recommend that the review division conduct a sensitivity analysis for all 15 of these subjects (*refer to sponsor inspection summary*).

Finally, during the sponsor inspection, the sponsor stated that the database for Protocol ITI-007-005 was unlocked approximately one month following database lock and unblinding of the study and then relocked one week later. This had not been disclosed in the NDA submission. We recommended that the review division send an information request in order to obtain confirmation from the sponsor regarding the reasons for the database unlock, identification of personnel with access to unblinded data between unblinding of the study and the database relock, and a list of all data that was changed from the time of database unlock to the relock.

## II. BACKGROUND

Lumateperone capsules are being developed by Intra-Cellular Therapies, Inc. under NDA 209500 (IND 79,690), for the treatment of schizophrenia in adults. The sponsor submitted one Phase 2 study, ITI-007-005, and one Phase 3 study, ITI-007-301, in support of the efficacy and safety of lumateperone for the treatment of schizophrenia. The review division requested inspections for both of these studies.

### Protocol ITI-007-005

*Title:* A randomized, double-blind, placebo-controlled, multi-center study to assess the antipsychotic efficacy of ITI-007 in patients with schizophrenia

*Subjects:* 335 randomized

*Sites:* 8 sites in the United States

*Study Initiation and Completion Dates:* 1/4/2012 – 8/13/2013

*Database Lock:* 11/1/2013

This was a Phase 2, randomized, double-blind, placebo-controlled study in subjects diagnosed with schizophrenia with an acute exacerbation of psychosis. Included were male or female subjects 18 to 55 years of age, diagnosis of schizophrenia, history of at least 3 months exposure

to one or more antipsychotic therapies, prior response to antipsychotic therapy within previous 5 years, and experiencing an acute exacerbation of psychosis.

The study consisted of four phases:

- Screening phase: 2 to 7 days prior to Day 1, washout of psychotropic medications
  - Double-blind treatment phase: 4 weeks inpatient, subjects randomized (1:1:1:1) to one of the following four study arms:
    - Placebo
    - Risperidone (active control) 2 mg Q AM Day 1, 4 mg Q AM starting on Day 2
    - ITI-007 60 mg Q AM Day 1 and throughout study
    - ITI-007 60 mg Q AM Day 1, 120 mg Q AM starting on Day 2
- The risperidone 4 mg and ITI-007 120 mg groups were titrated to the assigned doses over one day. To preserve the blind, investigational product was administered as one capsule in the morning on Day 1 and two capsules in the morning starting on Day 2 for all study arms.
- Stabilization phase: 5-day inpatient, stabilized on standard antipsychotic medication (open-label)
  - Safety Follow-up: ~2 weeks after the end of the stabilization phase

Concomitant medications were allowed on as as-needed basis for treatment of agitation, namely (lorazepam), insomnia (zaleplon, zolpidem), and extrapyramidal adverse events (benztropine, propranolol), with dose restrictions outlined in the protocol. These medications were not to be administered within 8 hours of efficacy or safety ratings.

The primary efficacy endpoint was the mean change in the Positive and Negative Syndrome Scale (PANSS) total score from baseline to Week 4. PANSS ratings were performed by a remote Central Rater (through the vendor (b) (4)).

#### Protocol ITI-007-301

*Title:* A randomized, double-blind, placebo-controlled, multi-center study to assess the antipsychotic efficacy of ITI-007 in patients with schizophrenia

*Subjects:* 450 randomized

*Sites:* 12 sites in the United States

*Study Initiation and Completion Dates:* 11/13/2014 – 7/20/2015

*Database Lock:* 8/17/2015

This was a Phase 3, randomized, double-blind, placebo-controlled study in subjects diagnosed with schizophrenia with an acute exacerbation of psychosis. The major eligibility criteria were similar to Protocol ITI-007-005.

The study design was also similar to Protocol ITI-007-005, but subjects were randomized (1:1:1) to one of three study arms during the 4-week double-blind treatment phase:

- Placebo
- ITI-007 40 mg Q AM
- ITI-007 60 mg Q AM

The primary efficacy endpoint was the mean change in the PANSS total score from baseline to Week 4. PANSS ratings were performed by a remote Central Rater (through the vendor (b) (4)).

### **Rationale for Site Selection**

The clinical sites were chosen primarily based on numbers of enrolled subjects and impact on the primary efficacy endpoint.

## **III. RESULTS**

### **1. Steven J. Glass, M.D.**

CRI Worldwide, LLC  
401 Route 73 North Lake  
Center Executive Park  
Suite 100  
Marlton, NJ 08053

Dr. Steven Glass is no longer employed by CRI Worldwide LLC, and his clinical site in Marlton, NJ has been closed. Dr. Glass is currently employed by the sponsor for this NDA, Intra-Cellular Therapies (*refer to sponsor inspection summary below*). CRI was acquired by PRA Health Sciences in 2013. The inspection of study records took place at PRA Health Sciences, located at 731 Arbor Way, Suite 100, Blue Bell, PA 19422.

At this site for Protocol ITI-007-005 (Site #13), 70 subjects were screened, 42 were enrolled, and 24 completed the study. Eighteen subjects discontinued the study due to subject request (n = 8), loss-to-follow up [noted as “other” in sponsor line listings] (n = 6), investigator opinion (n = 3), lack of efficacy (n = 1).

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data.

The primary efficacy endpoint data were PANSS total scores obtained via remote interviews conducted by (b) (4). After the PANSS interview, scores were recorded on a Remote Assessment Score Sheet and faxed to the clinical site. These score sheets, which

included scores for each individual PANSS item as well as the total score, were compared to sponsor data listings; no discrepancies were identified.

However, several inspectional observations were brought to the attention of the clinical investigator:

#### Lack of Documentation of Assessment of Potential Adverse Events

Potential adverse events were sometimes reported to the remote PANSS Central Rater by the subject during the interview, which were documented on the Potential Clinical Events Notification (PCEN) form that was sent to the site following the interview. Dr. Glass signed the form, as required by the sponsor, but did not always document the decision-making process with regard to whether or not the events reported on the form were in fact adverse events. Sometimes Dr. Glass would write “not an AE”; however, no further documentation was provided on the form or in the progress notes (e.g., whether or not the symptom was present in the subject’s prior medical history). Table 1 lists the potential adverse events noted on the PCEN form for this site that were not reported to the sponsor.

**Table 1. Potential Under-Reported Adverse Events, Protocol ITI-007-005 (Site #13)**

<b>Subject #/ Treatment Arm</b>	<b>Date of PANSS Interview</b>	<b>New or Worsening Symptom Reported during PANSS Interview*</b>	<b>Comments by Clinical Investigator</b>	<b>Comments</b>
(b) (6) / Risperidone	2/5/2013	Slurred speech (slight)	Not an AE	“Not an AE” added 6 months after form signed
(b) (6) / Lumateperone 120 mg	3/25/2013	Significant headache all day – almost a migraine	Not an AE	
(b) (6) / Lumateperone 120 mg	4/25/2013	Gas and heartburn		
(b) (6) / Lumateperone 60 mg	4/8/2013 4/24/2013	Tinnitus Constipation		Docusate was added as a concomitant medication for the treatment of constipation; however, this AE was not recorded
(b) (6) Lumateperone 120 mg	4/24/2014 5/2/2013	Headache Sleepy Nausea		

\*Potential Clinical Events Notification Form category “a new or worsening symptom or event that may or may not relate to the diagnosis under study”

*Reviewer's comment: The site lacked documentation for evaluation of potential adverse events reported during PANSS central interviews. With the exception of constipation, which required concomitant medication administration, it cannot be determined whether the other symptoms were adverse events or not.*

#### Consent for Optional Blood Draw for Genetic Sub-Study

Subjects could consent to a blood draw for genetic testing by signing an optional informed consent form that was separate from the main protocol consent form. Subject (b) (6) did not consent to the genetic sub-study; however, a blood sample for genetic testing was collected on 2/5/2013. (b) (4), which was handling the genetic testing for this sub-study, was contacted regarding this error on 2/6/2013 when the site completed the sample destruction/discard request form. The site obtained the certificate of sample destruction (dated 8/22/2013) from (b) (4).

*Reviewer comment: The clinical site identified the error quickly and acted appropriately in contacting (b) (4) to request destruction of the blood sample. However, it is unknown whether the site informed the IRB or the subject of this error.*

#### Subject Eligibility

Subject # (b) (6) had a positive urine toxicology screen for benzodiazepines, which should have excluded this subject from enrollment. Exclusion criterion #19 for Protocol ITI-007-005 is "a positive qualitative urine drug or alcohol test at screening, or evidence of either withdrawal from, or acute intoxication with cannabis, cocaine, opiates, amphetamines, alcohol, barbiturates, or hallucinogens or similar compounds." According to the FDA field investigator, Dr. Glass knew that the subject had been prescribed diazepam but did not consider that to be exclusionary. Dr. Glass completed a patient eligibility review form that included this laboratory result, and the (b) (4) Medical Monitor indicated that labs met eligibility criteria. It is unclear whether this was an error on the part of the Medical Monitor or an eligibility waiver. Subject # (b) (6) was then randomized to the risperidone treatment arm.

*Reviewer comment: Subject # (b) (6) had a positive urine drug screen on 1/22/2013 for benzodiazepines (the subject was also known to be taking diazepam). This subject's baseline visit was 1/28/2019, six days after the screening visit. The half-life of diazepam and its active metabolite (N-desmethyldiazepam) is up to 100 hours, which would require approximately 20 days (5 half-lives) to be cleared from the body. Therefore, for this subject, the baseline efficacy ratings were potentially confounded by the presence of this benzodiazepine. However, since this subject was randomized to risperidone, the active control, this would not impact the primary efficacy endpoint, which was the comparison of lumateperone vs. placebo.*

**2. Jim Aukstuolis, M.D.**

Woodland International Research Group, Inc.  
1012 Autumn Road, Suite 3  
Little Rock, AR 72211

At this site for Protocol ITI-007-005 (Site #17), 90 subjects were screened, 76 were randomized, and 66 completed the study. Ten subjects discontinued the study due to withdrawal of consent (n = 5), investigator's opinion (n = 2), lack of efficacy (n = 1), "other" (n = 1) and adverse event (n = 1). The subject who discontinued due to an adverse event was randomized to risperidone and experienced an elevated CPK.

For Protocol ITI-007-301 (Site #109), 79 subjects were screened, 62 were enrolled, and 52 completed the study. Ten subjects discontinued the study due to lack of efficacy (n = 8) and withdrawal of consent (n = 2). Subject (b) (6), randomized to placebo, discontinued the study on 2/13/2015 due to lack of efficacy, was stabilized on risperidone, discharged on (b) (6), and died on (b) (6). The narrative for this subject is included in the NDA submission.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for 13 of 76 (17%) subjects enrolled in Protocol ITI-007-005 and 15 of 62 (24%) enrolled subjects in Protocol ITI-007-301 was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data.

The primary efficacy endpoint data were PANSS total scores obtained via remote interviews conducted by (b) (4). After the PANSS interview, scores were recorded on a Remote Assessment Score Sheet and faxed to the clinical site. These score sheets, which included scores for each individual PANSS item as well as the total score, were compared to sponsor data listings; no discrepancies were identified.

However, several inspectional observations were brought to the attention of the clinical investigator:

**Lack of Documentation of Assessment of Potential Adverse Events**

There was no documentation on the Potential Clinical Events Notification (PCEN) forms from (b) (4) (or on any other source documents) to indicate that potential adverse events elicited by the remote PANSS Central Rater had been assessed. This was noted for 4 of 13 (31%) subject files audited for Protocol ITI-007-005 and 1 of 15 (7%) subject files audited for Protocol ITI-007-301. Table 2 lists the potential adverse events noted on the PCEN form for this site that were not reported to the sponsor.

**Table 2. Potential Under-Reported Adverse Events, Protocols ITI-007-005 (Site #17) and ITI-007-301 (Site #109)**

Subject Treatment Arm	Date of PANSS Interview	New or Worsening Symptom Reported During PANSS Interview*
(b) (6) Lumateperone 60 mg	2/14/2012	Itching on arms and back
(b) (6) Lumateperone 120 mg	4/17/2013	Head and stomach pain
	4/29/2019	Severe daily headaches
(b) (6) Placebo	7/18/2013	Vomiting
(b) (6) Placebo	7/19/2013	Leg pain
(b) (6) Lumateperone 60 mg	11/24/2014	Constipation, stomach cramps, lower back pain
	12/2/2014	Decreased appetite, stomach upset

\*Potential Clinical Events Notification Form category “a new or worsening symptom or event that may or may not relate to the diagnosis under study”

Dr. Aukstuolis acknowledged the lack of documentation regarding the assessment of potential adverse events noted during the central PANSS ratings. However, he did not consider the reported symptoms to be adverse events, as they were either related to the underlying disorder (e.g., delusion) or were present prior to the study (prior medical history). Dr. Aukstuolis also explained that symptoms he considered secondary to a reported adverse event were not reported (e.g., vomiting due to headache).

*Reviewer comment: The site lacked documentation for evaluation of potential adverse events (AEs) reported during PANSS central interviews. Therefore, for most of these potential AEs, it cannot be determined whether these were actual AEs. However, in his response, Dr. Aukstuolis stated that he did not report adverse events that he considered secondary, e.g. vomiting due to headache. It also appears that he did not consider worsening of a symptom present in the subject’s past medical history to be a reportable adverse event (e.g., severe headaches in a subject with history of intermittent headaches). Therefore, based on the clinical investigator’s response, there is evidence of under-reporting of adverse events in these two cases (i.e., as listed in Table 2 for Subjects (b) (6)).*

#### Consent for Optional Blood Draw for Genetic Sub-Study

Subjects could consent to a blood draw for genetic testing by signing an optional informed consent form that was separate from the main protocol informed consent form. During the inspection, it was discovered that Subject (b) (6) did not consent to the genetic sub-study; however, a blood sample was collected on 12/9/2014. After conclusion of the inspection, the site contacted (b) (4) requesting that this sample be destroyed. (b) (4) confirmed that the sample was in storage and that the request for destruction would be processed. Dr. Aukstuolis informed the IRB of this protocol deviation and contacted the subject to explain the error.

*Reviewer comment: The site did not realize that a blood sample was drawn in a subject who had declined participation. It is not known whether genetic testing was ever performed on this sample. According to the clinical investigator, processes have been put in place at this site to prevent recurrence of this issue.*

### Retention of Study Records

For Protocol ITI-007-301, the clinical investigator did not retain original source documentation containing vital signs taken between 11/19/2014 and 1/30/2015 for 38 of 79 (48%) consented subjects. Therefore, vital sign line listings could not be verified against source documents for 38 consented subjects, 10 of whom were screen failures and not randomized. No other investigational records were noted to be missing.

### **3. Tram Tran-Johnson, Pharm.D., PsyD**

CNRI-San Diego  
446 26<sup>th</sup> Street  
San Diego, CA 92102

Dr. Tran-Johnson was the clinical investigator for Protocol ITI-007-301 (Site #101). She retired in 2016 and was not available during this inspection. However, sub-investigators and other study personnel involved with this protocol were available.

At this site for Protocol ITI-007-301, 44 subjects were screened, 30 were randomized, and 25 subjects completed the study. Five subjects discontinued the study due to lack of efficacy (n = 4) and adverse events (n = 1). Subject (b) (6), randomized to ITI-007 60 mg, discontinued the study due to the adverse events of orthostatic hypotension and syncope.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for 16 of 30 (53%) subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data.

The primary efficacy endpoint data were PANSS total scores obtained via remote interviews conducted by (b) (4). After the PANSS interview, scores were recorded on a Remote Assessment Score Sheet and faxed to the clinical site. These score sheets, which included scores for each individual PANSS item as well as the total score, were compared to sponsor data listings; no discrepancies were identified.

However, several inspectional observations were brought to the attention of Dr. Benbow, now the lead psychiatrist for CNRI-San Diego and a subinvestigator for Protocol ITI-007-301 at Dr. Tran-Johnson's site.

### Under-reporting of Adverse Events

One adverse event occurring in one of 30 (3.3%) randomized subjects were not reported to the sponsor:

*Subject* (b) (6)

This subject was randomized to lumateperone 60 mg and experienced severe orthostatic hypotension and syncope approximately three hours post-dose on Day 1 of the study. Orthostatic hypotension was reported as an adverse event, but syncope was not reported.

The adverse event form was originally completed on 5/14/2015 (on the day of the event). This form had a field with “final AE diagnosis/term to be entered into CRF.” This field was initially completed as “syncope secondary to orthostatic hypotension” but was changed three days later to “orthostatic hypotension” only. In addition, this event was originally defined as a serious adverse event (SAE) but was changed to a non-SAE on 5/17/2015. Of note, this form included an “additional description/signs and symptoms” field that was completed with “syncope-associated symptom of orthostatic hypotension” on 5/19/2015; however, this field was not designated for entry into the CRF. Subject (b) (6) was discontinued from the study due to these adverse events.

Furthermore, a description of this event was available in the progress notes at the site. According to these notes, during assessment of standing vital signs, the subject became unresponsive and fell against the exam room table, being caught by site staff before hitting the floor. As site staff lowered the subject to the floor, the subject became verbally responsive. The subject was assessed by the sub-investigator, Dr. Benbow, shortly afterwards, and vital signs were taken. Supine blood pressure (BP) and heart rate (HR) were 91/56 mmHg, 59 bpm; sitting BP and HR were 89/53 mmHg, 66 bpm; and standing BP and HR were 69/37 mmHg, 72 bpm. Progress notes indicate that the orthostatic hypotension resolved after approximately 3 hours.

Dr. Benbow provided a response to the inspectional observations, stating that (b) (4), the CRO, had asked the site to report the terms hypotension, orthostasis, and syncope as separate adverse events. However, the Medical Director (an internist and also a subinvestigator) made a determination that the terms of orthostasis and syncope were not “stand alone” diagnoses as both were symptoms directly related to severe orthostatic hypotension. Therefore, the event term was changed to orthostatic hypotension.

*Reviewer comments: Syncope should have been reported as an adverse event term, regardless of the fact that it was considered secondary to the orthostatic hypotension. This additional case of syncope was provided to the review division so that they could recalculate incidence rates for syncope included in the proposed labeling. Additionally, the blood pressure/pulse readings obtained immediately after the event are not included in the sponsor’s data listings and may be important to the review division when assessing the overall severity of orthostatic hypotension associated with lumateperone.*

### Inadequate Case Histories

Subject (b) (6), randomized to lumateperone 60 mg, had a history of an emergency room visit for thoughts of suicide in (b) (6) as described in her medical record. However, this information was not transcribed as a lifetime history of suicidal ideation on the Columbia Suicide Severity Rating Scale (C-SSRS), which was required by protocol to be obtained at screening, baseline, or any other visits during the study.

Dr. Benbow responded that this subject was well known to staff, had consistently reported absence of suicidal ideation, and that this emergency room report from 2009 was “not an accurate representation of the subject’s history.” He stated that the reported suicidal ideation was “better explained by command auditory hallucinations, confounded by illicit drug and alcohol use, rather than a genuine suicidal ideation with intent to die.”

*Reviewer comment: It is difficult to determine whether this 2009 event was consistent with suicidal ideation. However, at a minimum, the clinical investigator should have either reported this incident in the C-SSRS lifetime rating or documented the rationale as to why this event was not consistent with suicidal ideation. Neither of these were done. Of note, the presence of suicidal ideation in 2009 would not have been exclusionary since this event occurred >2 years prior to screening.*

#### **4. Donald J. Garcia, Jr., M.D.**

Future Search Trials LP  
5508 Parkcrest Drive  
Suite 300  
Austin, TX 78731

At this site for Protocol ITI-007-301 (Site #108), 19 subjects were screened, 13 were randomized, and 8 subjects completed the study. Five subjects discontinued the study due to lack of efficacy (n = 2), withdrawal of consent (n= 1), loss to follow-up (n = 1), and noncompliance (n = 1). Subjects were admitted to the (b) (4), a skilled nursing facility, rather than a psychiatric hospital (*please refer to the summary of the sponsor inspection below for further details and reviewer comments on this issue*).

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, concomitant medications, protocol deviations, and primary efficacy endpoint data.

The primary efficacy endpoint data were PANSS total scores obtained via remote interviews conducted by (b) (4). After the PANSS interview, scores were recorded on a Remote Assessment Score Sheet and faxed to the clinical site. These score sheets, which included scores for each individual PANSS item as well as the total score, were compared to

sponsor data listings; no discrepancies were identified.

There was no evidence of under-reporting of adverse events. However, the FDA field investigator did not review any Potential Clinical Events Notification forms completed by the central (remote) PANSS raters as was done for the other clinical investigator inspections for this NDA (*see above clinical investigator inspection summaries*).

#### 5. Intra-Cellular Therapies, Inc.

Alexandria Center for Life Science  
430 East 29<sup>th</sup> Street, Suite 955  
New York, NY 10016

This inspection covered the sponsor practices related to Protocols ITI-007-005 and ITI-007-301 and focused on the four clinical investigator sites (Site #s 13, 17/109, 101, and 108) that had been selected for inspection for this application.

Records reviewed included, but were not limited to, SOPs, organizational charts, sponsor oversight, monitoring plans and reports, monitor job descriptions/CVs, vendor contracts, transfer of responsibilities, investigator agreements, financial disclosure forms, and records, Form 1572s, protocol deviations, adverse event reporting, and test article accountability.

