CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

209500Orig1s006

Trade Name:	CAPLYTA
Generic or Proper Name:	(lumateperone)
Sponsor:	Intra-Cellular Therapies
Approval Date:	December 17, 2021
Indication:	CAPLYTA is an atypical antipsychotic indicated for the treatment of: • Schizophrenia in adults. • Depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate.

CENTER FOR DRUG EVALUATION AND RESEARCH

209500Orig1s006

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APPLICATION NUMBER:

209500Orig1s006

APPROVAL LETTER

NDA 209500/S-005 & S-006

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT

Intra-Cellular Therapies, Inc.
Attention: Nicole L. Bradley, PharmD
Executive Director, Regulatory Affairs
430 East 29th St, Suite 900
New York, NY 10016

Dear Dr. Bradley:

Please refer to your supplemental new drug application (sNDA) dated February 17, 2021, received February 17, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Caplyta (lumateperone) capsules.

These Prior Approval supplemental new drug applications provide for the addition of the following indication: depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 209500/S-005 and S-006**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric studies requirement for ages 0 to 9 years because necessary studies are impossible or highly impracticable. This is because it is difficult to diagnosis bipolar disorder in children younger than 10 years and the prevalence rate of bipolar disorder for children younger then 10 years of age is low.

We are deferring submission of your pediatric studies for ages 10 to 17 years for this application because pediatric studies should be delayed until additional safety or effectiveness data have been collected.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

4192-1 Conduct a GLP juvenile animal study to assess the toxicology of lumateperone to support clinical trials of lumateperone in the intended pediatric population ages 10 to 17 years.

Final Protocol Submission: n/a
Study Completion: n/a
Final Report Submission: 02/2022

4192-2 Conduct an open-label, multiple oral dose study to demonstrate the safety, tolerability, and pharmacokinetics of lumateperone in patients ages 10 to 17 years with major depressive episode with bipolar I or II disorder (bipolar depression).

Final Protocol Submission: 05/2022
Study Completion: 05/2023
Final Report Submission: 11/2023

4192-3 Conduct a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of lumateperone for the treatment of major depressive episode associated with bipolar I or II disorder (bipolar depression) in patients aged 10 to 17 years.

Final Protocol Submission: 11/2023
Study Completion: 05/2027
Final Report Submission: 11/2027

4192-4 Conduct an open-label study to assess the long-term safety of lumateperone in patients aged 10 to 17 years with major depressive episode associated with bipolar I or II disorder (bipolar depression).

Final Protocol Submission: 11/2023
Study Completion: 11/2027
Final Report Submission: 05/2028

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 126701, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated February 17, 2021, containing the final report for the following postmarketing requirement listed in the December 20, 2019 approval letter.

3760-5 Conduct a clinical pharmacokinetic trial to evaluate if UGT enzyme inhibitors alter the PK of lumateperone and its metabolites (including metabolites IC201337 and IC201338) using fully validated assays and to determine appropriate dosing recommendations for CAPLYTA with regard to use of concomitant UGT enzyme inhibitors.

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there are postmarketing requirements and postmarketing commitments listed in the December 20, 2019 approval letter that are still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Tiffanie Taylor, Regulatory Project Manager, at Tiffanie.Taylor@fda.hhs.gov .

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, MD
Director
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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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.

/s/

TIFFANY R FARCHIONE
12/17/2021 06:02:24 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209500Orig1s006

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CAPLYTA safely and effectively. See full prescribing information for CAPLYTA.

CAPLYTA® (lumateperone) capsules, for oral use
Initial U.S. Approval: 2019

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis. (5.1)**
- **Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients. Closely monitor all antidepressant-treated patients for worsening and emergence of suicidal thoughts and behaviors. Safety and effectiveness of CAPLYTA have not been established in pediatric patients. (5.2, 8.4)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	12/2021
Indication and Usage (1)	12/2021
Dosage and Administration (2.1)	12/2021
Warnings and Precautions (5.2, 5.6, 5.8, 5.11)	12/2021

----------INDICATIONS AND USAGE----------

CAPLYTA is an atypical antipsychotic indicated for the treatment of:

- Schizophrenia in adults. (1)
- Depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate. (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended dosage of CAPLYTA is 42 mg once daily with or without food. (2.1)
- Dose titration is not required. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 42 mg (3)

----------CONTRAINDICATIONS----------

Known hypersensitivity to lumateperone or any components of CAPLYTA. (4)

----------WARNINGS AND PRECAUTIONS----------

- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis* Increased incidence of cerebrovascular adverse reactions (e.g., stroke and transient ischemic attack). (5.3)
- *Neuroleptic Malignant Syndrome* Manage with immediate discontinuation and close monitoring. (5.4)
- *Tardive Dyskinesia* Discontinue treatment if clinically appropriate. (5.5)
- *Metabolic Changes* Monitor for hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. (5.6)
- *Leukopenia, Neutropenia, and Agranulocytosis*: Perform complete blood counts (CBC) in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. Consider discontinuing CAPLYTA if clinically significant decline in WBC occurs in absence of other causative factors. (5.7)
- *Orthostatic Hypotension and Syncope* Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope. (5.8)
- *Seizures* Use cautiously in patients with a history of seizure or with conditions that lower seizure threshold. (5.10)
- *Potential for Cognitive and Motor Impairment* Use caution when operating machinery. (5.11)

----------ADVERSE REACTIONS----------

Most common adverse reactions in clinical trials (incidence $\geq$ 5% and greater than twice placebo) were (6.1):

- Schizophrenia: somnolence/sedation and dry mouth
- Bipolar depression: somnolence/sedation, dizziness, nausea, dry mouth.

To report SUSPECTED ADVERSE REACTIONS, contact Intra-Cellular Therapies, Inc. at 1-888-611-4824 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- CYP3A4 inducers: Avoid concomitant use. (2.2, 7.1)
- Moderate or strong CYP3A4 inhibitors: Avoid concomitant use. (2.2, 7.1)

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

- Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)
- Lactation: Breastfeeding not recommended. (8.2)
- Moderate or severe hepatic impairment: Avoid use. (2.3, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 12/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)].*

Suicidal Thoughts and Behaviors
Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adults in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors *[see Warnings and Precautions (5.2)].* The safety and effectiveness of CAPLYTA have not been established in pediatric patients *[see Use in Specific Populations (8.4)].*

1 INDICATIONS AND USAGE

CAPLYTA is indicated for the treatment of:

- Schizophrenia in adults *[see Clinical Studies (14.1)]*.
- Depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of CAPLYTA is 42 mg administered orally once daily with or without food. Dose titration is not required.

2.2 Dosage Recommendations for Concomitant Use with CYP3A4 Inducers and Moderate or Strong CYP3A4 Inhibitors

Coadministration with CYP3A4 Inducers

Avoid concomitant use of CAPLYTA with CYP3A4 inducers *[see Drug Interactions (7.1)]*.

Coadministration with Moderate or Strong CYP3A4 Inhibitors

Avoid concomitant use of CAPLYTA with moderate or strong CYP3A4 inhibitors *[see Drug Interactions (7.1)]*.

2.3 Dosage Recommendations for Patients with Hepatic Impairment

Avoid use of CAPLYTA in patients with moderate or severe hepatic impairment (Child-Pugh B or C) *[see Use in Specific Populations (8.6)]*.

3 DOSAGE FORMS AND STRENGTHS

CAPLYTA capsules are available as a 42 mg strength (equivalent to 60 mg lumateperone tosylate). The capsule has a blue cap and opaque white body imprinted with “ITI-007 42 mg.”

4 CONTRAINDICATIONS

CAPLYTA is contraindicated in patients with history of hypersensitivity reaction to lumateperone. Reactions have included pruritus, rash (e.g. allergic dermatitis, papular rash, and generalized rash), and urticaria.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was

about 4.5%, compared to a rate of about 2.6% in placebo-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.3)]*.