Clinical monitoring was conducted by (b)(4) for Protocol ITI-007-005 and (b)(4) for Protocol ITI-007-301. (b)(4) SOPs were followed for these protocols. Intra-Cellular SOPs, dated between 9/2018 and 3/2019, were not effective at the time the studies were conducted. In addition, the sponsor did not have an internal Quality Assurance unit or written procedures at the time these studies were conducted.

Two sites with noncompliance issues were identified by the respective CRO:

- Site #16, enrolling in Study ITI-007-005, had three major protocol deviations occurring in three subjects. For all three subjects, the baseline PANSS was obtained after subjects had received investigational product; therefore, no valid baseline PANSS total scores were obtained ((b)(6)/placebo, 1 (b)(6)/lumateperone 120 mg, (b)(6)/risperidone). These three major protocol deviations were included in the sponsor's line listings for the NDA submission. Corrective actions were implemented, the sponsor instituted a cap on randomization with close monitoring oversight, and the site was re-approved to enroll approximately four months following the enrollment cap.
- Site #106, enrolling in Study ITI-007-301, had repeated protocol deviations regarding the administration of lorazepam. The site was retrained in February 2015, but the deviations continued, and the site was closed to enrollment in April 2015. The major protocol deviations involving administration of lorazepam, which included total daily dose and proximity of dosing to PANSS evaluations deviations, occurred in at least 28 of 31 (90%) subjects at this site (*see further discussion regarding protocol deviations for concomitant medications below*). Not all of these protocol deviations were included in the data listings and subsequent responses to information requests.

Several inspectional observations were brought to the attention of the sponsor:

#### Protocol Deviations for Restricted Concomitant Medications

In the NDA submission as well as in subsequent submissions provided by the sponsor in response to information requests, inadequate information was included to evaluate the impact of protocol deviations related to restricted concomitant medications (i.e., lorazepam) on the primary efficacy endpoint (i.e., the change in PANSS total score). In addition, some protocol deviations related to these restricted concomitant medications were not reported at all.

#### *Inadequate Information in Major Protocol Deviations Listings*

Significantly more major protocol deviations were reported for Protocol ITI-007-005 compared to Protocol ITI-007-301. For example, five major protocol deviations were submitted for Protocol ITI-007-005 and 88 major protocol deviations were submitted for Protocol ITI-007-301. For ITI-007-005, deviation categories included investigational product administration, disallowed medications, and “other”. For Protocol ITI-007-301, deviation categories included prohibited medication, inclusion/exclusion criteria, and procedure/test.

Eighty-three of the 88 (94%) major protocol deviations included in the original NDA submission for Protocol ITI-007-301 were categorized as “prohibited medication” with the description “subject took lorazepam, benzotropine, or propranolol but failed to follow ‘Table 3’ of the protocol.” Specifically:

- Exhibit 1 (see below), which is a reproduction of “Table 3” from Protocols ITI-007-301 and ITI-007-005, specifies the maximum allowable daily dose and the maximum number of days per week for administration of lorazepam, benzotropine, and propranolol as well as timing restrictions for these concomitant medications with regard to efficacy or safety ratings.
- However, this major protocol deviation listing did not provide any information with regard to:
  - the actual concomitant medication administered, or
  - whether the protocol deviation pertained to a dosing deviation or timing restriction deviation.
- Information requests were sent to the sponsor asking for further details regarding “Table 3” major protocol deviations. The sponsor’s response noted additional protocol deviations that were not included in the major protocol deviations listing in the NDA submission.
- Information requests were also sent to the sponsor asking for lorazepam administration times so that timing restriction deviations could be determined as this specific deviation was considered the most significant deviation with potential impact on the primary efficacy endpoint.
- However, the sponsor responded that they could not provide lorazepam administration times since these data were not captured in eCRFs.
  - The sponsor noted that identification of the timing restriction deviations was dependent on the monitor identifying them during monitoring visits.
  - The sponsor further stated that the only way to identify all timing restriction

deviations for lorazepam, benztropine, and propranolol and submit this information to the review division was to review medication administration records (MARs).

- This MAR review was then requested by the review division (*see reviewer comments*).

**Exhibit 1. “Table 3” Reproduction from Protocol ITI-007-005 and ITI-007-301**

Medication	Study Period	Dosage Allowed	Timing Restrictions
Lorazepam	Screening Period through to Day 7, inclusive	Maximum of 6 mg/day	Not within 8 hours prior to PANSS, CGI, PSP or CDSS
	Day 8 through to Day 14, inclusive	Maximum of 4 mg/day	
	Day 15-Day 28, inclusive	Maximum of 2 mg/day on no more than 4 days/week	
Benzotropine	Screening Period through to Day 28, inclusive	Maximum of 4 mg/day	Not within 8 hours of SAS, BARS, or AIMS
Propranolol	Screening Period through to Day 28, inclusive	Maximum of 40 mg/day	

*Major Protocol Deviations Listing Incomplete*

In response to an information request, the sponsor provided further details for “Table 3” protocol deviations. A review of this list identified a number of protocol deviations consistent with the definition of major protocol deviation that were not included in the NDA submission. During the inspection, the sponsor commented that these additional unreported “Table 3 deviations”, all related to lorazepam being administered within 8 hours of the CGI-S assessment, did not impact the primary efficacy endpoint (i.e., the PANSS total score), and therefore were not considered to be major protocol deviations. Of note, this new definition of major protocol deviation for “Table 3 deviations” was not included in the CSR or Statistical Analysis Plan.

Additionally, when the sponsor submitted the lorazepam timing restriction protocol deviations, which would have met criteria for prohibited medication/Table 3 deviations (*see reviewer comments*), it was identified that many of those deviations were not included in the NDA submission or prior responses to information requests. Specifically, 13 additional major protocol deviations were identified for Protocol ITI-007-005 and 14 additional major protocol deviations were identified for Protocol ITI-007-301.

*Reviewer comments: Lorazepam was the most commonly used of these restricted concomitant medications. Although some of the other “Table 3 deviations” could impact efficacy, in discussions with the review division, it was noted that timing restriction deviations for lorazepam could have the most significant impact on the primary efficacy endpoint.*

*On 5/10/2019, the sponsor responded to an information request and submitted a summary of timing restriction deviations for lorazepam administration within 8 hours of central PANSS ratings for both protocols. Of note, the response also included copies of medication administration records (MARs). To verify that the data submitted in response to this information request was accurate, this reviewer went through approximately 30-40% of the MARs. No significant differences were noted with the data provided by the sponsor, namely:*

- *Lorazepam timing restriction deviations occurred in 14/335 (4.2%) of subjects enrolled in Protocol ITI-007-005. These 14 deviations occurred in the following treatment arms: placebo (n = 7), lumateperone 60 mg (n = 2), lumateperone 120 mg (n = 2), and risperidone (n = 3).*
- *Lorazepam timing restriction deviations occurred in 43/450 (9.6%) of subjects enrolled in Protocol ITI-007-301. These 43 deviations occurred in the following treatment arms: placebo (n = 19), lumateperone (n = 12), and lumateperone (n = 12).*

*Administration of lorazepam within 8 hours of the PANSS rating could confound efficacy. It is reassuring that most of these deviations occurred in the placebo groups for both protocols; therefore, these deviations would be more likely to benefit the placebo group compared to the lumateperone groups. These data have been discussed with the review division. In addition, as noted above, Site #106 was found by the sponsor/CRO to be noncompliant regarding lorazepam dosing in the study. We recommended that the review division conduct a sensitivity analysis with regard to this clinical site.*

### Monitoring

Clinical monitoring was conducted by (b) (4) for Protocol ITI-007-005 and (b) (4) for Protocol ITI-007-301. However, there was no process in place to document reconciliation of potential adverse events elicited during the central PANSS interviews.

Specifically, for the (b) (4) central interviews for PANSS ratings, the raters were to complete a Potential Clinical Events Notification (PCEN) form if the subject reported any signs/symptoms that could be an adverse event. After the interview, this form was faxed to the clinical site, and the clinical investigator was to sign the form indicating that the information was reviewed. As described in clinical investigator inspection summaries above, there was a lack of documentation at the sites regarding the clinical assessment of potential adverse events noted on these PCEN forms—in most cases, clinical investigators signed the form with no further comments regarding whether the signs/symptoms noted by the central rater should be considered an adverse event. Neither the (b) (4) nor (b) (4) Monitoring Plans included specific instructions about monitor review of the PCEN forms for the purpose of adverse event reconciliation. While some monitoring reports reviewed during the sponsor inspection specifically address signs/symptoms documented on the PCEN forms, others do not mention these forms. Therefore, it is unclear whether monitors routinely reviewed these forms for

reconciliation of potential adverse events.

#### Forced Randomization for Protocol ITI-007-005

The clinical study report for Protocol ITI-007-005 included some information about forced randomization of 25 subjects from five study sites due to a disproportionate distribution of study drug kits across sites. During the sponsor inspection, the FDA field investigators requested additional information about this process. According to the sponsor, there were three different categories for these forced randomizations:

- M1: manual randomizations, subject could have received the correct treatment allocation per randomization or could have led to incorrect treatment allocation
- F1: forced randomization by programmed algorithm to the correct treatment assignment per original randomization scheme
- F2: forced randomization by programmed algorithm to the incorrect treatment assignment

In response to an information request sent on 1/10/2019, the sponsor provided a list of 25 subjects affected by the forced randomization, including the category (M1, F1, F2) for each subject. The FDA field investigators verified the information in the sponsor's response. There was no evidence that any unblinding had occurred for the 25 subjects with forced randomization. During the sponsor inspection, the sponsor provided a randomization schedule. Upon review of this randomization schedule, this reviewer identified four additional subjects meeting the M1 category of forced randomization but which were not included in the sponsor's response to the information request.

**Table 4. Forced Randomization Categories M1 and F2 for Protocol ITI-007-005**

Category	Subject	Treatment Received Forced Randomization	Intended Treatment per Randomization Scheme	Subject Included in Sponsor Response to Information Request
M1	(b) (6)	Placebo	Lumateperone 60 mg	Yes
		Placebo	Placebo	Yes
		Placebo	Risperidone	Yes
		Placebo	Placebo	Yes
		Placebo	Lumateperone 120 mg	Yes
		Placebo	Lumateperone 60 mg	Yes
		Lumateperone 120 mg	Placebo	No
		Lumateperone 120 mg	Placebo	No
		Risperidone	Placebo	No
		Lumateperone 120 mg	Placebo	No
F2	(b) (6)	Lumateperone 60 mg	Placebo	Yes
		Placebo	Risperidone	Yes
		Lumateperone 120 mg	Placebo	Yes
		Lumateperone 120 mg	Lumateperone 60 mg	Yes
		Placebo	Risperidone	Yes
		Lumateperone 120 mg	Risperidone	Yes
		Lumateperone 60 mg	Risperidone	Yes

*Reviewer comment: We recommend that the review division perform a sensitivity analysis for the 15 subjects who did not receive the investigational product according to the randomization schedule.*

#### Changes in Centrally Rated PANSS Scores

(b) (4) was the vendor responsible for remote central PANSS interviews and ratings. A manual, the Remote Assessment Plan, which was specific to these protocols, outlined the process for the remote PANSS interviews, including the following:

- Several items on the PANSS interview regarding the subject’s behavior require information from collateral informants. Clinical sites were required to submit (via fax) a completed Interview Checklist to (b) (4) the day before the scheduled PANSS interview. The (b) (4) rater could, if needed, contact the site after the interview to clarify any information on this checklist.
- After the interview, (b) (4) faxed (or emailed) the Potential Clinical Events Notification Form (*as referenced above*) and the Remote Assessment Score Sheet (PANSS ratings) to the clinical site.
- The manual outlined a process whereby the site could query PANSS ratings.

During the inspection, the FDA field investigator requested audit trails for changes in PANSS scores affecting eligibility or leading to decreasing scores. In reviewing these audit trails, there were some changes in PANSS scores that were due to “site query”. For 2 of 335 (<1%) subjects enrolled in Protocol ITI-007-005 and 5/450 (1.1%) subjects enrolled in Protocol ITI-007-301, central PANSS ratings scores were changed at the request of a clinical investigator (see Table 4).

**Table 4. Changes to Central PANSS Total Scores Based on Site Query**

Site # Investigator	Subject	Treatment Arm	Study Day	PANSS Total Score	
				Original Score	Changed Score
Protocol ITI-007-005					
17Aukstuolis	(b) (6)	Risperidone	Baseline	66	73
17/Aukstuolis		Lumateperone 60 mg	Baseline	72	74
Protocol ITI-007-301					
101/Tran-Johnson	(b) (6)	Placebo	Baseline	68	75
101/Tran-Johnson		Lumateperone 60 mg	Day 28	79	85
105/Volk		Lumateperone 40 mg	Baseline	67	73
109/Aukstuolis		Lumateperone 40 mg	Baseline	68	77
109/Aukstuolis		Lumateperone 40 mg	Baseline	68	74

*Reviewer comment: An increase in baseline score was requested by four clinical sites involving six subjects, four randomized to lumateperone. Of note, the PANSS inclusion criterion for Protocol ITI-007-301 was a baseline score  $\geq 70$ ; Protocol ITI-007-005 did not*

*have this baseline criterion. There is no evidence that PANSS total scores were increased in an effort to meet inclusion criteria. Given the very small percentage of subjects involved, it is unlikely that these changes in baseline PANSS scores would affect the efficacy conclusions for either study.*

#### Database Unlock for Protocol ITI-007-005

The database was locked on 11/1/2013 by (b) (4), the CRO, after they received approval from Intracellular Therapies for a functional lock of the database and unblinding of the data. According to the sponsor, the database was unlocked on 12/3/2013 to correct some data discrepancies. The sponsor did not disclose this database unlock in the NDA submission or when an information request was sent asking for the date of the database lock. These data discrepancies prompting the database unlock reportedly included waist circumference recorded in inches rather than centimeters, an incorrect dose date, an incorrect birth year for a subject, and an incorrect suicide attempt year (i.e., 2007 and not 2010). The database was relocked on 12/10/2013. The sponsor states that blinding was appropriately maintained.

*Reviewer comment: We recommended that the review division send an information request in order to obtain confirmation from the sponsor regarding the reasons for the database unlock, identification of personnel with access to unblinded data between unblinding of the study and the database relock, and a list of all data that was changed from the time of database unlock to the relock.*

Other issues identified during the inspection included:

#### Clinical Site Qualification and Approval

For Protocol ITI-007-301, Site #108 (Dr. Garcia), subjects were admitted to the (b) (4), a skilled nursing facility, rather than a psychiatric hospital. Of note, while the protocol states that subjects are to be hospitalized during the study, the protocol does not specifically define “hospital” or “clinic”.

Clinical investigators complete a Site Information Questionnaire, which is reviewed by the CRO. If the site is being considered, a Site Qualification Visit is conducted with a site monitor and sponsor representatives. The Site Qualification Visit checklist includes criteria pertaining to site facilities and equipment. The FDA field investigators reviewed the Site Qualification Visit for Dr. Garcia’s site and noted that there was no specific documentation or evaluation with regard to the site’s mixed population (psychiatric subjects and non-psychiatric skilled nursing patients). The sponsor stated that this site had segregated areas for study and non-study participants.

*Reviewer comment: Although this site was approved by the sponsor as one of the clinical trial sites for Protocol ITI-007-301 in the treatment of schizophrenia, it was noted that this setting is a skilled nursing facility rather than a psychiatric hospital.*

Current Employees of Intra-Cellular/Former Clinical Investigators

A number of clinical investigators/sub investigators for Protocols ITI-007-005 or ITI-007-301 are now employees of the sponsor. The most significant of these personnel was Dr. Glass, as summarized below:

Stephen Glass, M.D.

- Clinical investigator Protocol ITI-007-005 (Site #13); 2012 – 2013
- Sub-investigator Protocol ITI-007-301 (Site #112/Dr. Krefetz); 2014 – 8/2015
- Retired from PRA in 6/2015
- Consultant to Intra-Cellular Therapies beginning 9/11/2015
- Senior Medical Director, Intra-Cellular Therapies beginning 2/1/2016 (letter dated 1/7/2016)

*Reviewer comment: Both the Intra-Cellular Therapies consulting agreement and employment offer were reviewed during the inspection. Review of the documents and discussions with the sponsor did not indicate any potential conflicts of interest for Dr. Glass or other personnel.*

*{See appended electronic signature page}*

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## MEMORANDUM

Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research

**Date:** July 8, 2019

**To:** Tiffany Farchione, MD, Director (Acting)  
Division of Psychiatry Products

**Through:** Dominic Chiapperino, PhD, Director  
Silvia Calderon, PhD, Senior Pharmacologist  
Controlled Substance Staff

**From:** Jovita Randall-Thompson, PhD, Pharmacologist  
Controlled Substance Staff

**Subject:** **Caplyta, NDA 209500**  
**Generic Name:** lumateperone (ITI-007)  
**Dosages:** (b) (4) 42-mg (free base) capsules (equivalent to (b) (4)  
(b) (4) 60 mg of lumateperone tosylate)  
**Formulation:** immediate-release (IR) capsules taken once a day  
**IND Number:** 079690  
**Indication:** Treatment of schizophrenia  
**Sponsor:** Intra-Cellular Therapies, Inc.  
**PDUFA Goal Date:** September 27, 2019

### Materials Reviewed:

- NDA 209500, eCTD 0001 and eCTD 0002, submitted June 5, 2018 and September 27, 2018
- Drug Abuse Liability Assessment (Module 2.7.4.2.)
- Evaluation of the Reinforcing Effects of ITI-007 and ITI-131 using a Self-administration Procedure in Cocaine-maintained Rats, Report RS1545
- Evaluation of the potential of ITI-007 and ITI-131 to Induce Tolerance and Dependence in Male Sprague Dawley Rats, Report RS1526
- Phase 1, 2, and 3 Study Reports ITI-007-001, ITI-007-002, ITI-007-003, ITI-007-005, ITI-007-006, ITI-007-009, ITI-007-017, ITI-007-018, ITI-007-020, ITI-007-301, and ITI-007-303

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## I. SUMMARY

### 1. Background

This memorandum responds to a consult request dated October 12, 2018 from the Division of Psychiatry Products (DPP) regarding lumateperone, trade name Caplyta (IND 79690 and NDA 209500).

Intra-Cellular Therapies, Inc. (Sponsor) submitted the new drug application (NDA) for lumateperone to treat patients diagnosed with schizophrenia. The NDA was granted fast track designation on November 13, 2017 and rolling review status on April 4, 2018.

Lumateperone is a dopamine receptor protein phosphorylation modulator (DPPM) that acts as a presynaptic partial agonist, and postsynaptic antagonist at dopamine 2 (D<sub>2</sub>) receptors. These actions lead to an overall reduction of dopaminergic signaling. Lumateperone also displays potent serotonin 2A (5-HT<sub>2A</sub>) receptor antagonism, moderate serotonin reuptake transporter (SERT) inhibition, and indirect modulation of glutamate (N-methyl-D-aspartate (NMDA) receptors) via downstream activation of dopamine 1 (D<sub>1</sub>) receptors.

Lumateperone is not approved or marketed in the United States or in other countries.

## 2. Conclusions

1. Lumateperone is a dopamine receptor protein phosphorylation modulator (DPPM) that acts as a presynaptic partial agonist and postsynaptic antagonist at D<sub>2</sub> receptors, and is a potent 5-HT<sub>2A</sub> antagonist. These actions lead to an overall reduction of dopaminergic signaling. The Sponsor states that lumateperone is not chemically or pharmacologically similar to any known drug of abuse, does not produce psychoactive effects that are abuse related, and thus has no abuse potential and is unlikely to be abused. Upon assessment of the pharmacology, chemistry, and the absence of abuse-related adverse events reports in clinical trials, CSS agrees with the Sponsor and concludes that lumateperone does not meet criteria to be scheduled under the Controlled Substance Act (CSA).
2. Binding assays show that at nanomolar concentrations lumateperone and its metabolites have moderate to high affinities for several receptors (D<sub>1</sub>, 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub> and SERT) associated with abuse. The Sponsor conducted functional assays with lumateperone to evaluate for agonist or antagonist activity of the drug at receptors known to be activated or blocked by drugs with abuse potential. Lumateperone did not produce agonist or antagonist activity associated with abuse-related effects. Also, it is the activation of the 5-HT<sub>2A</sub> receptor that is the primary underlying mechanism linked to the abuse-related effects of classic psychedelics like lysergic acid diethylamide (LSD), psilocin, and mescaline, which are full or partial agonists at this receptor. In contrast, lumateperone is a full antagonist.
3. In the nonclinical abuse and dependence studies conducted with lumateperone, there were no abuse signals found. Lumateperone did not show differences in lever responding compared to placebo when tested in a self-administration study, and it did not differ in withdrawal-related behavior compared to placebo when tested in a physical dependence and withdrawal study.
4. Abuse-related adverse events (AEs) were not reported in clinical trials. CSS conducted a review of the AEs collected during Phase 1, 2, and 3 studies and reviewed the abuse-related AE assessment conducted by the Sponsor. The clinical trial AE data did not demonstrate any evidence of misuse, abuse, diversion or dependence across a range of lumateperone doses. There were no subjective CNS effects of potential interest to abusers, such as mood elevation, stimulation, or hallucinogenic effects. The most frequent CNS-related AE were somnolence or sedation, commonly associated with other approved and unscheduled antipsychotics.

## 3. Recommendations

Based on the lack of an abuse signal found with lumateperone, CSS recommends not to include a Section 9, Drug Abuse and Dependence in the lumateperone label.

## II. DISCUSSION

### 1. Chemistry

#### 1.1 Drug Substance

Lumateperone tosylate's chemical properties:

- chemical name is 1-butanone, 1-(4-fluorophenyl)-4-[(6bR,10aS)-2,3,6b,9,10,10a-hexahydro-3-methyl-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl]-, 4-methylbenzenesulfonate
- molecular formula is C<sub>31</sub>H<sub>36</sub>FN<sub>3</sub>O<sub>4</sub>S
- molecular weight is 565.7 amu

#### 1.2 Drug Product

Lumateperone will be marketed as an immediate-release (b)(4) capsule for oral administration. (b)(4) 42 mg of lumateperone as the active ingredient. Dosage strengths are expressed as the free base equivalent, thus a (b)(4)

(b)(4) 60 mg of lumateperone tosylate is equivalent to 42 mg of the active moiety, see Sponsor's table below (**Table 1**) taken from the proposed lumateperone (CAPLYTA) label. The capsules are also formulated with a number of standard pharmaceutical excipients (mannitol, (b)(4), croscarmellose sodium, (b)(4), magnesium stearate, and (b)(4)).

**Table 1:** Lumateperone capsule strengths and identifying features

Capsule Strength	Equivalent to	Capsule Color	Capsule Markings
42 mg	60 mg lumateperone tosylate	Blue cap and opaque white body	"ITI-007 42 mg"

### 2. Nonclinical Pharmacology

#### 2.1 Pharmacokinetics in Animals and Humans

In humans, the predominant route of metabolism after oral administration of lumateperone is ketone reduction to the alcohol metabolite, IC200131. This metabolic pathway involves AKR1C1, an enzyme in the aldo-keto reductase superfamily. The phylogeny of the AKR1C subfamily indicates a divergent

evolutionary path between human and nonhuman enzymes (NDA 209500, Module 2.4, Nonclinical Overview). The AKR1C1 reductase is expressed only in humans. The tissue expression of AKR1C1 in humans leads to the formation of reduced lumateperone (and ether-linked O-glucuronides) in humans relative to nonhuman species. As such the metabolism of lumateperone is significantly different in humans, dogs, and rats (NDA 209500, Module 2.4, Nonclinical Overview).

In rats, which is the species used in nonclinical abuse-related studies, the major route of elimination of lumateperone is fecal excretion, while in humans, the major route of elimination is urinary excretion. Pharmacokinetic studies shown that rats (and dogs) lumateperone and its metabolites accumulate with increasing doses and the elimination of lumateperone metabolites is prolonged (Nonclinical Overview, NDA 209500, Module 2.4).

The PK absorption after a single dose of lumateperone (5 mg/kg) is shown below in the Sponsor's table (Table 2).

**Table 2: Pharmacokinetics: Absorption after a Single Dose**

Species/Strain: Rat/Sprague-Dawley			Postdose Sampling Times: plasma: 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h; bile: 0-2, 2-4, 4-6, 6-8, and 8-24 h									Study Reference: 6INTRP1R1				
Initial Age: Approximately 73 days			Method of Administration: oral gavage									Location in CTD: Section 2.6.4.3.3; Section 2.6.4.5.12				
Date of First Dose: NS			Feeding Conditions: fasted from 12 h predose until 4 h postdose									GLP Compliance: non-GLP				
Number of Animals/Sex/Group: 3 males/group			Vehicle/Formulation: 0.5% MC in deionized water									Assays: LC-MS/MS				
Number of Animals/Sex/Group/Time Point: 2-3 males/time point			Sample: plasma, bile													
Test Article	Sample	Analyte	Mean Plasma Levels (ng/mL)									T <sub>max</sub> (h)	C <sub>max</sub> (ng/mL)	t <sub>1/2</sub> (h)	AUC <sub>last</sub> (ng·h/mL)	
			0 h	0.25 h	0.5 h	1 h	2 h	4 h	6 h	8 h	24 h					
Lumateperone tosylate, 5 mg/kg	Plasma	IC200056	NF	17.93	18.17	21.13	15.64	7.68	6.24	2.40	BLQ	0.75	22.00	1.72	75.07	
		IC200161*	NF	20.70	17.73	16.07	15.19	8.39	8.28	3.31	BLQ	0.83	22.57	2.06	76.09	
		IC200131	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	ND	ND	ND	ND
	Bile	Analyte	Mean Bile Levels (ng/mL)													
			0-2 h		2-4 h		4-6 h		6-8 h		8-24 h					
			IC200056	29.09	6.39	3.74	1.99	1.58								
	IC200161*	230.50	99.37	125.53	62.30	24.74										

Note: IC200056 = free base of ITI-007 (parent compound); IC200161 = desmethyl metabolite; IC200131 = ketone-reduced metabolite. AUC<sub>last</sub> = area under the plasma concentration-time curve from Time 0 to the time of the last measurable sample; BLQ = below the limit of quantitation; C<sub>max</sub> = maximum plasma concentration; CTD = Common Technical Document; GLP = Good Laboratory Practice; LC-MS/MS = liquid chromatographic tandem mass spectrometry; MC = methylcellulose; ND = not determined; NF = not found; NS = not specified; t<sub>1/2</sub> = terminal half-life; T<sub>max</sub> = time of maximum plasma concentration.

\* In this study IC200130, a racemic mixture of IC200161 and its optical isomer, was used as a standard to detect and estimate IC200161 concentrations.

(Source: EDR, NDA 209500, Module 2.6.5 Pharmacokinetics Tabulated Summary, Table 2.6.5-3C2.7.4.2-3., page 11)

In an initial study (Report CXR0398S), brain, and plasma levels of lumateperone were determined after oral (10 mg/kg), intravenous (1.0 mg/kg), and intraperitoneal (2.0 mg/kg) administration in male rats. Concentrations of lumateperone were measurable in blood and brain after administration to Sprague Dawley rats. Concentrations of lumateperone in the brain were higher than those concentrations in the whole blood at both 1 and 4 hours for all three routes of administration. After oral administration, the C<sub>max</sub> of lumateperone in the blood was approximately 10 ng/ml whereas brain concentrations were 213 ng/ml at 60 minutes and 186 ng/ml at 240 minutes. There is rapid and sustained distribution of lumateperone into the brains of rats. The metabolites IC200161 and IC200131 were detected in the rat brain (Report CX0448S). IC200161 concentration levels in the brain were 5~11 times higher than their

respective plasma levels and varied by route of administration. IC200131 concentrations were at or near the limit of quantification for the assay regardless of route of administration.

## 2.2 Receptor Binding and Functional Assays

The Sponsor conducted various in vitro assays, see Sponsor table below (**Table 3**) with lumateperone and its metabolites tested at an array of abuse-related targets. Receptor binding and functional assay data on lumateperone and its metabolites collected in the various studies conducted by the Sponsor is discussed below. Additionally, the binding affinities of several major atypical antipsychotic medications and the antidepressant medication, fluoxetine, extrapolated; from the NIMH Psychoactive Drug Screening Program Database and Snyder et al., 2015<sup>1</sup>, are also presented for comparison by the Sponsor, see the Sponsor table below (**Table 4**).

Lumateperone tosylate was shown to have moderate to high affinities for the 5-HT<sub>2A</sub> (K<sub>i</sub>=0.5 nM), D<sub>2</sub> (K<sub>i</sub>=32 nM), and dopamine D<sub>1</sub> receptors (K<sub>i</sub>=52 nM), and SERT (K<sub>i</sub>=62 nM). In screens of lumateperone against nearly 70 receptors, ion channels, and enzymes at a single concentration of 100 nM, lumateperone had projected K<sub>i</sub> values at or below 100 nM at the D<sub>4</sub>, α<sub>1A</sub>, and α<sub>1B</sub> receptors; there was no significant activity at any of the other targets. In follow up studies, lumateperone had no significant affinity for mGluR<sub>1</sub> or mGluR<sub>5</sub> metabotropic glutamate receptors, and none for mu-opioid (MOP) receptors.

The in vitro pharmacological activity of lumateperone's major metabolites IC200161, and IC200131 were also screened against nearly 70 receptors, ion channels, and enzymes; both are pharmacologically active with similar pharmacological profiles to the parent lumateperone. IC200161 demonstrated nanomolar affinity for the 5-HT<sub>2A</sub>, α<sub>1A</sub> and α<sub>1B</sub> receptors, and SERT, and lower affinity for dopamine, and adrenergic receptors. IC200131 demonstrated nanomolar affinity for 5-HT<sub>2A</sub>, 5-HT<sub>1A</sub>, D<sub>4</sub>, α<sub>2A</sub>, and σ<sub>2</sub> receptors, and the serotonin transporter. The affinity of IC200131 for the other dopaminergic, and adrenergic receptors appeared to be reduced compared to lumateperone. IC200161, and IC200131 have no appreciable affinity for mGluR<sub>1</sub> or mGluR<sub>5</sub> metabotropic glutamate receptors.

In vitro pharmacology of other metabolites IC201308, IC201309, and secondary lumateperone metabolite IC200565, and two diastereoisomers of IC200131, IC200582, and IC200583 were examined. IC201308 showed specific interaction with 5-HT<sub>2A</sub>, D<sub>1</sub>, α<sub>1A</sub>, and MOP receptors. IC200582 and IC200583 demonstrated affinity for 5-HT<sub>2A</sub>, D<sub>4</sub>, and σ<sub>2</sub> receptors, and SERT. IC200565 demonstrated affinity for 5-HT<sub>2A</sub> and σ<sub>2</sub> receptors. IC201309 showed inhibition of the MOP receptor only, while IC201308 demonstrated an antagonist effect at the MOP receptor with an IC<sub>50</sub> of 140 nM. IC201309 demonstrated no functional activity at the MOP receptor.

Lumateperone simultaneously modulates serotonin, dopamine, and glutamate neurotransmission, without inducing abuse-related behavioral effects. Based on behavioral studies conducted and

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<sup>1</sup> Snyder GL, Vanover KE, Zhu H, Miller DB, O'Callaghan JP, Tomesch J, Li P, Zhang Q, Krishnan V, Hendrick JP, Nestler EJ, Davis RE, Wennogle LP, Mates S. (2015). Functional Profile of a Novel Modulator of Serotonin, Dopamine, and Glutamate Neurotransmission. *Psychopharmacology (Berl)*; 232(3):605-621.

described by the Sponsor, it is a potent antagonist at 5-HT<sub>2A</sub> receptors in vivo and shown to block the behavioral effects of quipazine, a hallucinogenic 5-HT<sub>2A</sub> receptor agonist (half-maximal effective dose ED50] = 0.12 mg/kg, oral). In addition, the Sponsor states that as a presynaptic partial agonist and postsynaptic antagonist at dopamine D<sub>2</sub> receptors in vivo, lumateperone reverses the behavioral effects of the psychomotor stimulant amphetamine. Lumateperone stimulate the phosphorylation of NMDA GluN2B receptors and indirectly increases glutamate neurotransmission. This indirect enhancement is in contrast to the pharmacological effects of drugs that directly block the NMDA channel such as phencyclidine and ketamine.

Furthermore, neither lumateperone nor its metabolite IC200131 demonstrated reinforcing effects in cocaine-trained rats in the self-administration study over a range of intravenous doses. In clinical trials, lumateperone did not demonstrate subjective CNS-related or potentially abuse-related AEs of interest in healthy subjects or subjects with schizophrenia.

**Table 3:** Overview of receptor ligand-binding studies

Study Number	Test System	Test Article	Relevant Findings
ITI DPI004	Recombinant human serotonin receptors and rat dopamine receptors	Lumateperone, IC200161	Lumateperone: 5-HT <sub>2A</sub> K <sub>i</sub> = 0.5nM; D <sub>2</sub> K <sub>i</sub> = 32 nM. IC200161 is also a potent ligand for 5-HT <sub>2A</sub> and D <sub>2</sub> receptors.
ITI DPI005	Recombinant 5-HT <sub>2A</sub> receptors expressed in HEK293E cells and CHO cells expressing D <sub>2</sub> receptors	Lumateperone	At nanomolar concentrations, lumateperone effectively reduced serotonin-induced increases in phosphoinositide turnover in HEK293E-transfected cells. Lumateperone reduced dopamine-induced reductions in cAMP generation in transfected CHO cells.
ITI NOV001	Recombinant human D <sub>2</sub> receptors and 5-HT <sub>2A</sub> , 5-HT <sub>2C</sub> , D <sub>2</sub> , alpha <sub>1A</sub> , and H <sub>1</sub> receptors from membranes	Lumateperone	Lumateperone demonstrated high affinity for 5-HT <sub>2A</sub> receptors in rat frontal cortex, lesser affinity for D <sub>2</sub> receptors in the rat striatum, and very low affinity for 5-HT <sub>2C</sub> receptors in the pig choroid plexus.
ITI NOV002	Various in vitro assay systems	Lumateperone	K <sub>i</sub> < 100 nM at 5-HT <sub>2A</sub> , D <sub>1</sub> , D <sub>2</sub> , D <sub>4</sub> , alpha <sub>1A</sub> and alpha <sub>1B</sub> receptors, and SERT.
ITI NOV003	Various in vitro assay systems	IC200161	K <sub>i</sub> < 100 nM at 5-HT <sub>2A</sub> , alpha <sub>1A</sub> and alpha <sub>1B</sub> receptors, and SERT.
ITI NOV004	Various in vitro assay systems	IC200131	K <sub>i</sub> values ≤ 1,000 nM at 5-HT <sub>2A</sub> , 5-HT <sub>1A</sub> , D <sub>4</sub> , alpha <sub>2A</sub> and sigma <sub>2</sub> receptors, and SERT.
ITI 10-7059	Various in vitro assay systems	IC200582	K <sub>i</sub> values ≤ 1,000 nM at 5-HT <sub>2A</sub> , D <sub>4</sub> , and sigma <sub>2</sub> receptors, and SERT.
ITI 10-7060	Various in vitro assay systems	IC200583	K <sub>i</sub> values ≤ 1,000 nM at 5-HT <sub>2A</sub> , D <sub>4</sub> , and sigma <sub>2</sub> receptors, and SERT.
ITI 10-7051	Various in vitro assay systems	IC200565	K <sub>i</sub> values ≤ 1,000 nM at 5-HT <sub>2A</sub> and sigma <sub>2</sub> receptors.
ITI NOV005	Recombinant human D <sub>1</sub> and D <sub>4.4</sub> receptors	Lumateperone, IC200161	K <sub>i</sub> = 20.4 nM and 39.7 nM at D <sub>1</sub> and D <sub>4.4</sub> dopamine receptors, respectively.
ITI-007-INT-AD17-01	Recombinant human D <sub>2S</sub> receptors	Lumateperone	IC <sub>50</sub> of lumateperone at D <sub>2S</sub> receptors was 69.8 nM.
ITI-007 INT D2	Recombinant human D <sub>2L</sub> receptors	Lumateperone	IC <sub>50</sub> of lumateperone at D <sub>2L</sub> receptors was 32 nM.
ITI NOV006	Recombinant human SERT receptors	Lumateperone, IC200161	Against SERT in the rat forebrain, human platelets, and the recombinant transporter in CHO cells, lumateperone K <sub>i</sub> was 46.2, 72.1, and 33 nM, respectively. In the same systems, IC200161 K <sub>i</sub> was 31.4, 78.4, and 390 nM, respectively.
ITI NOV007	Recombinant human receptors	Lumateperone, IC200161, IC200131	At alpha <sub>1A</sub> and alpha <sub>1B</sub> receptors, lumateperone K <sub>i</sub> was 20.2 and 9.58 nM, respectively. At the same receptors, IC200161 K <sub>i</sub> was 44.6 and 10.8 nM, respectively. IC200131 demonstrated <50% inhibition at 1-μM concentration at both alpha <sub>1A</sub> and alpha <sub>1B</sub> . Neither lumateperone, IC200161, nor IC200131 demonstrated appreciable affinity for either mGluR <sub>1</sub> or mGluR <sub>5</sub> .

**Table 3:** Overview of receptor ligand-binding studies (continued)

Study Number	Test System	Test Article	Relevant Findings
ITI-007 ITI EURO IC200056 IC201308 IC201309 Selectivity Panel	Various in vitro assay systems	Lumateperone, IC201308, IC201309	Lumateperone significantly inhibited 5-HT <sub>2A</sub> , 5-HT <sub>2B</sub> , D <sub>2S</sub> , and alpha <sub>1A</sub> receptors, and SERT. K <sub>i</sub> for the D <sub>1</sub> assay was 41 nM. IC201308 significantly inhibited 5-HT <sub>2A</sub> , D <sub>1</sub> , alpha <sub>1A</sub> , and μ-opioid receptors. K <sub>i</sub> for the D <sub>1</sub> assay was 22 nM. IC201309 inhibited μ-opioid receptors only, with K <sub>i</sub> of 85 nM.
ITI-007 ITI EURO IC201308 Functional Assay for MOP Activity	Recombinant human opioid receptors	IC201308	IC <sub>50</sub> of IC201308 at μ-opioid receptors was estimated at 140 nM.
ITI-007 ITI EURO IC201309 Functional Assay for MOP Activity	Recombinant human opioid receptors	IC201309	No estimates of IC <sub>50</sub> or EC <sub>50</sub> were determined for IC201309 at μ-opioid receptors because results showing an inhibition or stimulation >50% (threshold for significance) were not observed in this study.
ITI-007 ITI EURO IC200056 IC201308 IC201309 Receptor Binding K <sub>i</sub> Determinations	Recombinant human receptors	Lumateperone, IC201308, IC201309	At 5-HT transporters, 5-HT <sub>2A</sub> receptors, and D <sub>2L</sub> receptors, lumateperone K <sub>i</sub> values were 16, 10, and 49 nM respectively. At 5-HT <sub>2A</sub> receptors, IC201308 K <sub>i</sub> values were 11 nM. No K <sub>i</sub> or IC <sub>50</sub> values were determined for IC201309.

5-HT = serotonin; AMPA = α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid; cAMP = cyclic adenosine monophosphate; CHO = Chinese hamster ovary; D = dopamine receptor; EC<sub>50</sub> = half-maximal effective concentration; IC<sub>50</sub> = half-maximal inhibitory concentration; K<sub>i</sub> = inhibitory constant; mGluR = metabotropic glutamate receptor; SERT = serotonin transporter.

(Source: EDR, NDA 209500, Module 2.7.4.2, Drug Abuse Liability Assessment, Table 2.7.4.2-3., pages 18-19)

**Table 4:** Receptor binding affinity  $K_i$  (nM) of lumateperone as measured by radio ligand displacement assays: comparison with antipsychotic and antidepressant medications

Receptor	Lumateperone	Risperidone	Olanzapine	Aripiprazole	Fluoxetine
5-HT <sub>2A</sub>	0.5	0.5	2.5	9	141
D <sub>2</sub>	32	5.9	31	1.6	>10,000
D <sub>1</sub>	52	564	128	1,170	>10,000
SERT	62	>1,000	>1,000	240–405	0.9–20
<b>Ratios</b>					
D <sub>2</sub> /5-HT <sub>2A</sub>	60	12	12.4	0.18	>70
<b>Receptor</b>					
H <sub>1</sub>	>1,000	14	2	28	1,240
5-HT <sub>2C</sub>	173	63	7.1	130	69
$\alpha$ 1 Adrenergic	73	2.3	60	26	2,260
<b>Ratios</b>					
H <sub>1</sub> /5-HT <sub>2A</sub>	>2,000	28	1	3	8.8
5-HT <sub>2C</sub> /5-HT <sub>2A</sub>	320	126	3	14	0.5
$\alpha$ 1/5-HT <sub>2A</sub>	135	5	24	2.9	16

5-HT<sub>2A</sub> = serotonin 2A receptor; 5-HT<sub>2C</sub> = serotonin 2C receptor; D<sub>1</sub> = dopamine 1; D<sub>2</sub> = dopamine 2; H<sub>1</sub> = histamine subtype 1;  $K_i$  = inhibitory constant; SERT = serotonin transporter.

(Source: EDR, NDA 209500, Module 2.7.4.2, Drug Abuse Liability Assessment, Table 2.7.4.2-4., page 20)

## 2.3 Findings from Safety Pharmacology and Toxicology Studies

The following sections include a review of the toxicological studies conducted by the Sponsor that evaluated the general neurobehavioral effects of lumateperone when tested in single-dose and repeated-dose studies.

### Lumateperone Toxicity

Lumateperone administered orally was evaluated in 2 single dose toxicity study in rats, and in 6 repeated-dose toxicity studies, 1 in male and female mice (CD-1), 2 in male and female rats (Sprague-Dawley), and 3 in male and female dogs (Beagle).

Lumateperone produced neurobehavioral effects after a single dose and when repeatedly administered. Non-clinical observations that were reported included the following:

#### *Single-dose studies*

Observations were gathered over multiple drug doses and over several studies including: lumateperone at 0, 30, 100, or 300 mg/kg (PO), Report 06-A12-FE; lumateperone at 0, 5, 15, or 30 mg/kg/day (PO), Report 06N-P12-FC.

- Rats (males and females):
  - at dose 10, 15, 30, 100 mg/kg (PO) - decreased activity
  - at dose 300 mg/kg (PO) - tremors (females only)

#### *Repeated-dose studies*

For mice, observations were gathered over multiple drug doses and over several studies including: lumateperone at 0, 5, 15, 30 or 60 mg/kg/day (PO), with 30-day recovery period, Report 11217.