5.2 Suicidal Thoughts and Behaviors in Children, Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

Table 1: Risk Differences of the Number of Patients of Suicidal Thoughts and Behavior in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients

Age Range	Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1000 Patients Treated
	Increases Compared to Placebo
<18 years old	14 additional patients
18-24 years old	5 additional patients
	Decreases Compared to Placebo
25-64 years old	1 fewer patient
≥65 years old	6 fewer patients

*CAPLYTA is not approved for use in pediatric patients.

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing CAPLYTA, in patients whose depression is persistently worse, or who are experiencing suicidal thoughts or behaviors.

5.3 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials in elderly subjects with dementia, patients randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.

5.4 Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with administration of antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, delirium, and autonomic instability. Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If NMS is suspected, immediately discontinue CAPLYTA and provide intensive symptomatic treatment and monitoring.

5.5 Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. The risk appears to be highest among the elderly, especially elderly women, but it is not possible to predict which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of tardive dyskinesia and the likelihood that it will become irreversible increase with the duration of treatment and the cumulative dose. The syndrome can develop after a relatively brief treatment period, even at low doses. It may also occur after discontinuation of treatment.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, possibly masking the underlying process. The effect that symptomatic suppression has upon the long-term course of tardive dyskinesia is unknown.

Given these considerations, CAPLYTA should be prescribed in a manner most likely to reduce the risk of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: 1) who suffer from a chronic illness that is known to respond to antipsychotic drugs; and 2) for whom alternative, effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response. Periodically reassess the need for continued treatment.

If signs and symptoms of tardive dyskinesia appear in a patient on CAPLYTA, drug discontinuation should be considered. However, some patients may require treatment with CAPLYTA despite the presence of the syndrome.

5.6 Metabolic Changes

Antipsychotic drugs have caused metabolic changes, including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain. Although all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, has been reported in patients treated with antipsychotics. There have been reports of hyperglycemia in patients treated with CAPLYTA. Assess fasting plasma glucose before or soon after initiation of antipsychotic medication and monitor periodically during long-term treatment.

Schizophrenia

In pooled data from short-term (4- to 6-week), placebo-controlled trials of adult patients with schizophrenia, mean changes from baseline and the proportion of patients with shifts from normal to greater than normal levels of fasting glucose in patients treated with CAPLYTA were similar to those in patients treated with placebo.

In an uncontrolled open-label trial of CAPLYTA for up to 1 year in patients with stable schizophrenia, the percentages of patients with shifts in fasting glucose and insulin values from normal to high were 8% and 12%, respectively. 4.7% of patients with normal hemoglobin A1c (<6.5%) at baseline developed elevated levels (≥6.5%) post-baseline.

Bipolar Depression

In data from short-term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression trials, mean changes from baseline and the proportion of patients with shifts from normal to greater than normal levels of fasting glucose and insulin in patients treated with CAPLYTA were similar to those in patients treated with placebo.

Dyslipidemia

Antipsychotics have caused adverse alterations in lipids. Before or soon after initiation of antipsychotic medications, obtain a fasting lipid profile at baseline and monitor periodically during treatment.

Schizophrenia

In pooled data from short-term (4- to 6-week), placebo-controlled trials of adult patients with schizophrenia, mean changes from baseline and the proportion of patients with shifts to higher levels of fasting total cholesterol and triglycerides were similar in patients treated with CAPLYTA and placebo.

In an uncontrolled open-label trial of CAPLYTA for up to 1 year in patients with stable schizophrenia, the percentages of patients with a shift from normal to high were 8%, 5%, and 4% for total cholesterol, triglycerides, and LDL cholesterol, respectively.

Bipolar Depression

In data from short-term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression trials, mean changes from baseline and the proportion of patients with shifts to higher levels of fasting total cholesterol and triglycerides were similar in patients treated with CAPLYTA and placebo.

In an uncontrolled open-label trial of CAPLYTA for up to 6 months in patients with bipolar depression, the proportion of patients with a shift from normal to high were 10%, 5%, and 2% for total cholesterol, triglycerides, and LDL cholesterol, respectively.

Weight Gain

Weight gain has been observed with use of antipsychotics. Monitor weight at baseline and frequently thereafter.

Schizophrenia

In pooled data from placebo-controlled trials of adult patients with schizophrenia, mean changes from baseline and the proportion of patients with an increase in weight ≥7% from baseline to end of study was similar in patients treated with CAPLYTA and placebo.

In an uncontrolled open-label trial of CAPLYTA for up to 1 year in patients with stable schizophrenia, the mean change in body weight was approximately -2 kg (SD 5.6) at Day 175 and approximately - 3.2 kg (SD 7.4) at Day 350.

Bipolar Depression

In data from short-term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression trials, mean changes from baseline and the proportion of patients with an increase in weight ≥7% from baseline to end of study were similar in patients treated with CAPLYTA and placebo.

In an uncontrolled open-label trial of CAPLYTA for up to 6 months in patients with bipolar depression, the mean change in body weight was -0.01 kg (SD 3.1) at Day 175.

5.7 Leukopenia, Neutropenia, and Agranulocytosis

Leukopenia and neutropenia have been reported during treatment with antipsychotic agents, including CAPLYTA. Agranulocytosis (including fatal cases) has been reported with other agents in the class.

Possible risk factors for leukopenia and neutropenia include pre-existing low white blood cell count (WBC) or absolute neutrophil count (ANC) and history of drug-induced leukopenia or neutropenia. In patients with a pre-existing low WBC or ANC or a history of drug-induced leukopenia or neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of CAPLYTA at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue CAPLYTA in patients with absolute neutrophil count < $1000/mm^3$ and follow their WBC until recovery.

5.8 Orthostatic Hypotension and Syncope

Atypical antipsychotics cause orthostatic hypotension and syncope. Generally, the risk is greatest during initial dose administration. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension (e.g., elderly patients, patients with dehydration, hypovolemia, and concomitant treatment with antihypertensive medications), patients with known cardiovascular disease (history of myocardial infarction, ischemic heart disease, heart failure, or conduction abnormalities), and patients with cerebrovascular disease. CAPLYTA has not been evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease. Such patients were excluded from pre-marketing clinical trials.

Schizophrenia

In pooled data from short-term (4- to 6-week), placebo-controlled schizophrenia trials, the frequencies of orthostatic hypotension for CAPLYTA and placebo were 0.7% and 0%, respectively. The rates of syncope for CAPLYTA and placebo were 0.2% and 0.2%.

Bipolar Depression

In data from short-term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression trials, the frequencies of orthostatic hypotension for CAPLYTA and placebo were both 0%. The rates of syncope for CAPLYTA and placebo were 0.3% and 0.5%, respectively in the monotherapy trials, and there were no reports for CAPLYTA or placebo in the adjunctive therapy trial.

5.9 Falls

Antipsychotics, including CAPLYTA, may cause somnolence, postural hypotension, and motor and sensory instability, which may lead to falls and, consequently, fractures and other injuries. For patients with diseases, conditions or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and periodically during long-term treatment.

5.10 Seizures

Like other antipsychotic drugs, CAPLYTA may cause seizures. The risk is greatest in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in older patients.

5.11 Potential for Cognitive and Motor Impairment

CAPLYTA, like other antipsychotics, may cause somnolence and has the potential to impair judgment, thinking, and motor skills. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with CAPLYTA does not affect them adversely.

Schizophrenia

In short-term (i.e., 4- to 6-week), placebo-controlled clinical trials of patients with schizophrenia, somnolence and sedation were reported in 24% of CAPLYTA-treated patients, compared to 10% of placebo-treated patients.

Bipolar Depression

In short term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression clinical trials, somnolence and sedation were reported in 13% of CAPLYTA-treated patients, compared to 3% of placebo-treated patients.

5.12 Body Temperature Dysregulation

Atypical antipsychotics may disrupt the body's ability to reduce core body temperature. Strenuous exercise, exposure to extreme heat, dehydration, and anticholinergic medications may contribute to an elevation in core body temperature; use CAPLYTA with caution in patients who may experience these conditions.