- Mice (males and females):
  - at dose levels 15, 30, and 60 mg/kg/day (PO) - lethargic and ataxia
  - at dose level 60 mg/kg/day (PO) - ataxia and limping
  - at dose levels 15, 30, and 60 mg/kg/day (PO) - hypoactive
  - at dose levels 30 and 60 mg/kg/day (PO) - stereotypic head bob and uncoordinated gait
  - no relevant clinical signs were noted during recovery periods

For rats, non-clinical observations were gathered over multiple drug doses and over several studies including: lumateperone at 0, 5, 15, 30 mg/kg/day (PO) for 28 days, with one-month recovery period, Report 06-S12-GC; lumateperone at 0, 5, 15, or 60 mg/kg/day (PO) for 3 months, with one-month

recovery period, Report 11220; and ; lumateperone at 0, 5, 15, 30, or 60 mg/kg/day (PO) for 6 months, with 30-day recovery period, Report 11220.

- Rats (males and females):
  - at dose 60 mg/kg/day (PO) - body shakes, and decrease activity (females only)
  - at dose 60 mg/kg/day (PO) - head tilt
  - at doses 30 mg/kg/day (PO) - ataxia and unsteady gait (only females)
  - at dose levels 15 and 30 mg/kg/day (PO) - hypoactivity
  - at dose levels 30 mg/kg/day (PO) - lethargy
  - clinical signs were noted during recovery periods, following 60 mg/kg/day for 6 months observations included shaking body, and hypoactive; and for females only ataxia, unsteady and lethargic was reported

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For dogs, non-clinical observations were gathered over multiple drug doses and over several studies including: lumateperone at 0, 2.5, 5, 10, 15 mg/kg/day (PO) for 9 months, Report 11221; lumateperone at 0, 2.5, 5, or 10 mg/kg/day (PO) for 28 days, with one- month recovery period, Report 06-S16-GA; lumateperone at 0, 2.5, 5, 10, or 30 mg/kg/day (PO) for 90 days, with 45-day recovery period, Report 08-S16-MR; and lumateperone at 0, 10, 20, or 50 mg/kg (PO, single dose) and 10 mg/kg/day (PO) for 7 days, Report 06N-P16-FF.

- Dogs (males and females):
  - at dose 5, 10, 15 mg/kg/day (PO) - hypoactivity, lethargy, subdued, slow to respond, unsteady, reluctant to stand and walk, unable to stand and walk
  - at dose 5 and 10 mg/kg/day (PO) - decrease activity
  - at dose 10 and 15 mg/kg/day (PO) - tremors
  - at dose 20 and 50 mg/kg (single dose) - tremors
  - at dose 20 mg/kg (single dose) - tremors and decreased activity
  - at doses 10 mg/kg/day (PO) - subdued
  - at dose levels 15 and 30 mg/kg/day (PO) - hypoactivity
  - at dose levels 30 mg/kg/day (PO) - lethargy
  - no relevant clinical signs were noted during recovery periods

## 2.4 Animal Behavioral Studies

### General behavior study

#### *Functional Observation Behavioral test/ Study 06-S12-GC*

The behavioral effects of lumateperone were evaluated using a functional observation battery as part of a 28-day toxicology study in rats (Study 06-S12-GC). Dose levels used in the study (i.e., 5, 15, or 30 mg/kg/d, PO), were based on results from a dose range-finding study (Study No. 06N-P12-FC). On study Day 27, lumateperone  $C_{max}$  ranged from 4.07 to 26.80 ng/mL and from 19.70 to 58.87 ng/mL in male and female rats, respectively. The doses of lumateperone administered in this study (5-30 mg/kg) produced  $C_{max}$  values in male and female rats, respectively, that ranged from 35% to 233% and 171% to 511% of the mean  $C_{max}$  observed at steady state in humans administered the intended clinical dose of 42

mg/d (11.5 ng/mL) (Study ITI- 007-005, Table 16); PK data is presented in the Sponsor's table below (**Table 5**).

Observations were done once during the week before initiation of exposure to lumateperone, and during weeks 2, 4, and 7 (3 weeks after cessation of drug administration) following the start of drug treatment. No treatment related findings were noted. Also, locomotor activity (60-minute test sessions) was assessed. There were no drug-related differences in motor or locomotor activity for males or females at any dose level.

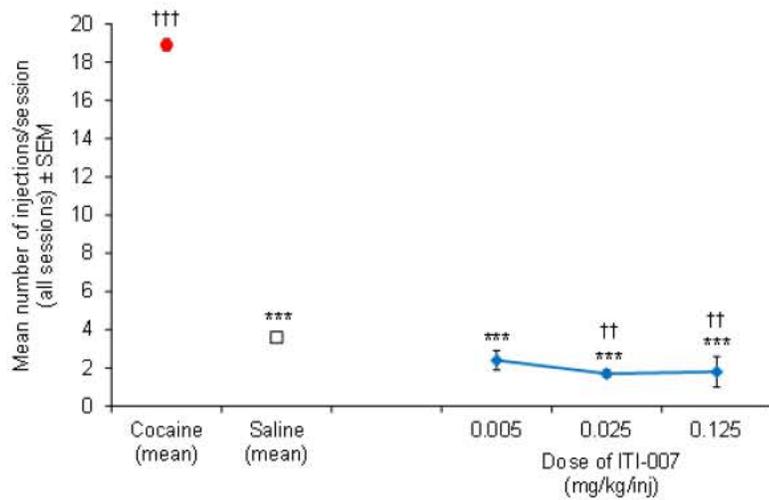
### **Abuse-related and physical dependence studies**

#### *Self-Administration/ Study RS1545*

A self-administration test (Study RS1545) was conducted to evaluate the abuse/dependence liability of lumateperone, and the metabolite IC200131 in cocaine-maintained male rats. Subjects were trained to self-administer a low dose of cocaine (0.29 mg/kg per injection) given intravenously (IV) on a fixed ratio 3 (FR3) reinforcement schedule and were then evaluated for the reinforcing effects of lumateperone and IC200131; saline was the control substance. A blood sampling experiment was carried out, lumateperone and IC200131 were evaluated (also metabolites IC200161 and IC200565), data is presented in the Sponsor's table below (**Table 5**). The  $C_{max}$  after intravenous injection of the equivalent mean accumulated drug intake for each of the doses of lumateperone taken in the self-administration study ranged between 70% and 1,871% of the reported clinical  $C_{max}$ , while the range for IC200131 was 19% to 207%. Clinical plasma concentrations were based on Phase 2 trial concentrations of lumateperone and IC200131 when reaching steady state. The Sponsor asserts that the reinforcing potential of lumateperone and the metabolite IC200131 has been investigated across concentrations from below the level of clinical exposure through multiples of clinical exposure. As shown in Table 4, a  $C_{max}$  range of 8.1–215.2 ng/mL for lumateperone and 5.4–59.1 ng/mL for IC200131 was reported in rats. The Sponsor thus estimates a 70% and 1,871% range in rats compared to clinical exposure ( $C_{max}$ ) for lumateperone, while the range for IC200131 was 19% to 207% of the reported clinical  $C_{max}$ . When considering the 61 ng/mL peak human plasma level at the therapeutic dose of lumateperone, it is likely that testing was evaluated at doses 2 to 3 times the therapeutic dose, however results reported at plasma levels below therapeutic plasma levels are considered insufficient. Because a high range of plasma levels above clinical therapeutic exposure was established the data provides a sufficient margin. According to the Sponsor the results of this study revealed that none of the doses of lumateperone (0.005, 0.025 or 0.125 mg/kg/injection IV) or IC200131 (0.005, 0.025 or 0.125 mg/kg/injection IV) maintained rates of IV self-administration either > 6 injections/session, or at a level significantly greater than the self-administration of saline. Results are illustrated in the Sponsor's figures below (**Figure 1 and 2**).

The Sponsor concluded that lumateperone, and its metabolite, IC200131, do not serve as positive reinforcers in cocaine-maintained rats. The Sponsor states that there was a significant reduction in the number of infusions of lumateperone taken by the rats at the two higher doses (0.025 and 0.125 mg/kg/injection, IV) when compared with their responding for the non-reinforcer, saline, and this indicates that this compound was probably aversive at high doses in rats. Based on the data presented the conclusion is acceptable.

**Figure 1: Reinforcing effects of lumateperone**

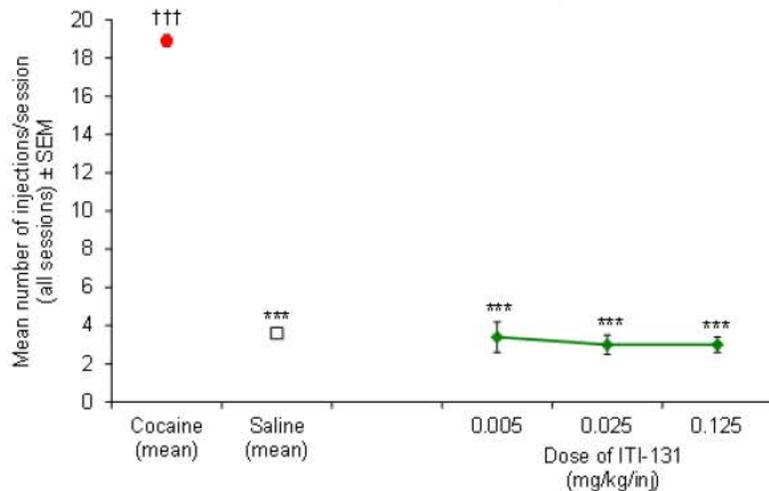


\*\*\* Significantly different from cocaine using the combined mean of before (1) and after (2) test compound administration by Dunnett's test ( $p < 0.001$ ).

†† or ††† Significantly different from saline by Williams' test ( $p < 0.01$  or  $p < 0.001$ ).

(Source: EDR, NDA 209500, Module 2.7.4.2, Drug Abuse Liability Assessment, Figure 2.7.4.2-4., page 28)

**Figure 2: Reinforcing effects of IC200131**



\*\*\* Significantly different from cocaine using the combined mean of before (1) and after (2) test compound administration by Dunnett's test ( $p < 0.001$ ).

††† Significantly different from saline by Williams' test ( $p < 0.001$ ).

(Source: EDR, NDA 209500, Module 2.7.4.2, Drug Abuse Liability Assessment, Figure 2.7.4.2-5., page 29)

*Nonclinical Dependence and withdrawal/ Study RS1526*

The aim of this study (Study RS1526) was to evaluate the potential of lumateperone (1.5, and 15 mg/kg, PO, QD) and metabolite IC200131 (1.5, and 15 mg/kg, PO, QD) to cause tolerance/sensitization, and/or physical dependence and withdrawal after 28 days in male Sprague-Dawley rats. Morphine (30 mg/kg PO, bid) was used as the positive control because of its ability to induce rapid tolerance and dependence, and produce a recognizable withdrawal syndrome in both humans and animals. A blood sampling experiment was carried out, lumateperone and IC200131 were evaluated (also metabolites IC200161 and IC200565), and data is presented in the Sponsor's table below (**Table 5**). At 15 mg/kg/d for 28 days in rats, lumateperone and IC200131 produced  $C_{max}$  values that were 140% and 110%, respectively, of the values measured in human plasma after a single oral dose of lumateperone (42 mg). Thus, the assessment of physical dependence and withdrawal behaviors was conducted at clinically relevant levels of exposure.

Lumateperone treatment of 1.5 mg/kg/day caused reddened descended testicles, hunched posture, subdued behavior, and increased body tone in  $\leq 40\%$  of rats during the drug exposure period. These signs diminished following drug discontinuation. Lumateperone treatment of 15 mg/kg/day produced hunched posture, subdued behavior, decreased body tone, ptosis, decreased locomotor activity, decreased reactivity to sound, decreased body tone, and reddened and descended testicles in  $\geq 40\%$  of rats during drug exposure. Signs that were observed in  $< 40\%$  of rats during 15 mg/kg of lumateperone exposure included erratic respiration, Straub tail, increased locomotor activity, increased body tone, increased reactivity to sound, tail rattling, and pink rear paws. These observations ceased following drug discontinuation.

There were no physiological signs, i.e., reductions in food, and water intake, body weight or body temperature changes to indicate physical dependence. The Sponsor concluded that neither lumateperone nor IC200131 produces tolerance or sensitization in male rats during repeated administration or a syndrome of behavioral and/or physical dependence on abrupt withdrawal. Based on the data presented the conclusion is acceptable.

**Table 5:** Summary of pharmacokinetic data in animal abuse-related studies

Study Number	Test System	Test Article/Dose/Route	Analyte	Sex	Pharmacokinetic Parameter	
					C <sub>max</sub> (ng/mL)	AUC <sub>last</sub> (ng·h/mL)
06-S12-GC	Rat, Sprague-Dawley	lumateperone, 5–30 mg/kg/d, oral	IC200056 <sup>a</sup>	Male	SD 0: 3.88–19.87 SD 27: 4.07–26.80	SD 0: 8.20–45.46 SD 27: 5.78–39.93
				Female	SD 0: 23.22–61.10 SD 27: 19.70–58.87	SD 0: 11.45–113.05 SD 27: 20.80–170.92
			IC200161	Male	SD 0: 1.35–49.27 SD 27: 6.38–167.00	SD 0: 0.93–79.16 SD 27: 8.93–306.83
				Female	SD 0: 4.14–202.50 SD 27: 30.63–241.67	SD 0: 5.04–356.71 SD 27: 36.61–745.51
S1545	Rat, Sprague-Dawley	lumateperone, 0.017–0.394 mg/kg, intravenous	IC200056 <sup>a</sup>	Male	8.1–215.2	5.4–112.7
			IC200161	Male	0.2–4.2	0.3–7.5
		IC200131, 0.023–0.569 mg/kg, Intravenous	IC200131	Male	5.4–59.1	2.7–57.1
			IC200565	Male	0.2–2.5	0.1–2.6
RS1526	Rat, Sprague-Dawley	lumateperone, 1.5–15 mg/kg/d, oral	IC200056 <sup>a</sup>	Male	SD 1: 1.1–6.2 SD 14: 0.6–9.5 SD 28: 1.0–12.1	SD 1: 6.1–43.9 SD 14: 4.1–63.3 SD 28: 4.1–72.8
				IC200161	Male	SD 1: 0.6–10.9 SD 14: 0.7–69.9 SD 28: 0.7–69.7
		IC200131, 1.5–15 mg/kg/d, oral	IC200131	Male	SD 1: 0.3–8.5 SD 14: 0.7–20.8 SD 28: 0.5–20.6	SD 1: 2.7–54.9 SD 14: 2.9–110.1 SD 28: 1.4–119.9
					IC200565	Male

AUC<sub>last</sub> = area under the curve up to the last measurable plasma concentration; C<sub>max</sub> = maximum plasma concentration; SD = study day.

<sup>a</sup>IC200056 is lumateperone free base.

(Source: EDR, NDA 209500, Module 2.7.4.2, Drug Abuse Liability Assessment, Table 2.7.4.2-5., page 24)

### 3. Clinical Pharmacology

#### 3.1 Absorption, Distribution, Metabolism, Elimination (ADME)

Lumateperone is rapidly absorbed with a bioavailability of 4.4% for the lumateperone capsule formulation. It is also extensively metabolized, and efficiently eliminated. However, lumateperone absorption is dose dependent and when given with food there is a lowered peak in the plasma  $C_{max}$ , increased median AUC (by 60%), and delayed  $T_{max}$  (Module 2.5 Clinical Overview; Report ITI-007-006 Part A).

In a bioavailability and mass balance study in healthy volunteers, following the administration of a single 40 mg lumateperone dose ( $2 \times 20$  mg capsules), half-life values for the lumateperone free base ranged from 1.73 to 3.16 hours (Clinical Report ITI-007-006). The  $T_{max}$  of lumateperone on average ranged from approximately 1 to 2 hours regardless of dose (NDA 209500, Module 2.5, Clinical Overview).

Across multiple-dose studies in patients with schizophrenia, on Day 5 the  $T_{max}$  of lumateperone was approximately 1 hour with a  $t_{1/2}$  ranging from approximately 1.42 to 4.01 hours. At steady state, lumateperone (42 mg on Day 1 and 84 mg on Days 2-8) mean  $C_{max}$  was 61.0 ng/mL and occurred at a median time of 2.5 hours after dosing, with an  $AUC_{0-inf}$  of 271 h·ng/mL (Module 2.5 Clinical Overview and Module 2.7.2 Summary of Clinical Pharmacology Studies).

After oral administration of lumateperone in , three pharmacologically active metabolites, IC200131, IC200161 and IC200565, were formed, accounting for approximately 18% of circulating total radioactivity (IC200161 = 1.3%, IC200131 = 9.4% and IC200565 = 5.3%) (Module 2.5 Clinical Overview). There were two other metabolites (IC201308 and IC201309) present in plasma but according to the Sponsor's pharmacology evaluation of lumateperone, including receptor binding results, these metabolites do not contribute to the efficacy of lumateperone. The average  $T_{max}$  value for all the three metabolites IC200131, IC200161, and IC200565 was 1.5 hour and at a dose regime of 42 mg on Day 1 and 84 mg on Days 2-8 of lumateperone,  $C_{max}$  values were 66.4, 28.4 and 32.5 ng/mL, respectively (Module 2.7.2 Summary of Clinical Pharmacology Studies Tables 2.7.2-14, 2.7.2-15 and 2.7.2-16; Report ITI-007-006 Part A and B). IC200131 terminal  $t_{1/2}$  (%CV) was 10.8 hours (38.2%), whereas IC200161 and IC200565 terminal  $t_{1/2}$  (%CV) values were 2.3 hours (21.6%), and 15.5 hours (29.2%), respectively (Module 2.7.2 Summary of Clinical Pharmacology Studies; Report ITI-007-016).

### 4. Clinical Adverse Events

#### 4.1 Clinical Studies

The Sponsor conducted clinical studies (Phases 1 through 3) to assess the efficacy, safety, and tolerability of lumateperone for the treatment of schizophrenia. Lumateperone is a modulator of serotonin, dopamine, and glutamate neurotransmission. It shares some pharmacological similarities with many approved second-generation antipsychotics that block dopamine  $D_2$  receptors and one or more serotonin receptors.

Clinical safety data were generated from 19 Phase 1, 2 and 3 clinical trials in healthy volunteers, subjects with dementia, patients with sleep maintenance insomnia, and subjects with stable schizophrenia (including studies in subjects with hepatic and renal impairment). There was one open-label Phase 3 clinical trial in patients with stable schizophrenia. The Sponsor analyzed data in four study/subject groupings (or tiers) as follows:

- Tier 1: Phase 2 and 3 efficacy studies in schizophrenia
- Tier 2: All subjects with schizophrenia
- Tier 3: All subjects (All studies)
- Tier 4: Studies in healthy volunteers

The safety assessment of potential abuse was based on the AE analyses of healthy subjects and subjects with schizophrenia analyzed in Tier 4 and Tiers 1 and 2, respectively).

A total of 134 healthy volunteers (Tier 4) were enrolled in nine clinical studies. A total of 1,478 subjects with schizophrenia (Tier 1) were randomized in three double-blind, placebo-controlled Phase 2 and 3 clinical studies, and a total of 1226 subjects with schizophrenia (Tier 2) enrolled into double-blind and open-label clinical studies. All subjects received at least one dose of lumateperone, or received risperidone as an active control, or were given placebo. Therefore, there is overlap in the subjects analyzed in Tier 1 and 2.

The Sponsor evaluated the efficacy of lumateperone for the treatment of schizophrenia in 3 large randomized, double-blind parallel-group, placebo-controlled clinical trials (Studies ITI-007-005, ITI-007-301, and ITI-007-302) conducted in patients with an acute exacerbation of schizophrenia. Lumateperone was dosed once daily (QD) for 28 days. The recommended dose of lumateperone tosylate is 60 mg, taken orally once daily (also see Draft Label, Section 1.14.1.3). The lumateperone dosing recommendation is based primarily on the results of the above three clinical efficacy studies in subjects with schizophrenia. The primary efficacy endpoint in the Phase 3 studies was based on significant improvements in the Positive and Negative Syndrome Scale (PANSS)<sup>2</sup> total score, as measured by change from baseline.

#### 4.2 Abuse-related Adverse Event Profile Through All Phases of Development

Many of the adverse drug reactions (ADRs) reported by the Sponsor were adverse events (AEs) considered to be reasonably associated with the potential abuse of lumateperone. This assessment was based on data from 17 Phase 1, 2 and 3 studies (double-blind and open-label).

In Tier 4 (n=134), healthy volunteers in all studies, there was a single potentially abuse related AE of euphoria in the placebo group. (The CRF does not provide any further helpful details.) There were a

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<sup>2</sup> Kay SR, Fiszbein A, Opler LA (1987). The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. *Schizophrenia Bull*; 2:261-276.

few AEs of somnolence, dizziness and feeling drunk which were not considered to be specifically abuse-related.

There were no reported AEs of overdose or drug abuse.

The AEs leading to study discontinuation in more than 2 subjects (>0.1%) were (in order of frequency): headache, alanine aminotransferase increased, and aspartate aminotransferase (ISS, p 112).

#### 4.3 Evidence of Abuse, Misuse and Diversion in Clinical Trials

There were no cases of diversion of study drug at any site participating in the completed through all phases of development (Phase 1, 2 and 3 studies).

There is no proposed Risk Evaluation and Mitigation Strategy (REMS).

#### 4.4 Physical Dependence Studies in Humans

The pharmacological data suggests that lumateperone lacks mechanisms associated with abuse potential or dependence liability. Rather, the drug's nonclinical pharmacological profile suggests that lumateperone would more likely impede or reverse the behavioral effects of hallucinogens, psychomotor stimulants, and potentially dissociative anesthetics.

Based on the nonclinical physical dependence assessment, a clinical evaluation of dependence and withdrawal was not recommended. The nonclinical data are consistent with the lack of any dependence and withdrawal AEs reported in Phase 2 and 3 studies lasting 4 to 6 weeks and evaluated by the Sponsor by reviewing all spontaneously reported AEs after discontinuation of lumateperone (Abuse liability assessment, page 42).

#### 5. Regulatory Issues and Assessment

None

#### 6. Other Relevant Information

None

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/s/  
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# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: June 17, 2019

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.  
Clinical Analyst  
Division of Cardiovascular and Renal Products /CDER

To: Jasmeet (Mona) Kalsi, RPM  
DPP

Subject: QT-IRT Consult to NDA 209500 (SDN : Email)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 6/4/2019 regarding the sponsor's QT related question. The QT-IRT reviewed the following materials:

- Sponsor's briefing material (SDN: [Email](#));
- Proposed [label](#) (Submission 0013);
- Previous [QT-IRT review](#) for NDA 209500 dated 02/11/2019 in DARRTS.

## 1 QT-IRT Comments to the Division

We recommend that the risk of QTc prolongation in the high exposure scenarios for parent and metabolites (e.g. hepatic impairment, CYP3A4 inhibitor or inducer) is described in section 5 of the label. If lumateperone is used in these situations without dose reduction or modification, then ECG monitoring is needed. In the TQT study, there was dose- and concentration-dependent QTc prolongation. At the supratherapeutic dose which corresponds to exposures with concomitant use of a strong CYP3A inhibitor, the largest mean increase in QTc is 16 ms (90% CI: 11.8, 19.8 ms).

Please see our previous consult review for our recommendations for labeling language for section 12.2.

## 2 Sponsor's Questions to the QT-IRT team

Regarding the results from Study ITI-007-017, the TQT Study for lumateperone, we believe we have found the source of the discrepancy between our results for QTcF values and those suggested by the FDA. Due to discrepancies between treatment and concentration data for a few visits for certain subjects, some data were excluded from our analyses that may have been included in the FDA analyses.

As described in the ITI-007-017 Expert Cardiac Safety Report (Report Version 1.0, 27 August 2018), Section 5.4, PK values for certain subjects were excluded from the PK-PD analysis. These were excluded from all analyses described in the report, not just the PK-PD analyses. The reasons for excluding these data were as follows:

- Subject (b) (6): There were no measurable plasma concentrations for most analytes for PK samples collected during the suprathreshold dose treatment period. The analytes with measurable plasma concentrations showed sequentially decreasing values, suggesting that this subject was not dosed at all during the suprathreshold dose period. These data were therefore excluded from the PK-PD analysis for this period.
- Subject (b) (6): There were no measurable plasma concentrations for most analytes for PK samples collected during Day 5 of the therapeutic dose period, and no measurable plasma concentrations for any analytes during the suprathreshold dose treatment period. The analytes with measurable plasma concentrations on Day 5 of the therapeutic dose period showed sequentially decreasing values, suggesting that this subject was not dosed on this day. Data from the suprathreshold dose period and from Day 5 of the therapeutic dose period were therefore excluded from the PK-PD analysis for this period.
- Subject (b) (6): There were no measurable plasma concentrations for most analytes for PK samples collected during on Day 5 of the suprathreshold dose treatment period. The analytes with measurable plasma concentrations showed sequentially decreasing values, suggesting that this subject was not dosed on this day. Data from Day 5 of the suprathreshold dose period were therefore excluded from the PK-PD analysis for this period.
- Subject (b) (6): During treatment period 2, the therapeutic dose period, the plasma concentration levels were two fold higher than the post-dose C<sub>max</sub>. Since there were no measurable plasma concentrations during treatment period 1, which was the placebo treatment period, treatment period 2 represented the subject's first exposure to active treatment. The PK samples for the pre-dose timepoint for period 2 were therefore excluded from the PK-PD analysis.

1. Can the Agency confirm whether data from these subjects were included or excluded from the analysis performed?
2. Can the Agency also please confirm the model used for the central tendency analysis?

### QT-IRT's response:

1. The FDA used the QTc analysis set as specified in sponsor's SAP for the central tendency analysis (by-timepoint analysis). We included the above mentioned four subjects (subject ids: ITI-007-017-<sup>(b) (6)</sup>, ITI-007-017-<sup>(b) (6)</sup>, ITI-007-017-<sup>(b) (6)</sup>, ITI-007-017-<sup>(b) (6)</sup>) in the analysis.
2. The IRT does not agree with the by-timepoint analysis conducted by the sponsor because data from all four periods were used which is not supported by the imbalanced study design, i.e., moxifloxacin was only administered in Period 4. In order to evaluate QT effect of the study drug, the FDA reviewer fitted linear mixed model using the data from the first three periods for Day 1 and Day 5 separately. The linear mixed model includes time, treatment, sequence, period, and time\*treatment interaction as fixed effects and subject (sequence) as a random effect. Compound symmetry covariance structure was used in the linear mixed model. Baseline values are also included in the model as a covariate.

### 3 BACKGROUND

We completed the QT-IRT review of NDA 209500 on 02/11/2019. Sponsor reported the results of QT assessment based on concentration-QT analysis using parent drug exposure as the covariate. FDA reviewers reported the by time analysis results as primary analysis. The reasons are as follows:

- The drug has multiple active metabolites which very likely contributed to the observed QT prolonging effect. There is inadequate data to support individual contribution from these metabolites and to support the modeling process with parent drug alone or with selected metabolites.
- There is apparent hysteresis in the  $\Delta QT_c$  vs parent drug concentration plot. Hysteresis can cause underprediction of drug effect based on parent drug concentration.

These concerns were included in a post-meeting note in the midcycle communication letter (DARRTS 04/09/2019). Both the Applicant's and FDA's central tendency analysis showed a significant QT prolonging effect at the supratherapeutic dose greater than predicted QT prolongation based on concentration-QT modeling.

We have conducted further sensitivity analysis, which showed that the results we obtained based on the prespecified analysis population is similar to the modified analysis population as proposed by the sponsor. We therefore recommend to include the results of the IRT analysis in section 12.2 as described in our previous review as it is based on the prespecified analysis population and what we consider to be the correct analysis model (see above).

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at [cderdcrpqt@fda.hhs.gov](mailto:cderdcrpqt@fda.hhs.gov)

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/s/  
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**DEPARTMENT OF HEALTH & HUMAN SERVICES**      Public Health Service

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Division of Pediatric and Maternal Health  
Office of New Drugs  
Center for Drug Evaluation and Research  
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**Division of Pediatric and Maternal Health Memorandum**

**Date:** June 4, 2019                      **Date Consulted:** October 16, 2018

**From:** Kristie Baisden, DO, Medical Officer, Maternal Health  
Division of Pediatric and Maternal Health (DPMH)

**Through:** Tamara Johnson, MD, Team Leader, Maternal Health  
Division of Pediatric and Maternal Health

Lynne Yao, MD, Director  
Division of Pediatric and Maternal Health

**To:** Jasmeet Kalsi, PharmD, Regulatory Project Manager (RPM)  
Division of Psychiatry Products (DPP)

**Drug:** Lumateperone Capsules

**NDA:** 209500

**Proposed Indication:** Treatment of schizophrenia

**Applicant:** Intra-cellular Therapies, Inc.

**Subject:** Pregnancy and Lactation labeling as part of original NDA application

**Materials Reviewed:**

- NDA 209500 submitted on September 27, 2018.
- Applicant's response to information request (IR) submitted November 20, 2018.
- DPMH Review of Risperdal (risperidone) NDA 20272 and Invega (paliperidone) NDA 21999 by Catherine Roca, MD, dated April 16, 2018. DARRTs Reference ID: 4248840.<sup>1</sup>

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<sup>1</sup> DPMH did not rely on data in the Risperdal NDA or Invega NDA or the agency's finding of safety and effectiveness for Risperdal or Invega to support labeling sections of this lumateperone NDA. Rather, the cross-

- DPMH Review of Seroquel (quetiapine) NDA 20639 by Catherine Roca, MD, dated November 21, 2018. DARRTs Reference ID: 4353144.<sup>2</sup>

**Consult Question:** DPP requests DPMH assistance with the PLLR labeling review for this new molecular entity (NME).

## INTRODUCTION

On September 27, 2018, the applicant, Intracellular Therapies, Inc., submitted a new NDA (209500) for a new molecular entity (NME), lumateperone for the treatment of schizophrenia. On October 16, 2018, DPP consulted DPMH to provide input on the proper format and content of the *Pregnancy, Lactation, and Females and Males of Reproductive Potential* subsections of lumateperone labeling to follow the Pregnancy and Lactation Labeling Rule (PLLR).

## REGULATORY HISTORY

- Lumateperone is a first-in-class antipsychotic that selectively modulates serotonin, dopamine, and glutamate neurotransmission.
- On November 13, 2017, lumateperone was granted Fast Track Designation.
- On October 25, 2018, the Agency sent the applicant an information request (IR) for any reported cases of drug exposure in pregnancy or lactation during clinical trials with lumateperone.
- On November 20, 2018, the applicant submitted the requested information.

## BACKGROUND

### Drug Characteristics<sup>3</sup>

- *Drug Class:* antipsychotic
- *Mechanism of action (MOA):* unclear; the efficacy of lumateperone in schizophrenia could be mediated through a combination of serotonin, dopamine, and glutamate modulation. Lumateperone is a serotonin 5-HT<sub>2A</sub> receptor antagonist, a dopamine D<sub>2</sub> receptor pre-synaptic partial agonist and post-synaptic antagonist, a dopamine D<sub>1</sub> receptor-dependent modulator of glutamate, and a serotonin reuptake inhibitor.
- *Dosage and Administration:* 42 mg oral once daily
- *Molecular weight:* 565.71 Daltons
- *Bioavailability:* 4.4%
- *Protein binding:* 97.4%
- *Half-life:* ~13 hours
- *Adverse reactions:* somnolence/sedation, nausea, dry mouth, dizziness, fatigue, vomiting

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reference to the Risperdal and Invega consult is included to avoid duplicating background information relevant to this class of products.

<sup>2</sup> DPMH did not rely on data in the Seroquel NDA or the agency's finding of safety and effectiveness for Seroquel to support labeling sections of this lumateperone NDA. Rather, the cross-reference to the Seroquel consult is included to avoid duplicating background information relevant to this class of products.

<sup>3</sup> Lumateperone (NDA 209500) proposed prescribing information

Condition: Schizophrenia and Pregnancy

- Schizophrenia is seen in less than 1 % of the adult population. Women generally have a later age of onset (twenties to thirties) than men do (late teens to early twenties). It is slightly more prevalent in men compared to women (1.4:1).<sup>4</sup>
- Untreated schizophrenia is associated with increased all-cause mortality, hospitalization, and risk of suicide.<sup>5,6</sup>
- Schizophrenia is commonly comorbid with cigarette use and substance abuse; approximately 62% of patients with schizophrenia smoke.<sup>7</sup>
- Pregnancy and schizophrenia are associated with the following adverse obstetrical outcomes: prematurity, low birth weight, small-for-gestational age, still birth, and low APGAR scores. It is not known if the adverse obstetrical outcomes are due to the disease itself or due to the social circumstances (lack of prenatal care, poor eating habits, smoking, use of illicit drugs) of pregnant women with schizophrenia.<sup>8,9</sup>

*Reviewer’s Comment*

*DPMH recommends including a Clinical Consideration in subsection 8.1 of labeling regarding the risks to the mother from untreated schizophrenia. Currently approved therapies for the treatment of schizophrenia are listed below in Table 1.*

**Table 1. Therapies Approved in the United States for Schizophrenia**

<b>First-Generation (Conventional) Therapies</b>	<b>Second-Generation (Atypical) Therapies</b>
Chlorpromazine	Asenapine
Fluphenazine	Clozapine
Mesoridazine	Cariprazine
Haloperidol	Iloperidone
Perphenazine	Lurasidone
Thioridazine	Olanzapine
Molindone	Paliperidone (extended release formulation of 9-hydroxy-risperidone)
Thiothixene	Quetiapine
Trifluoperazine	Risperidone
Loxapine	Ziprasidone
	Brexpiprazole
	Aripiprazole

Source: Applicant’s Table Section 2.5 Clinical Overview

<sup>4</sup> McGrath J, et al. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiol Rev.* 2008;30:67-76

<sup>5</sup> Hor K, Taylor M. Suicide and schizophrenia: a systematic review of rates and risk factors. *J Psychopharmacol.* 2010;24(4Suppl):81-90

<sup>6</sup> Kane JM, et al. Comprehensive versus usual community care for first episode psychosis: 2 year outcomes from the NIMH RAISE early treatment program. *Am J Psychiatry.* 2016; 173(4):362-72.

<sup>7</sup> Dickerson F, et al. Cigarette smoking by patients with serious mental illness, 1999-2016: an increasing disparity. *Psychiatr Serv.* 2018;69(2):147-153.

<sup>8</sup> Robinson, G. (2012). Treatment of Schizophrenia in Pregnancy and Postpartum. *J Popul Ther Clin Pharmacol,* 19 (3):e380-e386.

<sup>9</sup> Einarson, A and Boskovic, R. Use and safety of antipsychotic drugs during pregnancy. *J Psychiatr Pract.* 2009. 15 (3): 183-92.

*First-generation conventional therapies act primarily as dopamine D<sub>2</sub> receptor antagonists and are associated with adverse effects such as tardive dyskinesia, extrapyramidal symptoms (EPS), neuroleptic malignant syndrome (NMS), and hyperprolactinemia. Second-generation atypical antipsychotics (SGAs) act as antagonists of the serotonin 5-HT<sub>2A</sub> receptor and dopamine D<sub>2</sub> receptor. SGAs have a better motor side effect profile but are associated with other side effects (weight gain, type II diabetes, cognitive impairment, sedation, orthostatic hypotension, blurred vision, constipation, dizziness, loss of bladder control) due to nonselective interactions with receptor sites (such as 5-HT<sub>2C</sub>, histaminergic H<sub>1</sub>, alpha-adrenergic, and muscarinic receptors).*

*In clinical trials with lumateperone, adverse events described above for other antipsychotics were not observed at increased rates compared to placebo (e.g., hyperglycemia, hyperlipidemia, weight gain, and hyperprolactinemia). Lumateperone demonstrated a safety profile similar to placebo and an improved safety profile compared to risperidone for EPS, weight gain, metabolic abnormalities, and serum prolactin changes.*

## **REVIEW**

### ***PREGNANCY***

#### Nonclinical Experience

In animal reproduction studies, no teratogenicity was observed with oral administration of lumateperone to pregnant rats and rabbits during organogenesis at doses up to 2.4 and 9.7 times, respectively, of the maximum recommended human dose (MRHD) of 42 mg/day on a mg/m<sup>2</sup> basis. When pregnant rats were administered lumateperone during the period of organogenesis through lactation, the number of perinatal deaths of pups was increased at 4.9 times the MRHD, with no adverse effects on pups recorded at 2.4 times the MRHD. For more details, refer to the Nonclinical Review Darren Fegley, PhD.

#### Applicant's Review of Published Literature

The applicant did not perform a literature search related to lumateperone use and pregnancy.

#### DPMH's Review of Published Literature

PubMed, Embase, Micromedex<sup>10</sup>, TERIS<sup>11</sup>, Reprotox<sup>12</sup>, and Briggs<sup>13</sup> were searched using "lumateperone" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," and "miscarriage." No relevant publications were identified.

#### Clinical Trials

Pregnant women were excluded from all clinical trials in the developmental program for lumateperone. The applicant stated 6 pregnancy cases have been reported as of the time of the 120-day Safety Update. These pregnancy cases are summarized in Table 2 below.

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<sup>10</sup> Truven Health Analytics information, <http://www.micromedexsolutions.com/> Accessed 2/27/19.

<sup>11</sup> TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 2/27/19.

<sup>12</sup> Reprotox® Website: [www.Reprotox.org](http://www.Reprotox.org). REPROTOX® system Accessed 1/22/19.

<sup>13</sup> Briggs, GG. Freeman, RK. & Yaffe, SJ. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.

**Table 2: Reported Pregnancy Cases from Lumateperone Clinical Trials**

Patient ID	Relevant Maternal History	Timing of Exposure	Drug Exposure	Pregnancy outcome
(b) (6)	24 y.o. female with a history of SAB and bipolar disorder. Concomitant med: ibuprofen	Preconception to 5 weeks gestation	Unknown: lumateperone 40 mg or 60 mg or placebo (code not broken)	<b>Spontaneous abortion</b> at 8 weeks gestation
	32 y.o. female with a history of 6 normal births and anxiety. Concomitant meds: oral contraceptive	3 weeks gestation	Unknown: lumateperone 40 mg or 60 mg or placebo (code not broken)	<b>Elective termination</b> at 4 weeks gestation
	36 y.o. female with a history of active smoking, alcohol use, and schizophrenia.	Preconception to 2 weeks gestation	Lumateperone 60 mg	<b>Normal vaginal birth</b> at term  Healthy male infant (Weight 3.7 kg, Apgars 8/9, No abnormalities)
	28 y.o. female with a history of obesity, hypertension, diabetes, hypothyroid, asthma, and schizophrenia.	Preconception to 4 weeks gestation	Lumateperone 60 mg	<b>Spontaneous abortion</b> at 5 weeks gestation
	27 y.o. female with a history of 3 prior live births, schizophrenia, PTSD, smoking, and depression. Concomitant meds: doxepin, escitalopram	Preconception to 7 weeks gestation	Lumateperone 60 mg	<b>Ongoing pregnancy</b> (patient agrees to be followed)
	27 y.o. female with a history of 3 prior live births, schizophrenia, PTSD, and depression.	Preconception to 7 weeks gestation	Lumateperone 60 mg	<b>Ongoing pregnancy</b> (patients agrees to be followed)

Source: Reviewer's Table

*Reviewer's Comment*

*The pregnancy cases described above in Table 2 from lumateperone clinical trials are limited in the ability to assess for teratogenicity by the small number of exposed pregnancies, the short duration of exposure (although most were exposed during the first trimester only), and the inability to control for confounders such as underlying maternal disease and concomitant use of medications. These limited data are insufficient to establish any drug-associated risks for birth defects, miscarriage, or adverse maternal or fetal outcomes.*

*DPMH previously reviewed the published literature related to the use of antipsychotic drugs in pregnancy.<sup>14,15</sup> DPMH concluded neonates exposed to antipsychotic drugs during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Currently approved PLLR labeling for other antipsychotic drugs (e.g., risperidone, quetiapine, and paliperidone) includes a Clinical Consideration to monitor neonates for extrapyramidal and/or withdrawal symptoms and manage appropriately. In short-term clinical trials with lumateperone, the reported incidence of EPS in adults was 5.7% for lumateperone, 6.3% for placebo, and 10.6% for risperidone-treated patients.<sup>3</sup> Although the clinical trial data do not suggest an increased risk for EPS with lumateperone, this adverse reaction was reported and should be monitored for in newborn infants.*

*In addition, PLLR labeling for other antipsychotic drugs includes pregnancy exposure registry contact information for the National Pregnancy Registry for Atypical Antipsychotics. DPMH recommends including this information in lumateperone labeling so that pregnancy outcomes can be monitored.*

## **LACTATION**

### **Nonclinical Experience**

In a study in which pregnant rats were administered oral doses of 5, 15, and 30 mg/kg/day lumateperone tosylate (0.8, 2.4, and 4.9 times the MRHD on a mg/m<sup>2</sup> basis) during the period of organogenesis and through lactation, the number of live-born pups was decreased at 2.4 and 4.9 times the MRHD, and early postnatal deaths increased at a dose 4.9 times the MRHD. Impaired nursing by dams, and decreased body weight gain in pups were observed at 4.9 times, but not at 2.4 times, the MRHD. For more details, refer to the Nonclinical Review by Darren Fegley, PhD.

### **Applicant's Review of Published Literature**

The applicant did not perform a literature search related to lumateperone use and lactation.

### **DPMH's Review of Published Literature**

PubMed, Embase, Micromedex<sup>16</sup>, TERIS<sup>17</sup>, Reprotox<sup>18</sup>, and Briggs<sup>19</sup>, *Medications and Mother's Milk*<sup>20</sup>, and LactMed<sup>21</sup> were searched using "lumateperone" AND "breastfeeding" or "lactation." No relevant publications were identified.

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<sup>14</sup> DPMH PLLR Review of Risperdal NDA 20272 by Catherine Roca, MD, dated April 16, 2018. DARRTs Reference ID: 4248840. DPMH did not rely on data in the Risperdal NDA or Invega NDA or the agency's finding of safety and effectiveness for Risperdal or Invega to support labeling sections of this lumateperone NDA. Rather, the cross-reference to the Risperdal and Invega consult is included to avoid duplicating background information relevant to this class of products.

<sup>15</sup> DPMH PLLR Review of Seroquel (quetiapine) NDA 20639 by Catherine Roca, MD, dated November 21, 2018. DARRTs Reference ID: 4353144. DPMH did not rely on data in the Seroquel NDA or the agency's finding of safety and effectiveness for Seroquel to support labeling sections of this lumateperone NDA. Rather, the cross-reference to the Seroquel consult is included to avoid duplicating background information relevant to this class of products.

<sup>16</sup> Truven Health Analytics information, <http://www.micromedexsolutions.com/> Accessed 2/27/19

<sup>17</sup> TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 2/27/19

<sup>18</sup> Reprotox® Website: [www.Reprotox.org](http://www.Reprotox.org). REPROTOX® system Accessed 2/27/19

<sup>19</sup> Briggs, GG. Freeman, RK. & Yaffe, SJ. (2017). *Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk*. Philadelphia, Pa, Lippincott Williams & Wilkins.