5.13 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Antipsychotic drugs, including CAPLYTA, should be used cautiously in patients at risk for aspiration.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in detail in other sections of the labeling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Suicidal Thoughts and Behaviors *[see Boxed Warning, Warnings and Precautions (5.2)]*
- Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-related Psychosis *[see Warnings and Precautions (5.3)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.4)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.5)]*
- Metabolic Changes *[see Warnings and Precautions (5.6)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.7)]*
- Orthostatic Hypotension and Syncope *[see Warnings and Precautions (5.8)]*
- Falls *[see Warnings and Precautions (5.9)]*
- Seizures *[see Warnings and Precautions (5.10)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.11)]*
- Body Temperature Dysregulation *[see Warnings and Precautions (5.12)]*
- Dysphagia *[see Warnings and Precautions (5.13)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of CAPLYTA has been evaluated in placebo-controlled clinical trials in 2664 adult patients with schizophrenia and bipolar depression exposed to one or more doses. A total of 402 CAPLYTA-exposed patients had at least 6 months of exposure and 108 had at least 1 year of exposure to the 42-mg dose of CAPLYTA.

Schizophrenia

The following findings are based on the pooled short-term (4- to 6-week), placebo-controlled studies in adult patients with schizophrenia in which CAPLYTA was administered at a daily dose of 42 mg (N=406).

There was no single adverse reaction leading to discontinuation that occurred at a rate of >2% in CAPLYTA-treated patients.

The most common adverse reactions (incidence of at least 5% of patients exposed to CAPLYTA and greater than twice the rate of placebo) are somnolence/sedation and dry mouth.

Adverse reactions associated with CAPLYTA (incidence of at least 2% in patients exposed to CAPLYTA and greater than placebo) are shown in Table 2.

Table 2: Adverse Reactions Reported in ≥2% of CAPLYTA-Treated Patients and Occurred at a Greater Incidence than in Placebo-Treated Patients in 4- to 6-week Schizophrenia Trials

	CAPLYTA 42 mg (N=406)	Placebo (N=412)
Somnolence/Sedation	24%	10%
Nausea	9%	5%
Dry Mouth	6%	2%
Dizziness[1]	5%	3%
Creatine Phosphokinase Increased	4%	1%
Fatigue	3%	1%
Vomiting	3%	2%
Hepatic Transaminases Increased[2]	2%	1%
Decreased Appetite	2%	1%

[1] Dizziness, dizziness postural
[2] ALT, AST, "hepatic enzymes" increased, or liver function test abnormal

Bipolar Depression – Monotherapy

The following findings are based on the pooled short-term (6-week), placebo-controlled monotherapy bipolar depression studies in adult patients treated with CAPLYTA administered at a daily dose of 42 mg (N=372).

There was no single adverse reaction leading to discontinuation that occurred at a rate of >2% in CAPLYTA-treated patients.

The most common adverse reactions (incidence of at least 5% of patients exposed to CAPLYTA and greater than twice the rate of placebo) are somnolence/sedation, dizziness, nausea, and dry mouth.

Adverse reactions associated with CAPLYTA (incidence of at least 2% in patients exposed to CAPLYTA and greater than placebo) are shown in Table 3.

Table 3: Adverse Reactions Reported in ≥2% of CAPLYTA-Treated Patients and that Occurred at Greater Incidence than in the Placebo-Treated Patients in Pooled 6-week Monotherapy Bipolar Depression Trials

	CAPLYTA 42 mg (N=372)	Placebo (N=374)
Headache	14%	8%
Somnolence/Sedation	13%	3%
Dizziness[1]	8%	4%
Nausea	8%	3%
Dry mouth	5%	1%
Diarrhea	4%	2%
Vomiting	4%	0%
Abdominal pain[2]	2%	1%
Upper respiratory tract infection	2%	1%

[1] Dizziness, dizziness postural
[2] Abdominal discomfort, abdominal pain, abdominal pain upper and lower

Bipolar Depression - Adjunctive Therapy with Lithium or Valproate

The following findings are based on a 6-week, placebo-controlled adjunctive therapy bipolar depression study in adult patients treated with CAPLYTA administered at a daily dose of 42 mg (N=177).

There was no single adverse reaction leading to discontinuation that occurred at a rate of >2% in CAPLYTA-treated patients.

The most common adverse reactions (incidence of at least 5% of patients exposed to CAPLYTA and greater than twice the rate of placebo) are somnolence/sedation, dizziness, nausea, and dry mouth.

Adverse reactions associated with CAPLYTA (incidence of at least 2% in patients exposed to CAPLYTA and greater than placebo) are shown in Table 4.

Table 4: Adverse Reactions Reported in ≥2% of CAPLYTA-Treated Patients and that Occurred at Greater Incidence than in the Placebo-Treated Patients in a 6-Week Adjunctive Therapy Bipolar Depression Trial

	CAPLYTA 42 mg (N=177)	Placebo (N=175)
Somnolence/Sedation	13%	3%
Dizziness[1]	11%	2%
Nausea	9%	4%
Dry mouth	5%	1%
Vomiting	4%	0%
Diarrhea	3%	2%
Upper respiratory tract infection	3%	1%
Blurred vision	3%	1%
Increased blood prolactin	2%	0%

[1] Dizziness, dizziness postural

Dystonia

Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. Although these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Extrapyramidal Symptoms (EPS)

In the short-term, placebo-controlled schizophrenia and bipolar depression studies, data was objectively collected on the Simpson-Angus Scale (SAS) for EPS (total score ranges from 0 to 40), the Barnes Akathisia Rating Scale (BARS) for akathisia (total score ranges from 0 to 14) and the Abnormal Involuntary Movement Scale (AIMS) for dyskinesia (total score ranges from 0 to 28).

Schizophrenia

In the 4- to 6-week, placebo-controlled schizophrenia trials, the frequency of reported events related to extrapyramidal symptoms (EPS), including akathisia, extrapyramidal disorder, muscle spasms, restlessness, musculoskeletal stiffness, dyskinesia, dystonia, muscle twitching, tardive dyskinesia, tremor, drooling, and involuntary muscle contractions was 6.7% for CAPLYTA and 6.3% for placebo.

In the 4- to 6-week schizophrenia trials, the mean changes from baseline for CAPLYTA-treated patients and placebo-treated patients were 0.1 and 0 for the SAS, -0.1 and 0 for the BARS, and 0.1 and 0 for the AIMS, respectively.

Bipolar Depression

In the 6-week, monotherapy bipolar depression trials, the frequency of reported reactions related to EPS, including muscle spasms, dyskinesia, extrapyramidal disorder, movement disorder, tremor, restlessness, and akathisia was 1.3% for CAPLYTA and 1.1% for placebo.

In a 6-week, adjunctive therapy bipolar depression trial, the frequency of reported reactions related to EPS, including tremor, muscle spasms, akathisia, extrapyramidal disorder, gait disturbance, and restlessness was 4.0% for CAPLYTA and 2.3% for placebo.

In the 6-week, monotherapy bipolar depression trials, the mean changes from baseline for CAPLYTA-treated patients and placebo-treated patients were 0 and 0 for the SAS, -0.1 and -0.1 for the BARS, and 0 and 0 for the AIMS, respectively. In the 6-week adjunctive therapy bipolar depression trial, the mean changes from baseline for CAPLYTA-treated patients and placebo-treated patients were 0 and 0 for the SAS, 0 and -0.1 for the BARS, and 0and 0 for the AIMS, respectively.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with CAPLYTA

Table 5: Clinically Important Drug Interactions with CAPLYTA

Moderate or Strong CYP3A4 Inhibitors		
Clinical Impact	Concomitant use of CAPLYTA with moderate or strong CYP3A4 inhibitors increases lumateperone exposure *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions.	
Intervention	Avoid concomitant use of CAPLYTA with moderate or strong CYP3A4 inhibitors *[see Dosage and Administration (2.2)]*.	
Examples	*Moderate inhibitors*	Amprenavir, ciprofloxacin, cyclosporine, diltiazem, erythromycin, fluconazole, fluvoxamine, verapamil
	Strong inhibitors	Clarithromycin, grapefruit juice, itraconazole, voriconazole, nefazodone, ritonavir, nelfinavir
CYP3A4 Inducers		
Clinical Impact	Concomitant use of CAPLYTA with CYP3A4 inducers decreases the exposure of lumateperone *[see Clinical Pharmacology (12.3)]*.	
Intervention	Avoid concomitant use of CAPLYTA with CYP3A4 inducers *[see Dosage and Administration (2.2)]*.	
Examples	Carbamazepine, phenytoin, rifampin, St. John's wort, bosentan, efavirenz, etravirine, modafinil, nafcillin, aprepitant, armodafinil, pioglitazone, prednisone	

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 CAPLYTA, 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 antipsychotic drugs during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms following delivery *(see Clinical Considerations)*. Available data from case reports on CAPLYTA use in pregnant women are insufficient to establish any drug associated risks for 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 CAPLYTA, during pregnancy *(see Clinical Considerations)*. In animal reproduction studies, no malformations 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) of 42 mg/day on a mg/m^2 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 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 to 4% and 15 to 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 3.5, 10.5, 21, and 63 mg/kg/day lumateperone (0.8, 2.4, 4.9, and 14.6 times the MRHD on a mg/m^2 basis) during the period of organogenesis. No malformations were observed with lumateperone 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 2.1, 7, and 21 mg/kg/day lumateperone (1.0, 3.2, and 9.7 times the MRHD on a mg/m^2 basis) during the period of organogenesis. Lumateperone 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 3.5, 10.5, and 21 mg/kg/day lumateperone (0.8, 2.4, and 4.9 times the MRHD on a mg/m^2 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 and decreased body weight gain in pups were observed at 4.9 times, but not at 2.4 times, the MRHD.

Pregnant rats were treated with a human metabolite of lumateperone (reduced ketone metabolite) at oral doses of 15, 60, and 100 mg/kg/day (1.2, 19, and 27 times the exposure to this metabolite at the MRHD of lumateperone based on AUC plasma exposure) during the period of organogenesis. This metabolite did not cause adverse developmental effects at a dose 1.2 times the exposure at the MRHD of lumateperone; however, it caused an increase in visceral malformations (cleft palate) at 27 times and skeletal malformations at 19 times the exposure at the MRHD of lumateperone, a dose that induced maternal toxicity.

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.

8.3 Females and Males of Reproductive Potential

Infertility

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

8.4 Pediatric Use

Safety and effectiveness of CAPLYTA have not been established in pediatric patients.

Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric patients *[see Boxed Warning, Warnings and Precautions (5.2)]*.

8.5 Geriatric Use

Controlled clinical studies of CAPLYTA in the treatment of schizophrenia did not include any patients aged 65 or older to determine whether or not they respond differently from younger patients. Controlled clinical studies of CAPLYTA in the treatment of bipolar depression included patients aged 65 or older; the number of patients was not sufficient to determine whether or not they respond differently from younger patients.

Antipsychotic drugs increase the risk of death in elderly patients with dementia-related psychosis. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.1) and (5.3)]*.

8.6 Hepatic Impairment

Use of CAPLYTA is not recommended for patients with moderate (Child-Pugh class B) to severe hepatic impairment (Child-Pugh class C). Patients with moderate and severe hepatic impairment experienced higher exposure to lumateperone *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

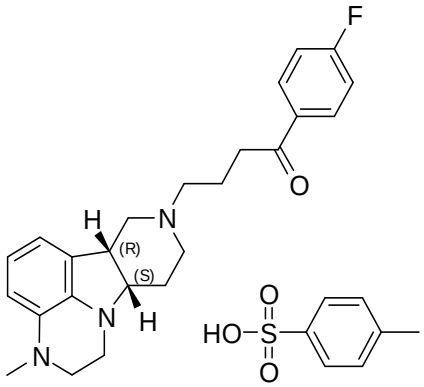
No dosage adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A).

10 OVERDOSAGE

No specific antidotes for CAPLYTA are known. In managing overdose, provide supportive care, including close medical supervision and monitoring and consider the possibility of multiple drug involvement. In case of overdose, consult a Certified Poison Control Center (1-800-222-1222 or www.poison.org).

11 DESCRIPTION

CAPLYTA capsules contains lumateperone, an atypical antipsychotic, present as lumateperone tosylate salt with the chemical name 4-((6b*R*,10a*S*)-3-methyl-2,3,6b,9,10,10*a*-hexahydro-1*H*,7*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxalin-8-yl)-1-(4-fluoro-phenyl)-butan-1-one 4-methylbenzenesulfonate. Its molecular formula is $C_{31}H_{36}FN_3O_4S$, and its molecular weight is 565.71 g/mol with the following structure:



CAPLYTA capsules are intended for oral administration. Each CAPLYTA capsule contains 42 mg of lumateperone (equivalent to 60 mg of lumateperone tosylate). Capsules include the following inactive ingredients: croscarmellose sodium, gelatin, magnesium stearate, mannitol, and talc. Colorants include titanium dioxide and FD&C blue #1 and red #3.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of lumateperone in the treatment of schizophrenia and depressive episodes associated with bipolar I or II disorder is unknown. However, the efficacy of lumateperone could be mediated through a combination of antagonist activity at central serotonin 5-HT_{2A} receptors and postsynaptic antagonist activity at central dopamine D_2 receptors.

12.2 Pharmacodynamics

Lumateperone has high binding affinity for serotonin 5-HT_{2A} receptors (K_i = 0.54 nM) and moderate binding affinity for dopamine D_2 (K_i = 32 nM) receptors. Lumateperone has moderate binding affinity for serotonin transporters (K_i = 33 nM). Lumateperone also has moderate binding affinity for dopamine D_1 (41 nM) and D_4 and

adrenergic alpha$_{1A}$ and alpha$_{1B}$ receptors (K_i projected at < 100 nM) but has low binding affinity (less than 50% inhibition at 100 nM) for muscarinic and histaminergic receptors.

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

Following once daily oral administration of CAPLYTA, lumateperone steady state is reached in about 5 days. Increase in steady-state exposure is approximately dose-proportional in the range of 21 mg to 56 mg. A large inter-subject variability in lumateperone PK parameters was observed, with coefficients of variation for C_{max} (peak plasma concentration) and AUC (area under the concentration vs time curve) ranging from 68% to 97% at steady state.

Absorption

The absolute bioavailability of lumateperone capsules is about 4.4%. C_{max} of lumateperone is reached approximately 1-2 hours after CAPLYTA dosing.

Effect of Food

Ingestion of a high-fat meal with CAPLYTA lowers lumateperone mean C_{max} by 33% and increases mean AUC by 9%. Median T_{max} was delayed about 1 hour (from 1 hour at fasted state to 2 hours in the presence of food).

Distribution

Protein binding of lumateperone is 97.4% at 5 µM (about 70-fold higher than therapeutic concentrations) in human plasma. The volume of distribution of lumateperone following intravenous administration is about 4.1 L/kg.

Elimination

The clearance of lumateperone is approximately 27.9 L/hour and the terminal half-life is about 18 hours after intravenous administration.

Metabolism

Lumateperone is extensively metabolized with more than twenty metabolites identified *in vivo*. After a single ^{14}C-labeled oral dose, lumateperone and glucuronidated metabolites represent about 2.8% and 51% of the total plasma radioactivity, respectively. *In vitro* studies show that multiple enzymes, including but not limited to uridine 5'-diphospho-glucuronosyltransferases (UDP-glucuronosyltransferase, UGT) 1A1, 1A4, and 2B15, aldoketoreductase (AKR)1C1, 1B10, and 1C4, and cytochrome P450 (CYP) 3A4, 2C8, and 1A2, are involved in the metabolism of lumateperone.