<sup>20</sup> Hale, Thomas (2017) *Medications and Mothers' Milk*. Amarillo, Texas. Hale Publishing.

<sup>21</sup> <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. LactMed is a National Library of Medicine (NLM)

## Clinical Trials

Lactating women were excluded from all clinical trials in the developmental program for lumateperone. The applicant stated there were no reported cases of exposure in lactation.

### *Reviewer's Comment*

*There are no available data on the presence of lumateperone in human milk, the effects on the breastfed infant, or the effects on milk production. However, there are published reports of sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) in breastfed infants exposed to antipsychotics.<sup>22</sup>*

## ***FEMALES AND MALES OF REPRODUCTIVE POTENTIAL***

### Nonclinical Experience

Female rats were treated with oral doses of 5, 15, 30 or 60 mg/kg/day lumateperone tosylate (0.8, 2.4, 4.9, and 9.7 times the MRHD on a mg/m<sup>2</sup> basis) prior to mating and continuing through conception and implantation. Estrus cycle irregularities were observed at doses  $\geq$ 15 mg/kg/day. Decreases in the median number of corpora lutea and implantation sites, and increases in the number of non-gravid uteruses, were recorded at 60 mg/kg/day. Decreased gestation body weight and body weight gain, and increases in time to mating were observed at 30 and 60 mg/kg/day.

Male rats were treated with oral doses of 5, 15, 30 or 60 mg/kg/day lumateperone tosylate (0.8, 2.4, 4.9, and 9.7 times the MRHD on a mg/m<sup>2</sup> basis) for 9 weeks prior to mating and throughout the 14 days of mating. Decreased sperm motility, changes in sperm morphology, reduced epididymal counts, and adverse histopathology changes in testes and epididymides were observed at 30 and 60 mg/kg/day. For more details, refer to the Nonclinical Review by Darren Fegley, PhD.

### Applicant's Review of Published Literature

The applicant did not perform a literature search related to lumateperone use and fertility.

### DPMH's Review of Published Literature

PubMed, Embase, Reprotox<sup>12</sup> were searched using, "lumateperone" AND "fertility," "infertility," "contraception," and "oral contraceptives." No relevant publications were identified.

### *Reviewer's Comment*

*No human data are available to inform the effect of lumateperone on human fertility. Other antipsychotics have been associated with hyperprolactinemia which can lead to amenorrhea, oligomenorrhea, and infertility.<sup>14,15</sup> However, lumateperone therapy did not increase serum prolactin levels in clinical trials. Nevertheless, animal data suggest lumateperone may impact male and female fertility (at levels 2.4 times higher than the MHRD).*

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database with information on drugs and lactation geared toward healthcare providers and nursing women. LactMed provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 2/27/19

<sup>22</sup> DPMH Review of Risperdal (risperidone) NDA 20272 and Invega (paliperidone) NDA 21999 by Catherine Roca, MD, dated April 16, 2018. DARRTs Reference ID: 4248840

## **DISCUSSION AND CONCLUSIONS**

### Pregnancy

DPMH recommends subsection 8.1 of labeling include a Pregnancy Exposure Registry heading with contact information for the National Pregnancy Registry for Atypical Antipsychotics, so that pregnancy outcomes can be monitored following exposure to lumateperone in pregnant women. The Risk Summary heading should describe the limited available pregnancy data from case reports on lumateperone use in pregnant women, which are insufficient to establish any drug-associated risks of birth defects, miscarriage, or adverse maternal or fetal outcomes.

In addition, DPMH recommends including a Clinical Considerations heading that describes the risk to the mother with untreated underlying schizophrenia. Finally, DPMH recommends including a Clinical Considerations heading that recommends monitoring the neonate for EPS signs and symptoms which have been reported in the published literature with the use of antipsychotics.

### Lactation

DPMH recommends subsection 8.2 of labeling include a Risk Summary heading that states there are no data on the presence of lumateperone in human or animal milk, the effects on the breastfed infant, or the effects on milk production. There are published reports of sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) in breastfed infants exposed to antipsychotics. DPMH recommends including a Clinical Consideration to monitoring the breastfed infants for potential adverse reactions. In addition, DPMH recommends including the following risk/benefit statement, “the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for lumateperone and any potential adverse effects on the breastfed infant from lumateperone or from the underlying maternal condition.”

### Females and Males of Reproductive Potential

DPMH recommends subsection 8.3 briefly describe the available animal data which suggest lumateperone may impact male and female fertility. There are no available human data on the effects of lumateperone on fertility. Pregnancy testing and contraception headings are not recommended because available data do not suggest lumateperone causes embryo-fetal toxicity.

## **LABELING RECOMMENDATIONS**

DPMH revised Highlights, subsections 8.1, 8.2, 8.3, and section 17 of labeling for compliance with the PLLR. DPMH refers to the final NDA action for final labeling.

## DPMH Proposed Lumateperone Pregnancy and Lactation Labeling

### HIGHLIGHTS OF PRESCRIBING INFORMATION

#### -----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)

### FULL PRESCRIBING INFORMATION

#### 8 USE IN SPECIFIC POPULATIONS

##### 8.1 Pregnancy

###### Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including lumateperone, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or online at <http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/>.

###### Risk Summary

Neonates exposed to antipsychotics drugs (including lumateperone) during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms following delivery (*see Clinical Considerations*). Available data from case reports on lumateperone use in pregnant women are insufficient to establish any drug associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother associated with untreated schizophrenia and with exposure to antipsychotics, including lumateperone, during pregnancy (*see Clinical Considerations*). In animal reproduction studies, no adverse developmental effects were observed with oral administration of lumateperone to pregnant rats and rabbits during organogenesis at doses up to 2.4 and 9.7 times, respectively, the maximum recommended human dose (MRHD). When pregnant rats were administered lumateperone during the period of organogenesis through lactation, the number of perinatal deaths of pups was increased at 4.9 times the MRHD, with no adverse effects on pups recorded at 2.4 times the MRHD (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

###### Clinical Considerations

###### *Disease associated maternal and/or embryo/fetal risk*

There is risk to the mother from untreated schizophrenia, including increased risk of relapse, hospitalization, and suicide. Schizophrenia is associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

###### *Fetal/neonatal adverse reactions*

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were

exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

## Data

### *Animal Data*

Pregnant rats were treated with oral doses of 5, 15, 30, and 90 mg/kg/day lumateperone tosylate (0.8, 2.4, 4.9, and 14.6 times the MRHD on a mg/m<sup>2</sup> basis) during the period of organogenesis. Lumateperone was not teratogenic and did not cause adverse developmental effects at doses up to 2.4 times the MRHD. Findings of decreased body weight were observed in fetuses at 4.9 and 14.6 times the MRHD. Findings of incomplete ossification, and increased incidences of visceral and skeletal variations, were recorded in fetuses at 14.6 times the MRHD, a dose that induced maternal toxicity.

Pregnant rabbits were treated with oral doses of 3, 10, and 30 mg/kg/day lumateperone tosylate (1.0, 3.2, and 9.7 times the MRHD on a mg/m<sup>2</sup> basis) during the period of organogenesis. Lumateperone was not teratogenic and did not cause adverse developmental effects at doses up to 9.7 times the MRHD.

In a study in which pregnant rats were administered oral doses of 5, 15, and 30 mg/kg/day lumateperone tosylate (0.8, 2.4, and 4.9 times the MRHD on a mg/m<sup>2</sup> basis) during the period of organogenesis and through lactation, the number of live-born pups was decreased at 2.4 and 4.9 times the MRHD, and early postnatal deaths increased at a dose 4.9 times the MRHD. Impaired nursing by dams, and decreased body weight gain in pups were observed at 4.9 times, but not at 2.4 times, the MRHD.

## **8.2 Lactation**

### Risk Summary

There are no available data on the presence of lumateperone in human or animal milk, the effect on the breastfed infant, or the effect on milk production. There are published reports of sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) in breastfed infants exposed to antipsychotics (*see Clinical Considerations*)<sup>(b) (4)</sup>

[REDACTED]

[REDACTED]<sup>(b) (4)</sup>

## **8.3 Females and Males of Reproductive Potential**

### Infertility

Based on findings in animal studies, lumateperone may impair male and female fertility [*see Nonclinical Toxicology (13.1)*].

## 17 PATIENT COUNSELING

### Pregnancy

Advise pregnant women to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with lumateperone. Advise patients that lumateperone used during the third trimester may cause extrapyramidal and/or withdrawal symptoms (agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) in a neonate. Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to lumateperone during pregnancy [see *Use in Specific Populations (8.1)*].

### Lactation

Advise

(b) (4)

[see *Use in Specific Populations (8.2)*].

### Infertility

Advise males and females of reproductive potential that CAPLYTA may impair fertility [see *Use in Specific Populations (8.3)*].

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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KRISTIE W BAISDEN  
06/04/2019 12:27:17 PM

TAMARA N JOHNSON  
06/04/2019 04:39:34 PM

LYNNE P YAO  
06/11/2019 09:13:13 AM

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LABELS AND LABELING REVIEW  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

\*\*\* This document contains proprietary information that cannot be released to the public\*\*\*

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Date of This Review:	May 23, 2019
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 209500
Product Name and Strength:	Caplyta (lumateperone) capsules, (b) (4) 42 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Intra-Cellular Therapies, Inc.
FDA Received Date:	November 5, 2018, and May 16, 2019
OSE RCM #:	2018-2109
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

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## PURPOSE OF REVIEW

As part of the approval process for Caplyta<sup>a</sup> (lumateperone) capsules, (b) (4) 42 mg, the Division of Psychiatry Products (DPP) requested that we review the proposed labels and labeling for areas that may lead to medication errors.

## MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
ISMP Newsletters	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review

\*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 1 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3, below, include the identified medication error issues with the submitted labels and labeling, DMEPA's rationale for concern, and the proposed recommendations to minimize the risk for medication errors.

Table 2: Identified Issues and Recommendations for Division of Psychiatry Products

Prescribing Information			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information			
1.	<u>Section 2.1 Recommended Dosage:</u> The recommended dosage statement (i.e., " <i>The recommended dose</i> ")	Lack of clarity may lead to wrong dose and wrong frequency of administration medication errors.	Consider revising the statement to read: "The recommended dosage of Caplyta is 42 mg once daily".

<sup>a</sup> The proposed proprietary name, Caplyta, was found conditionally acceptable in OSE Review #2018-26428670, dated December 20, 2018.

	of Caplyta is 42 mg/day") is not clearly stated.		
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Table 3: Identified Issues and Recommendations for Intra-Cellular Therapies, Inc. (entire table to be conveyed to Applicant)

Blister Labels			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The NDC number (located beneath the "manufactured by" statement) is not preceded by "NDC".	The NDC number should be preceded by "NDC" so that it may be readily identified as the NDC number.	Revise the labels such that "NDC" precedes the NDC number.
2.	The NDC number associated with the linear barcode is lacking the beginning number "7".	The missing number may lead to confusion or errors in product identification.	Ensure the NDC number associated with the linear barcode is correct. Revise as appropriate.
Commercial Carton Labeling			
1.	The cartons do not have a linear barcode.	The linear barcode is used as a means of product identification to help reduce medication errors.	Add the product's linear barcode to each individual carton per 21 CFR 201.25(c)(2).
2.	The following statement is on the principal display panel (PDP): (b) (4) visit www.caplyta.com".	The statement detracts attention from important information on the PDP such as the proprietary name, established name, and strength.	Consider relocating the statement to the back panel.
Professional Sample Carton Labeling			
1.	The following statement is on the principal display panel (PDP): (b) (4) visit www.caplyta.com".	The statement detracts attention from important information on the PDP such as the proprietary name, established name, and strength.	Consider relocating the statement to the back panel.
2.	The "professional sample" statements lack prominence.	Per 21 CFR 203.38(c) "Each sample unit shall bear a label that clearly denotes its status as a drug sample".	Consider the use of a bold font to increase the prominence of the

			statements: "Professional Sample. Not for Sale".
3.	The "30 DAY SUPPLY" statement on the 42 mg strength professional sample carton is too prominent.	The statement competes in prominence with other important information (e.g., the proprietary name, established name, and strength) due to its size (on the PDP and side panel) and close proximity to the statement of strength (on the PDP).	Decrease the size of the "30 DAY SUPPLY" statement (on the PDP and side panel) and decrease its proximity to the statement of strength (on the PDP).

2 CONCLUSION

Our evaluation of the proposed labels and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to the Applicant so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Caplyta that Intra-Cellular Therapies, Inc. submitted on November 5, 2018.

Table 4. Relevant Product Information for Caplyta <sup>***</sup>	
Initial Approval Date	N/A
Active Ingredient	lumateperone
Indication	Treatment of schizophrenia
Route of Administration	Oral
Dosage Form	Capsule
Strengths	(b) (4) 42 mg
Dose and Frequency	<p>The recommended dose of Caplyta is 42 mg once daily.</p> <ul style="list-style-type: none"> <li>• When coadministering with a moderate or strong CYP3A4 inhibitor such as diltiazem or itraconazole, a reduced dose should be considered.</li> <li>• For patients with moderate to severe hepatic impairment (Child-Pugh class B or C), a reduced dose should be considered.</li> </ul>
How Supplied	30-count cartons. Each carton contains 3 blister packs of 10 capsules.
Storage	Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Container Closure	(b) (4) blisters

## APPENDIX F. LABELS AND LABELING

### F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>b</sup> along with postmarket medication error data, we reviewed the following Caplyta labels and labeling submitted by Intra-Cellular Therapies, Inc. on November 5, 2018 and May 16, 2019.

- Blister labels received on May 16, 2019
- Commercial carton labeling received on May 16, 2019
- Professional sample carton labeling received on May 16, 2019
- Prescribing Information (image not shown) received on November 5, 2018

### F.2 Labels and Labeling Images (not to scale)

#### Blister Labels



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<sup>b</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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LORETTA HOLMES  
05/23/2019 03:02:05 PM

SEVAN H KOLEJIAN  
05/23/2019 03:40:06 PM

## Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA
Submission Number	209500
Submission Date	9/27/2018
Date Consult Received	10/16/2018
Clinical Division	DPP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult regarding the sponsor's QT evaluation. The QT-IRT reviewed the following materials:

- Previous QT-IRT review dated 10/12/2017 in DARRTS ([link](#));
- Previous QT-IRT review dated 02/22/2018 in DARRTS ([link](#));
- Previous QT-IRT review dated 04/18/2018 in DARRTS ([link](#));
- Cardiac safety report for Study # ITI-007-017 (SDN # 0005; [link](#))
- Clinical study report for Study # ITI-007-017 (SDN # 0005; [link](#)); and
- Proposed product label (SDN # 0005; [link](#)).

### 1 SUMMARY

Dose-dependent QTc prolongation effect of lumateperone capsules was detected in this QT assessment.

The effect of lumateperone was evaluated in clinical study # ITI-007-017. The highest dose that was evaluated was 180 mg QD for 5 days, which covers the clinically relevant worst-case exposure scenario (a strong CYP inhibitors, section 3.1). The data from study ITI-007-017 was analyzed using central tendency analysis as the primary analysis, which suggest that lumateperone is associated with dose-dependent QTc prolonging effect at the therapeutic dose level (refer to section 4.3) – see Table 1 for overall results. The findings of this analysis are further supported by the available nonclinical data (section 3.1), exposure-response analysis (section 4.5), and categorical analysis (section 4.4). Assay sensitivity was established by concentration-QTc analysis (Table 2).

**Table 1: The Point Estimates and the 90% CIs – Drug Effect (FDA Analysis)**

ECG parameter	Treatment	Concentration	$\Delta\Delta$ QTcF(ms)	90% CI (ms)
QTc	ITI-007 60 mg*	Day 5, 2 hrs	4.9	(0.9, 8.9)
QTc	ITI-007 180 mg*	Day 5, 2 hrs	15.8	(11.8, 19.8)

\* Dose levels in the proposed label is expressed in the base form; dose levels in the rest of the document is expressed in the salt form.

**Table 2: The Point Estimates and the 90% CIs – Positive Control (FDA Analysis)**

ECG parameter	Treatment	Concentration	$\Delta\Delta$ QTcF(ms)	90% CI (ms)
QTc	Moxifloxacin	1941.9 ng/mL	11.7	(6.3, 17.1)

### 1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

### 1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

## 2 PROPOSED LABEL

Our changes are highlighted ([addition](#), [deletion](#)). This is a suggestion only and we defer final labeling decisions to the Division.

### 12.2 Pharmacodynamics

#### Cardiac Electrophysiology

(b) (4)  
QTcF interval was evaluated in a randomized, placebo- and active- (moxifloxacin 400 mg) controlled, four-arm crossover study utilizing concentration-QTc effect modelling in 33 patients with schizophrenia. The (b) (4) placebo-corrected change from baseline QTcF (90% two-sided upper confidence interval) values of 4.9<sup>(b) (4)</sup> (8.9<sup>(b) (4)</sup>) and 15.8<sup>(b) (4)</sup> (19.8<sup>(b) (4)</sup>) ms (b) (4) for the 42 mg and the suprathreshold dose of 126 mg CAPLYTA, respectively, administered orally once daily for 5 days. (b) (4)

*Reviewer's comments: The sponsor has proposed to report concentration-QTc model predictions using parent drug exposure as the covariate. Sponsor's model has a major limitation as suggested by hysteresis between lumateperone exposure and  $\Delta$ QTcF. The observation may have resulted from potential contributions to the QT prolonging effect by its major metabolites. Therefore, we recommend reporting study findings based on central tendency analysis by FDA analysis which was based on a linear mixed model using the data from the first 3 periods.*

## 3 SPONSOR'S SUBMISSION

### 3.1 OVERVIEW

Intra-Cellular Therapies, Inc. is developing lumateperone (IC200056) capsules for the treatment of schizophrenia. Lumateperone is a serotonin 5-HT<sub>2A</sub> receptor antagonist, a dopamine D<sub>2</sub> receptor pre-synaptic partial agonist and post-synaptic antagonist, a dopamine D<sub>1</sub> receptor dependent modulator of glutamate, and a serotonin reuptake inhibitor. Although the mechanism is unclear, the effects are believed to be mediated through a combination of serotonin, dopamine, and glutamate modulation. The recommended dose of is once daily 42 mg (capsules (b) (4) 42 mg) equivalent to 60 mg lumateperone tosylate.

The QT-IRT reviewed the sponsor's substitution requests for TQT study (IND-079690 on 12-Oct-2017 and 22-Feb-2018) and recommended the sponsor to conduct a TQT study as

per the ICH E14 guidelines. On both incidences, the exposures of lumateperone (120 mg qd) from submitted studies (ITI-007-005, ITI-007-301, and ITI-007-302) did not cover the highest clinically relevant scenario of exposures corresponding to strong CYP3A inhibition (3-fold higher exposures from drug interaction with itraconazole) for the potential therapeutic dose of 60 mg QD. The QT-IRT reviewed the protocol for study ITI-007-017 and the following major comments were conveyed to the sponsor (IND-079690 on 18-Apr-2018):

- *We disagree with the current study design because the positive control is administered during period 4. We recommend the sponsor considers a parallel TQT study with nested crossover for moxifloxacin and placebo.*
- *We do not believe 16 subjects will provide sufficient power to demonstrate assay sensitivity using exposure-response analysis. The references that sponsor cited only evaluated sample size for exposure response analysis of study drug. The sponsor should provide sample size justification for their assay sensitivity analysis.*
- *The adequacy of choice of 180 mg dose would be a review issue based on whether it can reasonably cover the worst-case scenario exposure (i.e., 3-fold exposures with CYP3A4 inhibition) for the therapeutic dose of 60 mg QD.*

Study ITI-007-017 is a randomized, double-blind, placebo- and active- (open-label; moxifloxacin 400 mg) controlled, four-arm crossover study in patients (n=33) with schizophrenia. The sponsor used 60 mg as therapeutic dose (Period 1 or 2) and 180 mg as suprathreshold dose (Period 2 or 3) sequentially once daily for 5 days without a washout period. Patients were randomized to receive one of two blinded treatment sequences: 1) placebo followed by the therapeutic dose & escalation to suprathreshold dose; or 2) the therapeutic dose & escalation to the suprathreshold dose followed by placebo. PK samples were collected on Day 1 and Day 5 (up to 24h post-dose) for determination of plasma concentrations of parent (IC200056) and its metabolites (IC200131, IC200161, IC200565, IC201308, and IC201309). The sponsor used concentration-QTc effect modeling as the primary analysis.

Considering the worst-case scenario of drug interaction with a strong CYP inhibitors such as diltiazem or itraconazole resulted in increased (by 2 to 3-fold) the exposure of lumateperone, the selected 180 mg as suprathreshold dose appears reasonable. Administration of 180 mg (qd for 5 days) resulted in an approximately dose-proportional increase in exposure in Study ITI-007-017 (Table 9).

In vitro, lumateperone and at least two of the major metabolites, IC200131 and IC200161 were tested in hERG channel assays. The IC50 values were estimated to be <0.3 uM, 0.52 uM, and 0.34 uM, respectively. Nonclinical cardiac safety data on IC200565, IC201308, or IC201309 are not available at the time of this review.

## 3.2 SPONSOR'S RESULTS

### 3.2.1 Central tendency analysis

***Reviewer's comment:*** *Both the sponsor's analysis and FDA analysis show that the suprathreshold dose has significant QT prolongation for both Day 1 and Day 5. The by timepoint analysis presented by the sponsor using data from all four time periods is not*

*appropriate as it cannot properly adjust the study design deficiency with moxifloxacin only administered in Period 4. In order to evaluate QT effect of the study drug, the FDA reviewer fitted linear mixed model using the data from the first 3 periods. The largest point estimate (upper bound of 90% CI) for suprathreshold dose was 20.0 ms (24.8 ms) and 15.8 ms (19.8 ms) in sponsor's analysis and FDA's analysis, respectively. Please see section 4.3 for additional details.*

### **3.2.1.1 Assay Sensitivity**

Exposure-response analysis was used for assay sensitivity analysis. Please see section 4.5 for additional details.