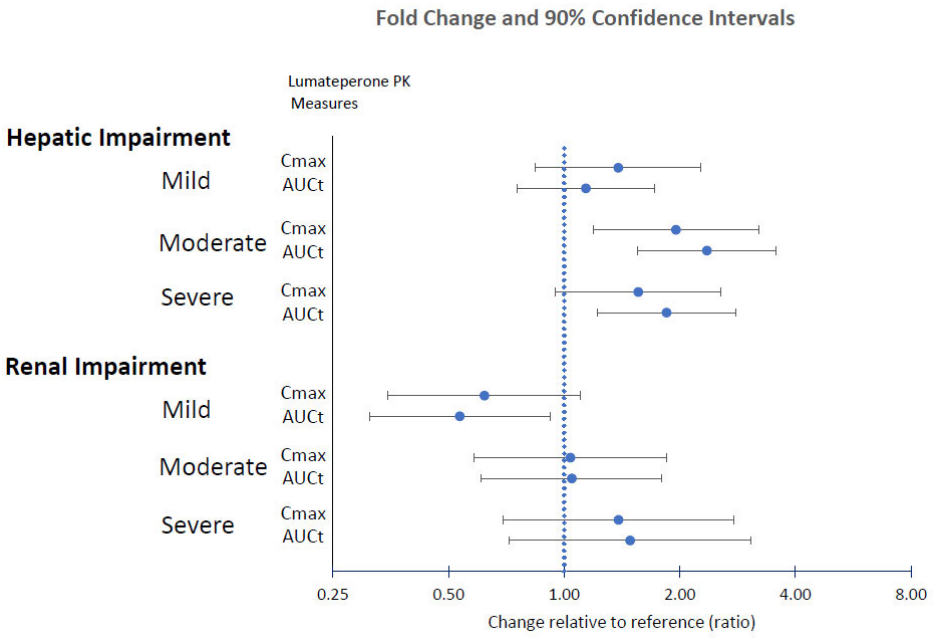
Excretion

In a human mass-balance study, 58% and 29% of the radioactive dose was recovered in the urine and feces, respectively. Less than 1% of the dose was excreted as unchanged lumateperone in the urine.

Specific Populations

Effects of hepatic or renal impairment on lumateperone exposure are presented in Figure 1. No clinically significant differences in the pharmacokinetics of lumateperone were observed based on age, sex, or race.

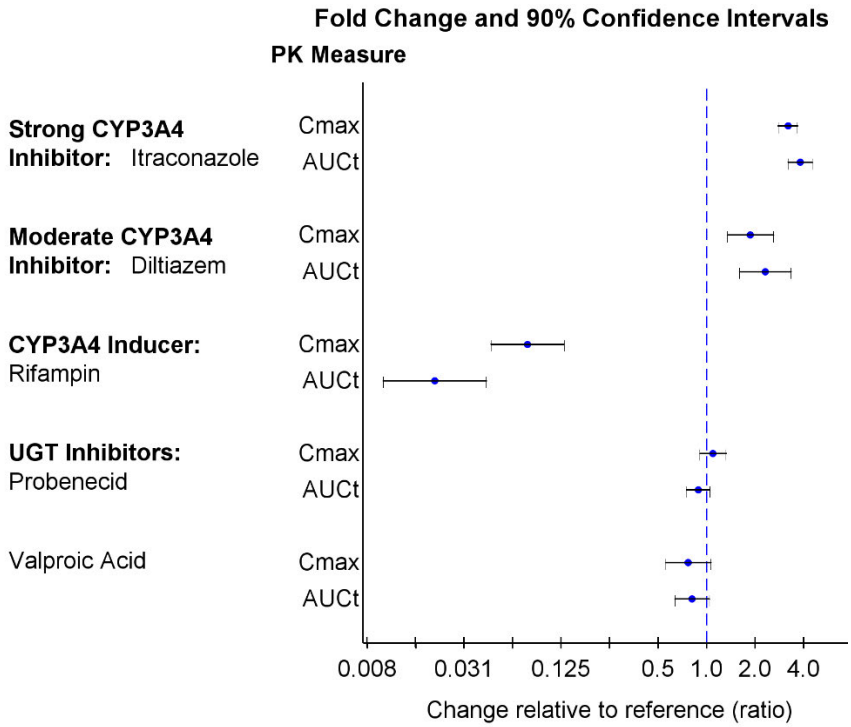
Figure 1: Effects of Intrinsic Factors on Lumateperone Pharmacokinetics



Drug Interaction Studies

Clinical Studies
The effects of other drugs on the exposures of lumateperone are presented in Figure 2.

Figure 2: Effects of Other Drugs on Lumateperone Pharmacokinetics



CYP3A4 substrates: No clinically significant differences in the pharmacokinetics of midazolam (CYP3A4 substrate) or its metabolite 1-hydroxymidazolam were observed when used concomitantly with single or multiple doses of lumateperone in patients with schizophrenia.

In Vitro Studies

Lumateperone showed little to no inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. It showed no induction of CYP1A2, CYP2B6, or CYP3A4.

Lumateperone did not appear to be a P-gp or BCRP substrate. It showed little to no inhibition of OCT2, OAT1, OAT3, OATP1B3, or OATP1B1.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were conducted in rats and mice, and results showed no carcinogenic potential in either species.

In Sprague-Dawley rats, males were administered lumateperone (free base) at oral doses of 3.5, 7 or 14 mg/kg/day and females were administered lumateperone at oral doses of 3.5, 10.5, or 21 mg/kg/day for the first 385 days, then doses were reduced for the two higher dose groups so that the females were administered 3.5, 7 or 14 mg/kg/day, respectively, for the duration of the study. In this study the no adverse effect level for neoplastic lesions was determined to be 14 mg/kg/day (84 mg/m^2/day) for males and 10.5/7 mg/kg/day (42 mg/m^2/day) for females, which are 1.6 times (females) to 3.2 times (males) the MRHD on a mg/m^2 basis.

Male and female CD-1 mice were administered lumateperone at oral doses of 3.5, 10.5 or 21 mg/kg/day for the first 35 days, then doses were reduced to 1.4, 4.9, and 14 mg/kg/day, respectively, for the duration of the study. In this study, the no adverse effect level for neoplastic lesions was determined to be 10.5/4.9 mg/kg/day (15 mg/m^2/day) for each sex which is 0.6 times the MRHD on a mg/m^2 basis.

Mutagenesis

No evidence of mutagenic potential was found in the *in vitro* bacterial reverse mutation assay (Ames test) and the mouse lymphoma test without metabolic activation. Lumateperone was positive in the Ames test only in the presence of metabolic activation and only in the TA1537 strain and was positive in the mouse lymphoma test only in the presence of metabolic activation and only at high concentrations that inhibited cell growth; together these results were thought to be related to solubility limits and/or nonspecific effects on cellular function. Lumateperone was negative for clastogenic activity in the *in vivo* micronucleus assay in rats and was not genotoxic in the *in vivo* Comet assay in rats.

Impairment of Fertility

Female rats were treated with oral doses of 3.5, 10.5, 21 or 42 mg/kg/day lumateperone (free base) (0.8, 2.4, 4.9, and 9.7 times the MRHD on a mg/m^2 basis) prior to mating and continuing through conception and implantation. Estrus cycle irregularities were observed at doses ≥10.5 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 42 mg/kg/day. Decreased gestation body weight and body weight gain, and increases in time to mating, were observed at 21 and 42 mg/kg/day.

Male rats were treated with oral doses of 3.5, 10.5, 21 or 42 mg/kg/day lumateperone (0.8, 2.4, 4.9, and 9.7 times the MRHD on a mg/m^2 basis) for 9 weeks prior to mating and throughout 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 21 and 42 mg/kg/day.

13.2 Animal Toxicology and/or Pharmacology

Oral administration of lumateperone caused systemic intracytoplasmic accumulation of pigmented material in dogs, rats, and mice at clinically relevant exposures (AUC). Intracytoplasmic pigmentation appeared to be localized in lysosomes. Accumulation of pigmented material persisted without reversal at the end of 1- to 2-month drug-free periods. Pigmented material was observed in the brain and spinal cord of all three species, and in the heart and eye of rats. Although the composition of the pigmented material was not established, the material is likely polymers or protein adducts formed from aniline metabolites of lumateperone.

In the dog, accumulation of pigmented material in the brain and spinal cord was associated with neuronal degeneration and necrosis, followed by axonal degeneration and histiocytic inflammation after oral administration of lumateperone for up to 9 months. In the rat, accumulation of pigmented material was associated with degenerative changes and signs of an inflammatory response in the spinal cord, peripheral nervous system, eye, and heart after oral administration of lumateperone for up to 2 years. Although overt degenerative changes were not observed in the rat brain, the presence of pigment-containing infiltrating macrophages is consistent with an inflammatory response.

The role of intracytoplasmic pigmented material in causing these lesions was not definitively established; however, the colocalization of pigmented material in tissues with degenerative changes and signs of inflammation is supportive. Alternatively, the aniline metabolites of lumateperone may undergo metabolic activation forming reactive metabolites that contribute to the observed toxicities. The role of intracellular accumulation of lumateperone or its non-aniline metabolites in these toxicities could not be ruled out.

The aniline metabolites thought to be responsible for these toxicities were detected in dogs and rats but were not present in humans at quantifiable levels. Based on all the available evidence, these toxicities do not appear to be relevant to humans.

14 CLINICAL STUDIES

14.1 Schizophrenia

CAPLYTA was evaluated for the treatment of schizophrenia in two placebo-controlled trials.

Study 1 (NCT01499563) was a four-week, randomized, double-blind, placebo-controlled, multi-center study in adult patients with a diagnosis of schizophrenia according to the DSM-IV-TR criteria. The primary efficacy measure was change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score at Week 4. The PANSS is a 30-item scale used to measure symptoms of schizophrenia. Each item is rated by a clinician on a seven-point scale. A score of 1 indicates the absence of symptoms, and a score of 7 indicates extremely severe symptoms. The PANSS total score may range from 30 to 210 with higher scores reflecting greater overall symptom severity.

A total of 335 patients were randomized to receive CAPLYTA 42 mg, CAPLYTA 84 mg (two times the recommended daily dose), an active comparator, or placebo. The study was not designed to allow for efficacy comparison of CAPLYTA and the active comparator. Demographic and baseline disease characteristics were similar for the CAPLYTA, active comparator, and placebo groups. Median age was 42 years (range 20 to 55 years). 17% were female, 19% were Caucasian, and 78% were African American.

Compared to the placebo group, patients randomized to CAPLYTA 42 mg showed a statistically significant reduction from baseline to Day 28 in the PANSS total score. The treatment effect in the CAPLYTA 84 mg group (vs. placebo) was not statistically significant. The results of Study 1 are shown in Table 6.

Study 2 (NCT02282761) was a four-week, randomized, double-blind, placebo-controlled, multi-center study in adult patients with a diagnosis of schizophrenia according to the DSM-5 criteria. The primary efficacy measure was change from baseline in the PANSS total score at Week 4.

A total of 450 patients were randomized to receive CAPLYTA 28 mg (two-thirds the recommended daily dose), CAPLYTA 42 mg, or placebo. Demographic and baseline disease characteristics were similar for the CAPLYTA and placebo groups. Median age was 44 years (range 19 to 60 years); 23% were female, 26% were Caucasian and 66% were African American.

Compared to the placebo group, patients randomized to CAPLYTA 42 mg showed a statistically significant reduction from baseline to Day 28 in the PANSS total score. The treatment effect in the CAPLYTA 28 mg group (vs. placebo) was not statistically significant. The results of Study 2 are shown in Table 6.

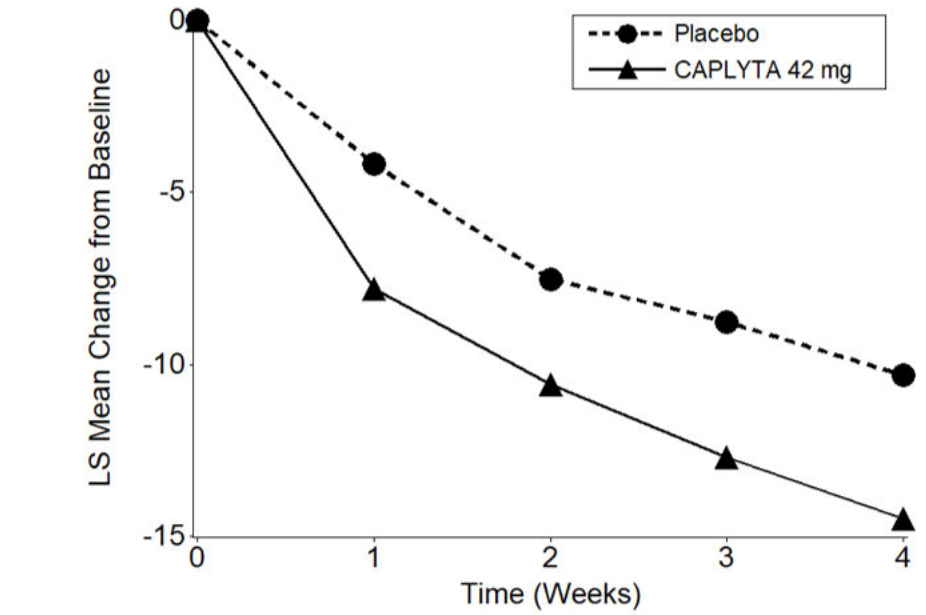
Studies 1 and 2 did not include any patients aged 65 or older. Examination of subgroups by sex and race did not suggest differences in response in either study.

Table 6: Primary Efficacy Results for Change from Baseline in PANSS Total Score in Patients with Schizophrenia (Studies 1 and 2)

			Primary Efficacy Endpoint: PANSS Total Score		
Study Number	**Treatment Group**	**N**	**Mean Baseline Score (SD)**	**LS Mean Change from Baseline (SE)**	**Placebo-subtracted Difference (95% CI)**
1	CAPLYTA (42 mg)*	84	88.1 (11.0)	-13.2 (1.7)	-5.8 (-10.5, -1.1) [a]
	Placebo	85	86.3 (13.1)	-7.4 (1.7)	--
2	CAPLYTA (42 mg)*	150	90.0 (9.6)	-14.5 (1.3)	-4.2 (-7.8, -0.6)
	Placebo	150	89.0 (10.3)	-10.3 (1.3)	--

The PANSS total score may range from 30 to 210; higher scores reflect greater symptom severity.
SD: standard deviation; SE: standard error; LS Mean: least squares mean; CI: unadjusted confidence interval.
[a] Difference (drug minus placebo) in LS mean change from baseline not adjusted for sample size increase after unblinded interim analysis.
*Statistically significantly superior to placebo.

Figure 3: Change from Baseline in PANSS Total Score by Time (Weeks) in Patients with Schizophrenia in Study 2.



14.2 Depressive Episodes Associated with Bipolar I or II Disorder (Bipolar Depression)

Monotherapy

The efficacy of CAPLYTA, as monotherapy, was established in a 6-week, randomized, double-blind, placebo-controlled, multi-center study in adult patients who met DSM-5 criteria for depressive episodes associated with bipolar

I or bipolar II disorder (Study 3; NCT03249376). The primary efficacy measure was the change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score at Week 6. The MADRS is a 10-item clinician-rated scale with total scores ranging from 0 (no depressive features) to 60 (maximum score). The secondary endpoint was the change from baseline in Clinical Global Impression-Bipolar-Severity of Illness scale (CGI-BP-S) total score at Week 6. The CGI-BP-S total score is a clinician-rated scale that measures the patient's current illness state on a 21-point scale that assesses depression, mania, and overall illness, where a higher score is associated with greater illness severity.