#### **3.2.1.1.1 QT bias assessment**

The sponsor performed QT bias assessment, which was not reviewed because assay sensitivity was established with the moxifloxacin treatment.

### **3.2.2 Categorical Analysis**

Sponsor presented the results for subjects with >25% increase from baseline measures. FDA reviewer performed the standard categorical analysis using ADEG data set provided by the sponsor. We included all the subjects provided in the ADEG data set except one non-treated subject. Please see section 4.4 for additional details.

### **3.2.3 Safety Analysis**

The Safety Population included a total of 32 subjects treated with ITI- 007 60 mg, 31 subjects treated with ITI-007 180 mg, 31 subjects treated with Placebo, and 29 subjects treated with moxifloxacin 400 mg.

There were no deaths or SAEs reported.

A total of 3 subjects discontinued the study drug due to a TEAE (2 of which also discontinued the study). All TEAEs were considered related to study medication, none were considered serious.

The most frequently reported TEAE by preferred term included: somnolence (25.8%, 6.3%, 0%, and 3.4% with the ITI-007 180 mg, 60 mg, placebo, and moxifloxacin treatments, respectively) and dizziness (22.6%, 15.6%, 9.7%, and 6.9% with the ITI-007 180 mg, 60 mg, placebo, and moxifloxacin treatments, respectively). Most TEAEs were considered drug-related and mild or moderate in severity; one severe TEAE was reported (syncope) in the 180 mg arm.

***Reviewer's comment:*** *Subject 01-030 reported a severe TEAE of syncope. None of the QTc intervals for this subject were >450 ms.*

*None of the other events identified to be of clinical importance per the ICH E14 guidelines (i.e. seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study).*

### **3.2.4 Exposure-Response Analysis**

The sponsor performed PK-PD analyses to explore the relationship between the change from baseline in QTc intervals ( $\Delta$ QTcF) and plasma concentrations of lumateperone

(IC200056, the parent drug), as well as the metabolites, IC200161, IC200131, IC200565, IC201308 and IC201309 using a linear mixed-effects modeling approach. The models included plasma concentration of each moiety, time since first dose (categorical), treatment (active=1 vs placebo=0), and centered baseline QTcF as the covariates, as well as random subject effects on plasma concentration and the intercept.

The sponsor's model predicted placebo-corrected change from baseline QTcF (90% two-sided upper confidence interval) values of 3.7 (4.9) and 8.5 (11.3) ms at the mean peak parent plasma levels for the therapeutic dose 42 mg and the suprathreshold dose of 126 mg, respectively, administered orally once daily for 5 days.

***Reviewer's comments:*** *The sponsor's models with individual moiety's concentration as the exposure metric suggested statistically significant, positive slopes between  $\Delta QTcF$  and drug-related exposure. Except for the models based on IC200565 and IC201308, all the other models appear to under predict the maximum effect on  $\Delta \Delta QTcF$  especially in the suprathreshold treatment group. The sponsor has proposed to include model predictions based on parent drug exposure in the product label.*

*The reviewer does not agree with sponsor's proposal to report model predictions based on parent drug exposure. Even though the study is not powered for central tendency analysis, the significantly smaller effect predicted from the concentration-QTc model raised concern. In addition, the analysis with single exposure metrics may not be justified by the fact that multiple drug-related moieties demonstrate in vitro activities in hERG assays. The observed hysteresis (especially for the parent drug) also suggests that a direct effect, linear model with a single exposure metric may not be adequate.*

*The reviewer conducted concentration-QTc analysis including all moieties in the linear mixed effect model. However, reviewer's analysis also has major limitations as stated in section 4.5. Therefore, the reviewer has concerns using concentration-QTc analysis as the primary analysis for this study. As a conservative measure, the reviewer recommends reporting study finding based on central tendency analysis.*

## **4 REVIEWERS' ASSESSMENT**

### **4.1 EVALUATION OF THE QT/RR CORRECTION METHOD**

The sponsor used QTcF for the primary analysis, which is acceptable as no significant increases or decreases in heart rate (i.e. mean < 10 bpm) were observed (see Sections 4.3.2 and 4.5).

### **4.2 ECG ASSESSMENTS**

#### **4.2.1 Overall**

Overall ECG acquisition and interpretation in this study appears acceptable.

#### **4.2.2 QT bias assessment**

Not applicable

### 4.3 CENTRAL TENDENCY ANALYSIS

#### 4.3.1 QTc

The statistical reviewer used mixed model to analyze the  $\Delta QTcF$  effect. We subset the data set from Period 1 to Period 3 and used that subset for the subsequent analyses. The model includes time, treatment, sequence, period, and time x treatment interaction as fixed effects and subject (sequence) as a random effect. Baseline values are also included in the model as a covariate. Analysis results are listed in Table 3.

**Table 3: Analysis Results of  $\Delta QTcF$  and  $\Delta\Delta QTcF$  for ITI-007 180 mg and ITI-007 60 mg groups**

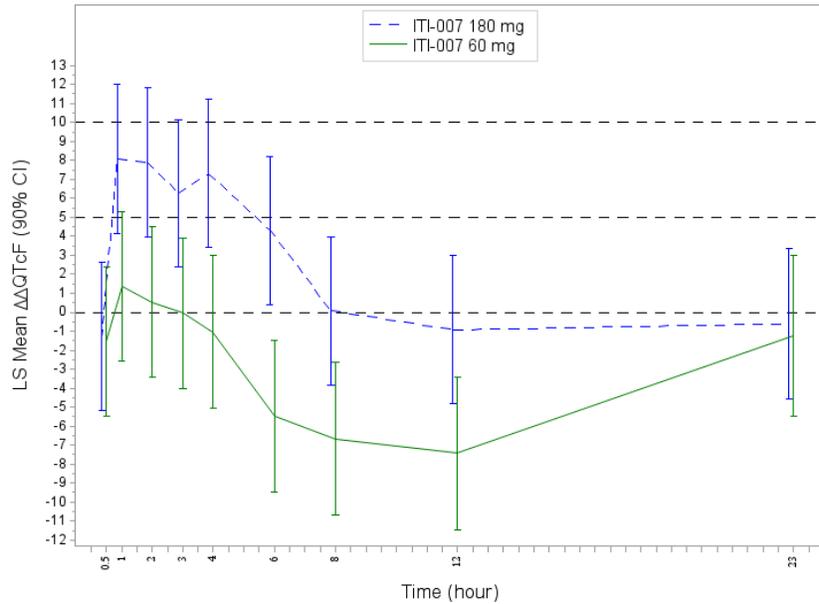
		Treatment Group							
		ITI-007 180 mg				ITI-007 60 mg			
		$\Delta QTcF$	Placebo	$\Delta\Delta QTcF$		$\Delta QTcF$	Placebo	$\Delta\Delta QTcF$	
Day	Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	0.5	0.9	2.2	-1.3	(-5.2, 2.6)	0.6	2.2	-1.6	(-5.5, 2.4)
1	1	10.0	1.9	8.1	(4.2, 12.0)	3.2	1.9	1.4	(-2.5, 5.3)
1	2	10.8	2.9	7.9	(4.0, 11.8)	3.4	2.9	0.5	(-3.4, 4.5)
1	3	7.3	1.0	6.3	(2.4, 10.2)	0.9	1.0	-0.1	(-4.0, 3.9)
1	4	8.6	1.3	7.3	(3.4, 11.2)	0.2	1.3	-1.0	(-5.1, 3.0)
1	6	1.3	-3.0	4.3	(0.4, 8.2)	-8.5	-3.0	-5.5	(-9.5, -1.5)
1	8	-3.4	-3.4	0.1	(-3.8, 4.0)	-10.1	-3.4	-6.7	(-10.7, -2.7)
1	12	-2.9	-1.9	-0.9	(-4.8, 3.0)	-9.4	-1.9	-7.4	(-11.5, -3.4)
1	23	-1.5	-0.9	-0.6	(-4.5, 3.3)	-2.1	-0.9	-1.2	(-5.5, 3.0)
5	0.5	-1.7	-0.2	-1.5	(-5.5, 2.4)	-4.8	-0.2	-4.6	(-8.6, -0.7)
5	1	6.4	-3.5	9.9	(6.0, 13.9)	0.5	-3.5	4.0	(0.1, 8.0)
5	2	13.8	-2.0	15.8	(11.8, 19.8)	2.9	-2.0	4.9	(0.9, 8.9)
5	3	9.6	-2.4	12.0	(8.1, 16.0)	-0.3	-2.4	2.2	(-1.7, 6.1)
5	4	9.6	-1.7	11.4	(7.4, 15.3)	0.7	-1.7	2.4	(-1.5, 6.3)
5	6	2.3	-7.7	10.0	(6.0, 13.9)	-3.0	-7.7	4.7	(0.7, 8.6)
5	8	-0.3	-7.3	7.0	(3.0, 11.0)	-4.7	-7.3	2.6	(-1.3, 6.5)
5	12	-2.5	-7.3	4.8	(0.8, 8.8)	-6.8	-7.3	0.5	(-3.5, 4.5)
5	23	-2.1	-1.5	-0.6	(-4.7, 3.4)	-4.7	-1.5	-3.2	(-7.2, 0.9)

For Day 1, the largest upper bounds of the 2-sided 90% CI for the mean difference between ITI-007 180 mg and placebo, and between ITI-007 60 mg and placebo were 19.8 ms and 8.9 ms, respectively.

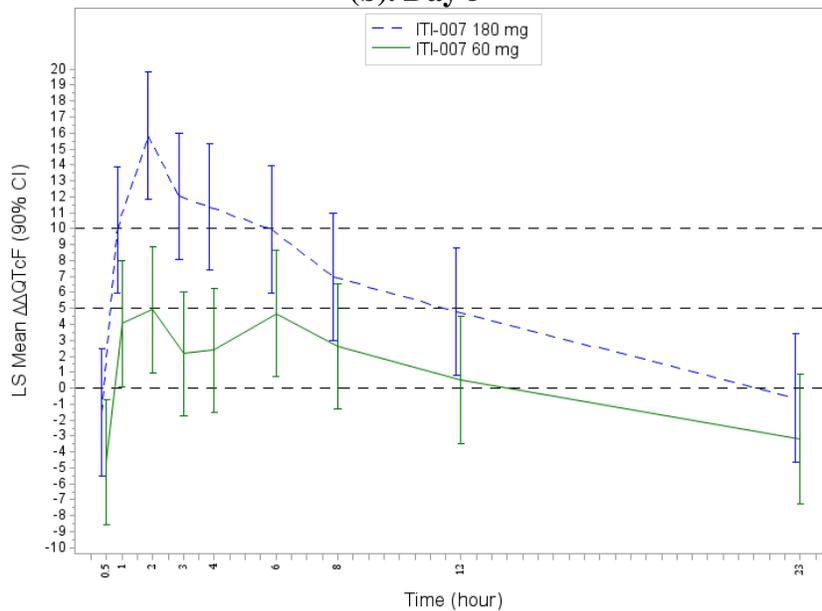
For Day 5, the largest upper bounds of the 2-sided 90% CI for the mean difference between ITI-007 180 mg and placebo, and between ITI-007 60 mg and placebo were 12.0 ms and 5.3 ms, respectively.

Figure 1 displays the time profile of  $\Delta\Delta QTcF$  for different treatment groups for Day 1 and Day 5.

**Figure 1: Mean and 90% CI  $\Delta\Delta$ QTcF Time Course (unadjusted CIs).  
(a). Day 1**



**(b). Day 5**



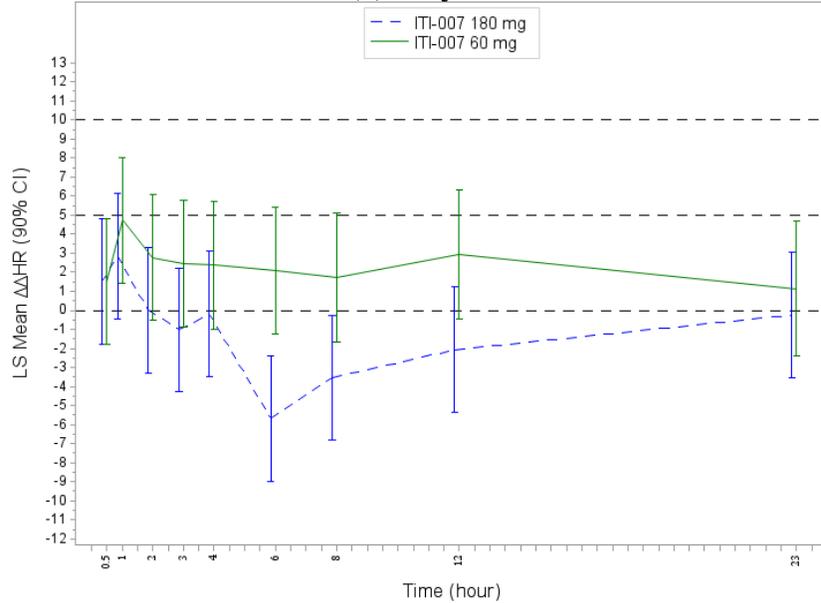
#### 4.3.1.1 Assay sensitivity

Primary method for assay sensitivity was exposure-response analysis. Please see section 4.5.1 for details.

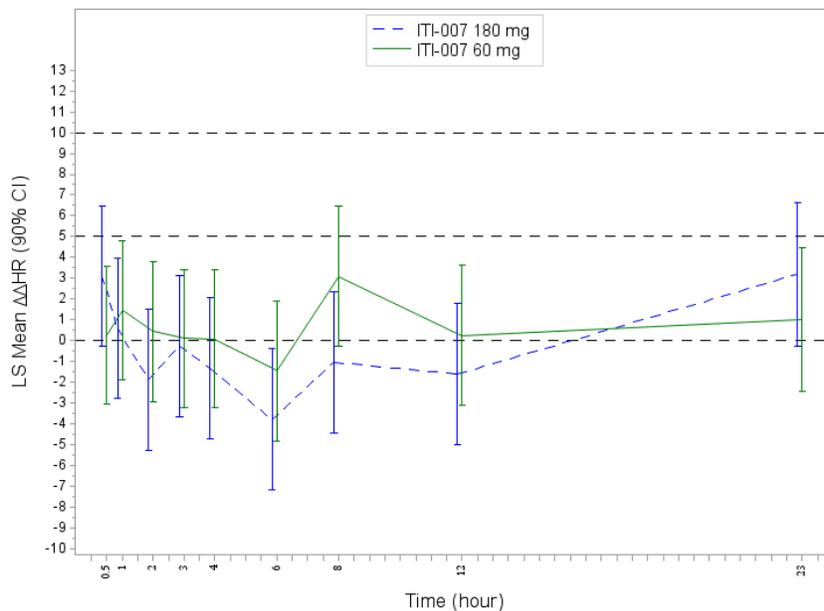
#### 4.3.2 HR

The same statistical analysis was performed based on HR (Figure 2). The largest upper limits of 90% CI for the QRS mean differences between ITI-007 180 mg and placebo and ITI-007 60 mg and placebo were less than 10 bpm for both Day 1 and Day 5.

**Figure 2: Mean and 90% CI  $\Delta\Delta$ HR Time Course**  
**(a). Day 1**



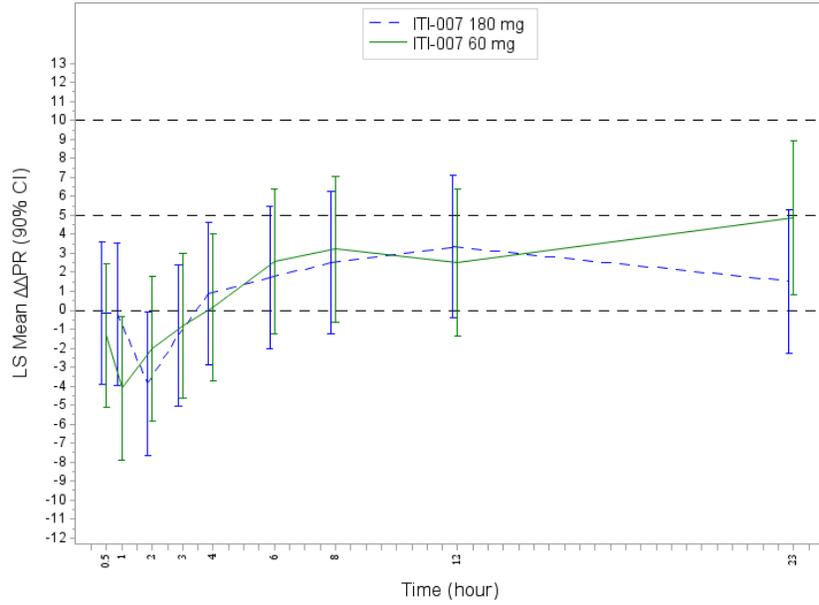
**(b). Day 5**



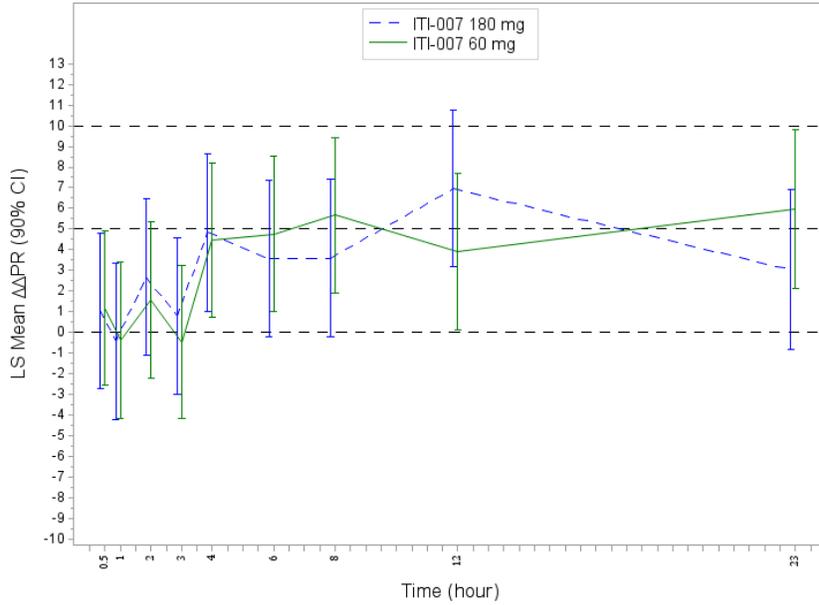
### 4.3.3 PR

The same statistical analysis was performed based on PR interval. The largest upper limits of 90% CI for the PR mean differences between ITI-007 180 mg and placebo and ITI-007 60 mg and placebo were less than 10 ms for Day 1. But for Day 5, the largest upper limits of 90% CI for mean differences between ITI-007 180 mg and placebo and ITI-007 60 mg and placebo were 10.7 ms and 9.8 ms respectively.

**Figure 3: Mean and 90% CI  $\Delta$ APR Time Course  
(a). Day 1**



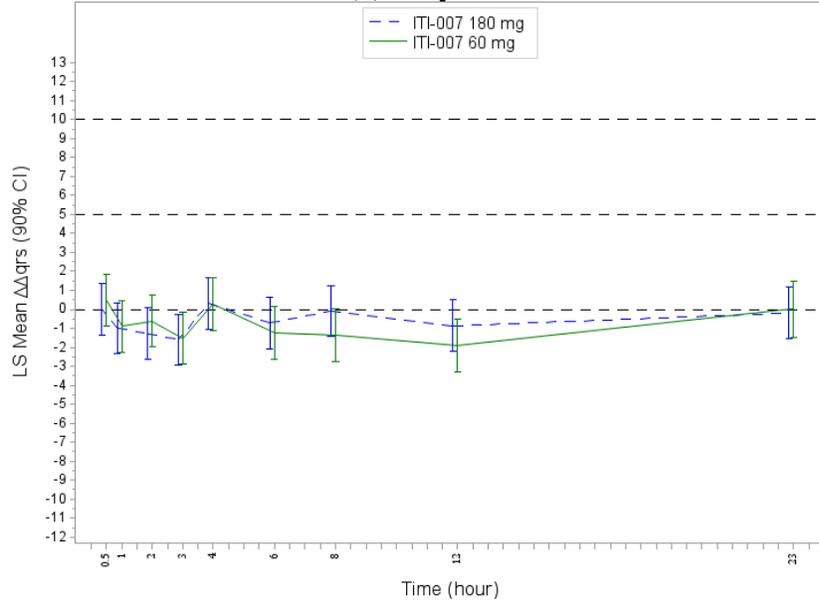
**(b). Day 5**



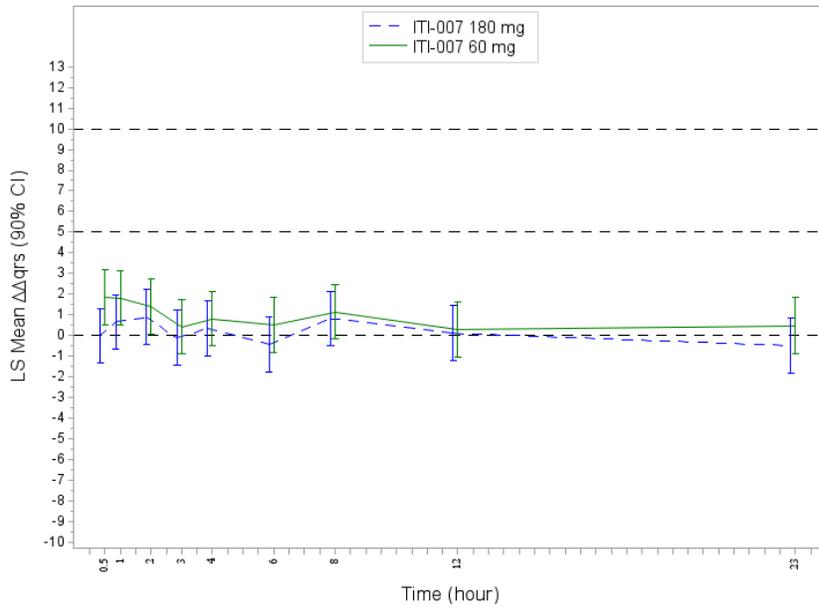
#### 4.3.4 QRS

The same statistical analysis was performed based on QRS interval (Figure 4). The largest upper limits of 90% CI for the QRS mean differences between ITI-007 180 mg and placebo and ITI-007 60 mg and placebo were less than 10 ms for both Day 1 and 5.