A total of 381 patients were randomized to receive CAPLYTA 42 mg or placebo. Demographic and baseline characteristics were similar for the CAPLYTA and placebo groups. Median age was 45 (range 18 to 72). 58% were female, 91% were Caucasian, and 8% were African-American.

Compared to the placebo group, patients randomized to CAPLYTA 42 mg showed a statistically significant improvement from baseline to Day 43 in the MADRS total score and CGI-BP-S total score. The results of Study 3 are shown in Table 7.

Examination of subgroups by age, sex, and race did not suggest differences in response in the study.

Adjunctive Therapy with Lithium or Valproate

The efficacy of CAPLYTA, as adjunctive therapy with lithium or valproate, was established in a 6-week, randomized, double-blind, placebo-controlled, multi-center study in adult patients who met DSM-5 criteria for depressive episodes associated with bipolar I or bipolar II disorder (Study 4; NCT02600507). The primary efficacy measure was the change from baseline in MADRS total score at Week 6. The secondary endpoint was the change from baseline in CGI-BP-S depression score at Week 6. The CGI-BP-S depression score is a clinician-rated scale that measures the patient's current illness state on a 7-point scale, where a higher score is associated with greater illness severity.

A total of 529 patients were randomized to receive CAPLYTA 28 mg (two-thirds the recommended daily dose), CAPLYTA 42 mg, or placebo. Demographic and baseline characteristics were similar for the CAPLYTA and placebo groups. Median age was 46 (range 18 to 74). 58% were female, 88% were Caucasian, and 11% were African-American.

Compared to the placebo group, patients randomized to CAPLYTA 42 mg showed a statistically significant improvement from baseline to Day 43 in the MADRS total score and CGI-BP-S depression score. The treatment effect in the CAPLYTA 28 mg group (vs. placebo) was not statistically significant. The results of Study 4 are shown in Table 7.

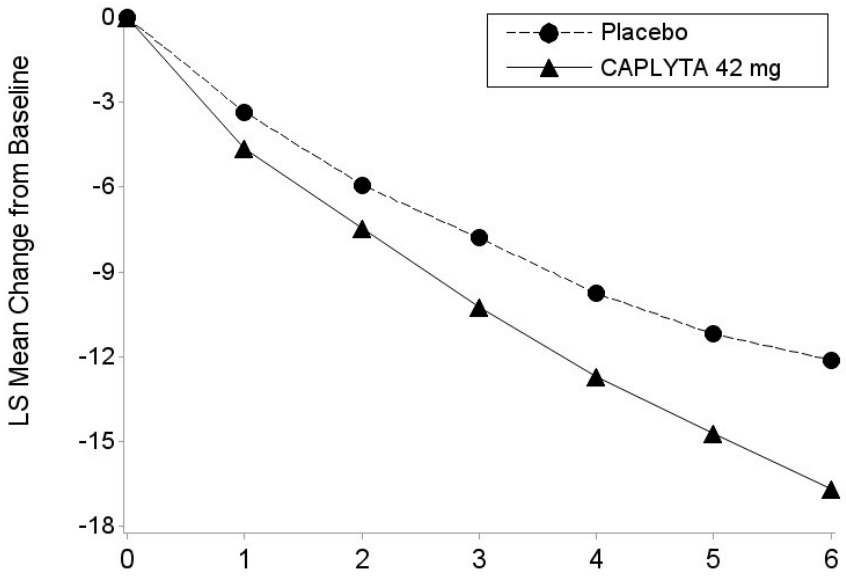
Examination of subgroups by age, sex, and race did not suggest differences in response in the study.

Table 7: Primary Efficacy Results from Bipolar Depression Trials (Studies 3 and 4)

Study Number	Treatment Group	N	Primary Efficacy Endpoint: MADRS Total Score		
			Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Monotherapy					
3	CAPLYTA (42 mg)*	188	30.8 (4.9)	-16.7 (0.7)	-4.6 (-6.3, -2.8)
	Placebo	188	30.3 (4.6)	-12.1 (0.7)	
Adjunctive Therapy					
4	CAPLYTA (42 mg)* + lithium or valproate	174	32.2 (5.0)	-16.9 (0.8)	-2.4 (-4.4, -0.4)
	Placebo + lithium or valproate	174	32.1 (5.2)	-14.5 (0.8)	

The MADRS total score ranges from 0 to 60; higher scores reflect greater symptom severity
SD: standard deviation; SE: standard error; LS Mean: least squares mean; CI: confidence interval
[a] Difference (drug minus placebo) in LS mean change from baseline
*Statistically significantly superior to placebo.

Figure 4. Change from Baseline in MADRS Total Score by Visits (Study 3) in Patients With Depressive Episodes Associated with Bipolar I or II Disorder (Monotherapy)



Number of Patients							
Placebo:	188	185	184	181	176	172	166
CAPLYTA 42 mg:	188	188	178	173	171	170	169

LS mean = least squares mean.

16 HOW SUPPLIED/ STORAGE AND HANDLING

CAPLYTA (lumateperone) capsules are supplied as follows:

Capsule Strength	Capsule Color	Imprint Codes	Package Configuration	NDC Code
42 mg	Blue cap and opaque white body	ITI-007 42 mg	Box of 30 (3 Blister Packs of 10 capsules)	72060-142-30
42 mg	Blue cap and opaque white body	ITI-007 42 mg	Bottle of 30	72060-142-40

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]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Medication Guide).

Suicidal Thoughts and Behavior
Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and instruct them to report such symptoms to their healthcare provider *[see Boxed Warning, Warnings and Precautions (5.2)]*.

Neuroleptic Malignant Syndrome
Counsel patients about a potentially fatal adverse reaction, Neuroleptic Malignant Syndrome (NMS), that has been reported with administration of antipsychotic drugs. Advise patients, family members, or caregivers to contact the healthcare provider or to report to the emergency room if they experience signs and symptoms of NMS *[see Warnings and Precautions (5.4)]*.

Tardive Dyskinesia
Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their healthcare provider if these abnormal movements occur *[see Warnings and Precautions (5.5)]*.

Metabolic Changes
Educate patients about the risk of metabolic changes, how to recognize symptoms of hyperglycemia and diabetes mellitus, and the need for specific monitoring, including blood glucose, lipids, and weight *[see Warnings and Precautions (5.6)]*.

Leukopenia/Neutropenia
Advise patients with a pre-existing low WBC or a history of drug induced leukopenia/ neutropenia that they should have their CBC monitored while taking CAPLYTA *[see Warnings and Precautions (5.7)]*.

Orthostatic Hypotension and Syncope
Educate patients about the risk of orthostatic hypotension and syncope, especially early in treatment, and also at times of re-initiating treatment *[see Warnings and Precautions (5.8)]*.

Interference with Cognitive and Motor Performance
Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that CAPLYTA therapy does not affect them adversely *[see Warnings and Precautions (5.11)]*.

Heat Exposure and Dehydration
Educate patients regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.12)]*.

Concomitant Medications
Advise patients to inform their health care providers of any changes to their current prescription or over-the-counter medications because there is a potential for interactions *[see Drug Interactions (7.1)]*.

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

Lactation
Advise females not to breastfeed during treatment with lumateperone *[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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New York, NY 10016

MEDICATION GUIDE

CAPLYTA (kap-LITE-ah)
(lumateperone)
capsules

What is the most important information I should know about CAPLYTA?

CAPLYTA may cause serious side effects, including:

- **Increased risk of death in elderly people with dementia related psychosis.** Medicines like CAPLYTA can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). CAPLYTA is not approved for the treatment of people with dementia-related psychosis.
- **Increased risk of suicidal thoughts and actions.** CAPLYTA and antidepressant medicines may increase suicidal thoughts and actions in some children, adolescents, and young adults **especially within the first few months of treatment or when the dose is changed.**
  - Depression and other mental illnesses are the most important causes of suicidal thoughts and actions.

  How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?
  - Pay close attention to any changes, especially sudden changes in mood, behaviors, thoughts, or feelings. This is very important when CAPLYTA or the antidepressant medicine is started or when the dose is changed.
  - Call your healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings, or if you develop suicidal thoughts or actions.
  - Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you have concerns about symptoms.