**Figure 4: Mean and 90% CI  $\Delta\Delta$ QRS Time-course**  
**(a). Day 1**



**(b). Day 5**



#### 4.4 CATEGORICAL ANALYSIS

##### 4.4.1 QTc

Table 4 lists the number of subjects as well as the number of observations whose QTcF values are  $\leq 450$  ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

**Table 4: Categorical Analysis for QTcF**

Treatment Group	Total N		Value<=450 ms		450 ms<Value<=480 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
ITI-007 180 mg	31	520	29 (93.5%)	516 (99.2%)	2 (6.5%)	4 (0.8%)
ITI-007 60 mg	32	523	32 (100%)	523 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	28	245	27 (96.4%)	241 (98.4%)	1 (3.6%)	4 (1.6%)
Placebo	31	537	30 (96.8%)	535 (99.6%)	1 (3.2%)	2 (0.4%)

Table 5 lists the categorical analysis results for  $\Delta$ QTcF. No subject's change from baseline was above 60 ms.

**Table 5: Categorical Analysis of  $\Delta$ QTcF**

Treatment Group	Total N		Value<=30 ms		30 ms<Value<=60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
ITI-007 180 mg	29	494	25 (86.2%)	481 (97.4%)	4 (13.8%)	13 (2.6%)
ITI-007 60 mg	29	480	28 (96.6%)	479 (99.8%)	1 (3.4%)	1 (0.2%)
Moxifloxacin 400 mg	28	245	26 (92.9%)	240 (98.0%)	2 (7.1%)	5 (2.0%)
Placebo	30	522	30 (100%)	522 (100%)	0 (0.0%)	0 (0.0%)

Note: Some of the subjects did not have baseline values for QTcF.

#### 4.4.2 PR

The outlier analysis results for PR are presented in Table 6. There were three and five subjects who experienced PR interval greater than 200 ms in ITI-007 180 mg group and ITI-007 60 mg group, respectively.

**Table 6: Categorical Analysis for PR**

Treatment Group	T		Value<=200 ms		200 ms<Value<=220 ms		Value>220 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
ITI-007 180 mg	31	520	28 (90.3%)	493 (94.8%)	1 (3.2%)	17 (3.3%)	2 (6.5%)	10 (1.9%)
ITI-007 60 mg	32	523	27 (84.4%)	498 (95.2%)	3 (9.4%)	19 (3.6%)	2 (6.3%)	6 (1.1%)
Moxifloxacin 400 mg	28	245	26 (92.9%)	241 (98.4%)	2 (7.1%)	4 (1.6%)	0 (0.0%)	0 (0.0%)
Placebo	31	537	28 (90.3%)	516 (96.1%)	1 (3.2%)	16 (3.0%)	2 (6.5%)	5 (0.9%)

#### 4.4.3 QRS

The outlier analysis results for QRS are presented in Table 7. There are no subjects who experienced QRS interval greater than 110 ms in both in ITI-007 60 mg and ITI-007 180 mg groups.

**Table 7: Categorical Analysis for QRS**

Treatment Group	T		Value<=100 ms		100 ms<Value<=110 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
ITI-007 180 mg	31	520	27 (87.1%)	474 (91.2%)	4 (12.9%)	46 (8.8%)
ITI-007 60 mg	32	523	24 (75.0%)	471 (90.1%)	8 (25.0%)	52 (9.9%)
Moxifloxacin 400 mg	28	245	24 (85.7%)	221 (90.2%)	4 (14.3%)	24 (9.8%)
Placebo	31	537	25 (80.6%)	488 (90.9%)	6 (19.4%)	49 (9.1%)

#### 4.4.4 HR

The outlier analysis results for HR are presented in Table 8. There are seven and five subjects who experienced HR greater than 100 bpm in ITI-007 180 mg group and ITI-007 60 mg group respectively.

**Table 8: Categorical Analysis for HR**

Treatment Group	Total N		Value<=100 bpm		Value>100 bpm	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
ITI-007 180 mg	31	520	24 (77.4%)	510 (98.1%)	7 (22.6%)	10 (1.9%)
ITI-007 60 mg	32	523	27 (84.4%)	511 (97.7%)	5 (15.6%)	12 (2.3%)
Moxifloxacin 400 mg	28	245	23 (82.1%)	238 (97.1%)	5 (17.9%)	7 (2.9%)
Placebo	31	537	23 (74.2%)	526 (98.0%)	8 (25.8%)	11 (2.0%)

#### 4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between  $\Delta$ QTcF and concentration of lumateperone (IC200056) or its metabolites (IC20013, IC200161, IC200565, IC201308, and IC201309).

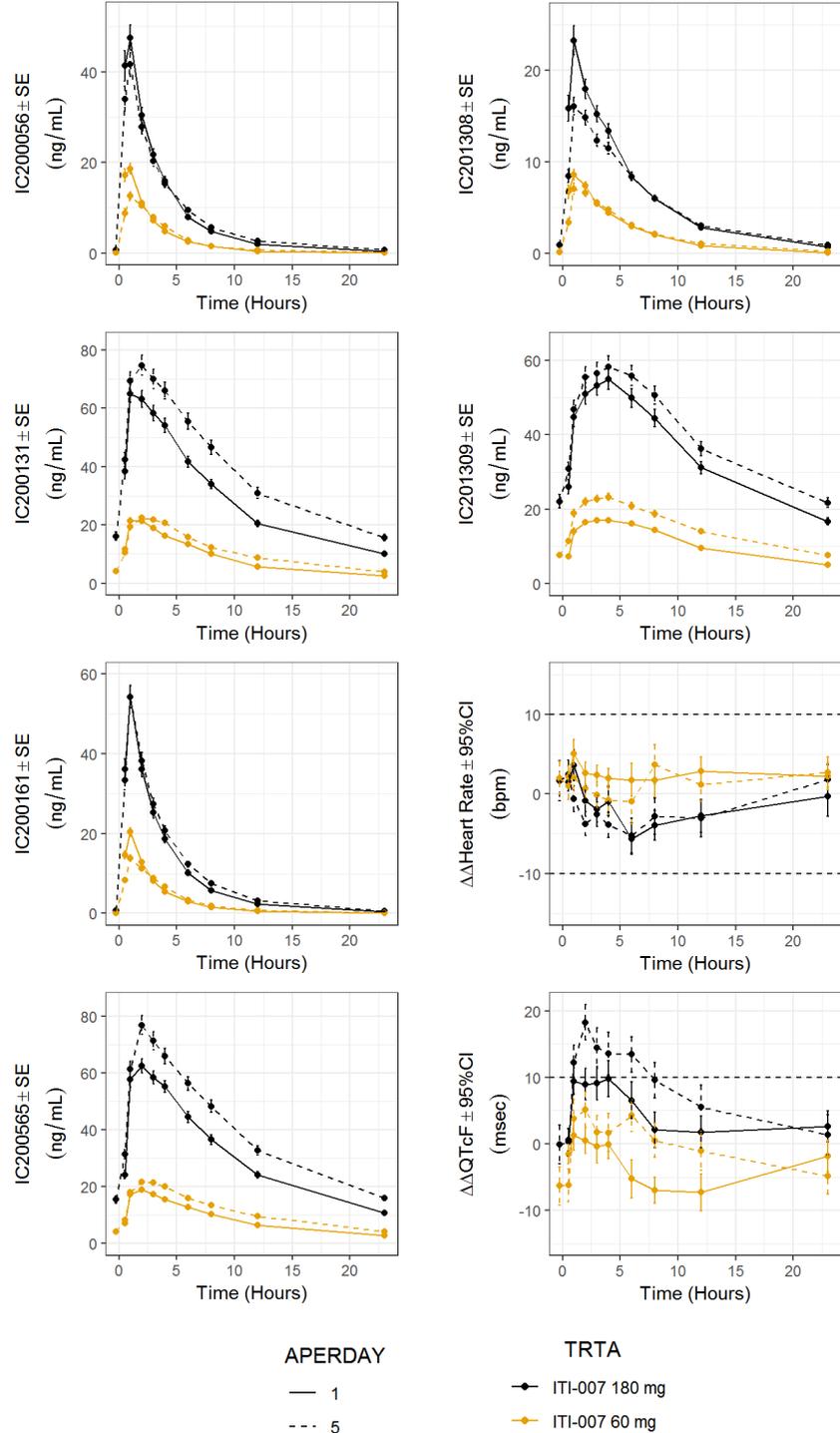
Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and  $\Delta$ QTcF; and 3) presence of non-linear relationship.

An evaluation of the time-course of drug concentration and changes in  $\Delta$ HR and  $\Delta$ QTcF is shown in Figure 5, which shows an absence of significant changes in HR. There is an approximately dose-proportional increase in lumateperone and its metabolite concentrations without considerable accumulation on Day 5. The time at maximum effect on  $\Delta$ QTcF appears to correlate better with Tmax of lumateperone (IC200056). However, the assessment of hysteresis (Figure 6) indicated a 1-2 h delay between the mean peak plasma concentrations and the peak effect of  $\Delta$ QTcF for IC200056, IC200161, IC200131, and IC201308.

**Table 9. Mean maximum concentration (ng/mL) of drug-related moieties (Day 5).**

Treatment	IC200056	IC200131	IC200161	IC200565	IC201308	IC201309
ITI-007 180 mg	52.2	73.4	61.9	74.6	22.2	54.6
ITI-007 60 mg	19.2	26.9	20.3	24.6	8.9	23.2

**Figure 5: Time course of drug concentration - lumateperone (IC200056) and its metabolites (IC200131; IC200161; IC200565; IC201308; and IC201309), heart rate, and QTcF.**



**Figure 6: Assessment of hysteresis (IC200056 and its metabolites, IC200131, IC200161, IC200565, IC201308, and IC201309)**

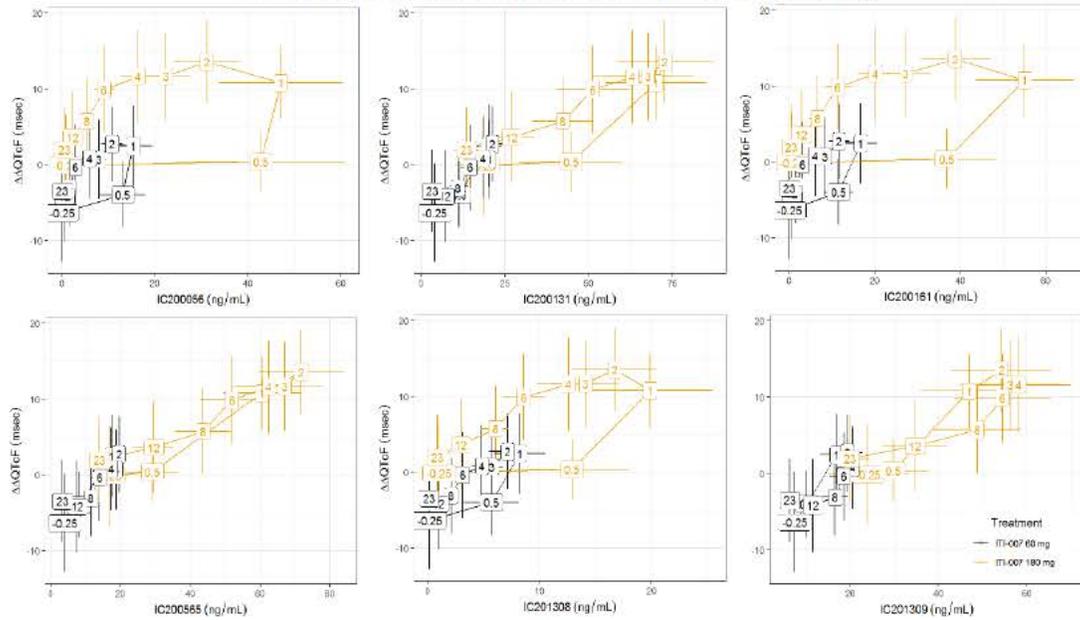
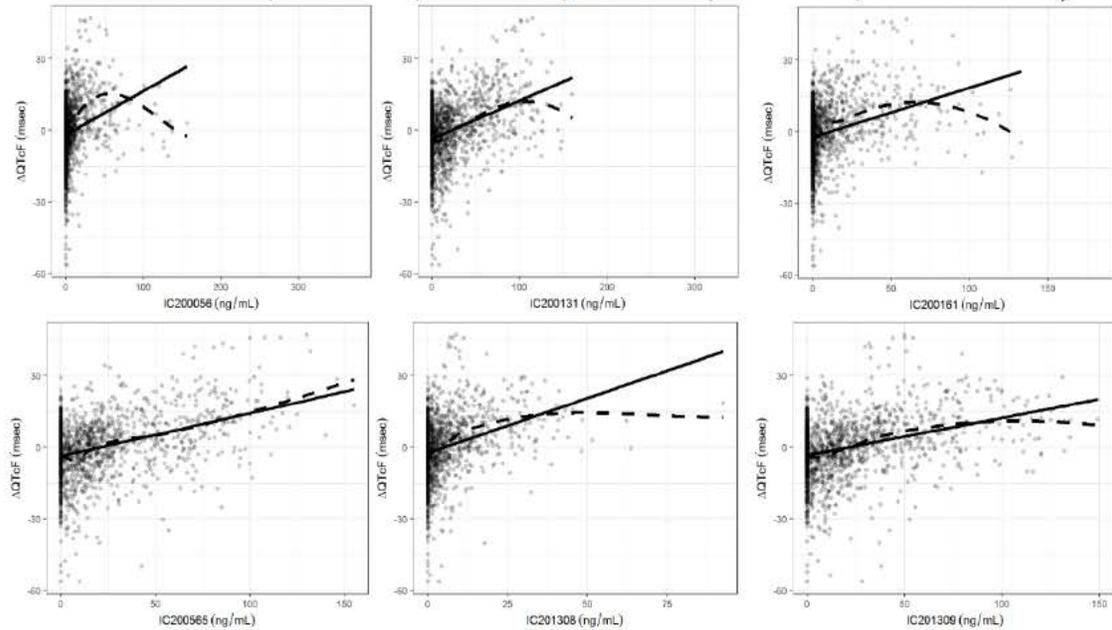


Figure 7 shows the relationship between drug concentrations and  $\Delta QTcF$ . Except for IC200565, there appears to be deviation from linearity in the high exposure ranges.

**Figure 7: Assessment of linearity of concentration-QTc relationship (IC200056 and its metabolites, IC200131, IC200161, IC200565, IC201308, and IC201309)**



The reviewer explored concentration-QTc models using IC200565 as the only exposure metric or including all drug-related concentrations as the exposure metrics. Compared with sponsor's model, reviewer used time since last dose and study day as fixed effects. Including an interaction between time and study day does not improve model fitting.

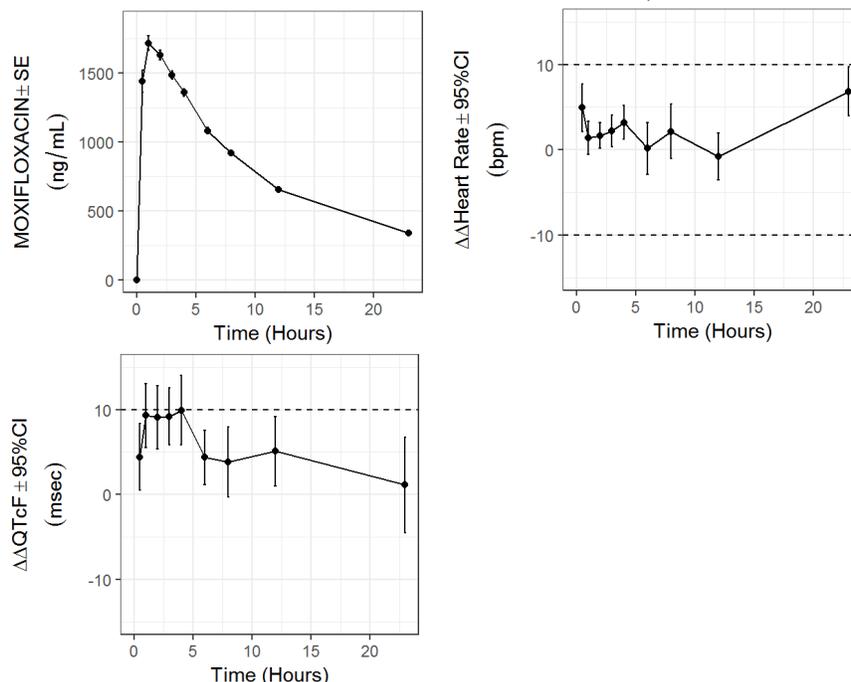
The model using IC200565 as the exposure metric suggests a significant ( $p=0.05$ ), negative treatment effect and a significant ( $p=0.05$ ), positive exposure-response relationship. The predicted effects on  $\Delta\Delta QTcF$  are 2.4 ms (upper bound of 90% CI: 3.4 ms) and 12.0 ms (13.4 ms) at the therapeutic and suprathreshold dose. The model using all drug related moiety as the exposure metrics suggested a positive correlation with IC200565 ( $p=0.05$ ). The 95% CI of the estimated slope for the other moieties included 0. The predicted effects on  $\Delta\Delta QTcF$  are 2.0 ms (upper bound of 90% CI: 3.0 ms) and 10.5 ms (12.4 ms) at the therapeutic and suprathreshold dose.

The analysis with single exposure metrics may not be fully justified by the fact that multiple drug-related moieties (e.g. at least parent drug, IC200131, and IC200161) demonstrated in vitro activities in hERG assays. The analysis using multiple exposure metrics can be confounded by the correlations between these drug-related exposure metrics, and it may not be justified due to a lack of information on the nonclinical cardiac safety profiles of certain metabolites. Therefore, in the reviewer's opinion, concentration-QTc analysis may not be appropriate as the primary analysis in this study.

#### 4.5.1 Assay sensitivity

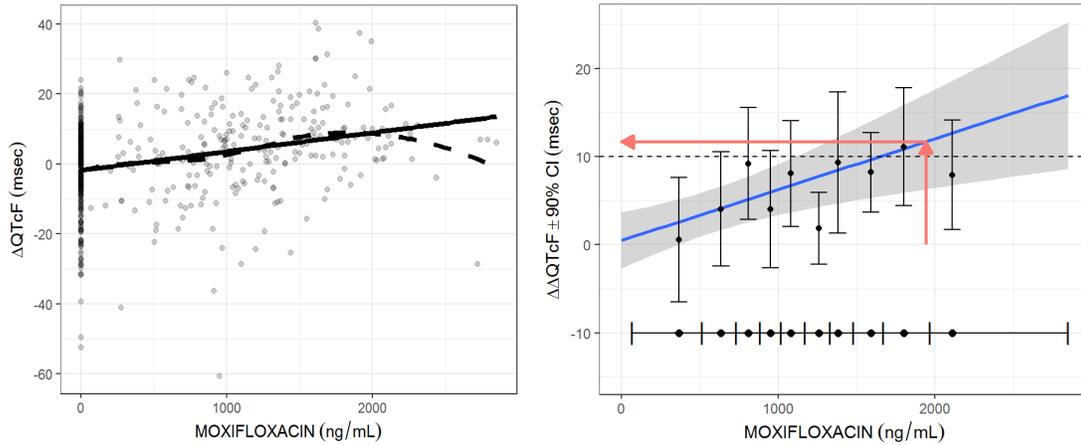
To demonstrate assay sensitivity, the sponsor included oral moxifloxacin 400 mg as a positive control to detect small increases from baseline for QTcF in this study. The PK profile in the moxifloxacin group are generally consistent with the ascending, peak, and descending phases of historical data (Figure 9).

**Figure 8: Time course of moxifloxacin concentration, heart rate and QTcF**



Concentration-response analysis of moxifloxacin data indicated a positive slope in the relationship between  $\Delta\text{QTcF}$  and the plasma concentration of moxifloxacin. The lower limit of the two-sided 90% confidence interval at the observed mean peak concentrations of moxifloxacin is above 5 ms. Therefore, assay sensitivity is established.

**Figure 9: Assessment of linearity of concentration-QTc relationship (Left) and goodness-of-fit plot for QTc (Right) of moxifloxacin**



#### 4.6 SAFETY ASSESSMENTS

See section 3.2.3.

#### 4.7 OTHER ECG INTERVALS

Overall, no clinically significant changes in PR or QRS were observed.

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