  Call a healthcare provider right away if you or your family member have any of the following symptoms, especially if they are new, worse, or worry you:
  - thoughts about suicide or dying
  - new or worse depression
  - feeling very agitated or restless
  - trouble sleeping (insomnia)
  - acting aggressive, being angry, or violent
  - an extreme increase in activity and talking (mania)
  - attempts to commit suicide
  - new or worse anxiety
  - panic attacks
  - new or worse irritability
  - acting on dangerous impulses
  - other unusual changes in behavior or mood

What is CAPLYTA?

CAPLYTA is a prescription medicine used in adults:

- to treat schizophrenia
- alone to treat depressive episodes that happen with bipolar I or bipolar II disorder (bipolar depression)
- with the medicine lithium or valproate to treat depressive episodes that happen with bipolar I or bipolar II disorder (bipolar depression)

It is not known if CAPLYTA is safe and effective in children.

Do not take CAPLYTA if you are allergic to lumateperone or any of the ingredients in CAPLYTA. See the end of this Medication Guide for a complete list of ingredients in CAPLYTA.

Before taking CAPLYTA, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had heart problems or a stroke
- have or have had low or high blood pressure
- have or have had diabetes or high blood sugar, or a family history of diabetes or high blood sugar. Your healthcare provider should check your blood sugar before you start and during treatment with CAPLYTA.
- have or have had high levels of total cholesterol, LDL cholesterol, or triglycerides or low levels of HDL cholesterol
- have or have had seizures (convulsions)
- have or have had kidney or liver problems
- have or have had a low white blood cell count
- are pregnant or plan to become pregnant. CAPLYTA may harm your unborn baby. Taking CAPLYTA during your third trimester of pregnancy may cause your baby to have abnormal muscle movements or withdrawal symptoms after birth. Talk to your healthcare provider about the risk to your unborn baby if you take CAPLYTA during pregnancy.
  - Tell your healthcare provider if you become pregnant or think you are pregnant during treatment with CAPLYTA.
  - If you become pregnant during treatment with CAPLYTA, talk to your healthcare provider about registering with the National Pregnancy Registry for Atypical Antipsychotics. You can register by calling 1-866-961-2388 or go to

http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

- are breastfeeding or plan to breastfeed. It is not known if CAPLYTA passes into your breast milk. You should not breastfeed during treatment with CAPLYTA. Talk to your healthcare provider about the best way to feed your baby during treatment with CAPLYTA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

CAPLYTA and other medicines may affect each other causing possible serious side effects. CAPLYTA may affect the way other medicines work, and other medicines may affect how CAPLYTA works.

Your healthcare provider can tell you if it is safe to take CAPLYTA with your other medicines. Do not start or stop any medicines during treatment with CAPLYTA without first talking to your healthcare provider.

Know the medicines you take. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

How should I take CAPLYTA?

- Take CAPLYTA exactly as your healthcare provider tells you to take it. Do not change the dose or stop taking CAPLYTA without first talking to your healthcare provider.
- Take CAPLYTA 1 time each day with or without food.
- If you take too much CAPLYTA, call your healthcare provider or Poison Control Center at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What should I avoid while taking CAPLYTA?

- Do not drive, operate machinery, or do other dangerous activities until you know how CAPLYTA affects you. CAPLYTA may make you drowsy.
- Do not become too hot or dehydrated during treatment with CAPLYTA.
  - Do not exercise too much.
  - In hot weather, stay inside in a cool place if possible.
  - Stay out of the sun.
  - Do not wear too much clothing or heavy clothing.
  - Drink plenty of water.

What are the possible side effects of CAPLYTA?

CAPLYTA may cause serious side effects, including:

- **See "What is the most important information I should know about CAPLYTA?"**
- **Stroke (cerebrovascular problems) in elderly people with dementia-related psychosis that can lead to death.**
- **Neuroleptic malignant syndrome (NMS) is a serious condition that can lead to death.** Call your healthcare provider or go to the nearest hospital emergency room right away if you have some or all of the following signs and symptoms of NMS:
  - high fever
  - changes in your breathing, heart rate, and blood pressure
  - increased sweating
  - confusion
  - stiff muscles
- **Uncontrolled body movements (tardive dyskinesia).** CAPLYTA may cause movements that you cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop taking CAPLYTA. Tardive dyskinesia may also start after you stop taking CAPLYTA.
- **Problems with your metabolism such as:**
  - **high blood sugar (hyperglycemia) and diabetes.** Increases in blood sugar can happen in some people who take CAPLYTA. Extremely high blood sugar can lead to coma or death. Your healthcare provider should check your blood sugar before you start, or soon after you start CAPLYTA, and then regularly during long term treatment with CAPLYTA.

    Call your healthcare provider if you have any of these symptoms of high blood sugar during treatment with CAPLYTA:
    - feel very thirsty
    - feel very hungry
    - feel sick to your stomach
    - need to urinate more than usual
    - feel weak or tired
    - feel confused, or your breath smells fruity
  - **increased fat levels (cholesterol and triglycerides) in your blood.** Your healthcare provider should check the fat levels in your blood before you start, or soon after you start CAPLYTA, and then periodically during treatment with CAPLYTA.
  - w**eight gain.** You and your healthcare provider should check your weight before you start and often during treatment with CAPLYTA.

- **Low white blood cell count**. Your healthcare provider may do blood tests during the first few months of treatment with CAPLYTA.
- **Decreased blood pressure (orthostatic hypotension).** You may feel lightheaded or faint when you rise too quickly from a sitting or lying position.
- **Falls.** CAPLYTA may make you sleepy or dizzy, may cause a decrease in your blood pressure when changing position (orthostatic hypotension), and can slow your thinking and motor skills which may lead to falls that can cause fractures or other injuries.
- **Seizures (convulsions).**
- **Sleepiness, drowsiness, feeling tired, difficulty thinking and doing normal activities.** See "What should I avoid while taking CAPLYTA?"
- **Problems controlling your body temperature so that you feel too warm.** See "What should I avoid while taking CAPLYTA?"
- **Difficulty swallowing** that can cause food or liquid to get into your lungs.

The most common side effects of CAPLYTA include sleepiness, dizziness, nausea, and dry mouth.

CAPLYTA may cause fertility problems in females and males. Talk to your healthcare provider if this is a concern for you.

These are not all the possible side effects of CAPLYTA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CAPLYTA?

- Store CAPLYTA at room temperature between 68°F to 77°F (20°C to 25°C).

Keep CAPLYTA and all medicines out of the reach of children.

General information about the safe and effective use of CAPLYTA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CAPLYTA for a condition for which it was not prescribed. Do not give CAPLYTA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about CAPLYTA that is written for healthcare professionals.

What are the ingredients in CAPLYTA?

Active ingredient: lumateperone

Inactive ingredients: croscarmellose sodium, gelatin, magnesium stearate, mannitol, and talc. Colorants include titanium dioxide and FD&C blue #1 and red #3

Distributed by: Intra-Cellular Therapies, Inc., New York, NY 10016

For more information, go to www.CAPLYTA.com or call (888) 252-4824

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: 12/2021

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209500Orig1s006

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review
Clinical Microbiology/Virology

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA efficacy supplement
Application Number(s)	209500; supplements 05, 06
Priority or Standard	Standard
Submit Date(s)	2/17/2021
Received Date(s)	2/17/2021
PDUFA Goal Date	12/17/2021
Division/Office	Division of Psychiatry (DP)/Office of Neuroscience (ON)
Review Completion Date	12/17/2021
Established/Proper Name	Lumateperone
(Proposed) Trade Name	Caplyta
Pharmacologic Class	Antipsychotic
Code name	ITI-007
Applicant	Intra-Cellular Therapies
Dosage form	Capsules
Applicant proposed Dosing Regimen	42 mg once daily orally
Applicant Proposed Indication(s)/Population(s)	Monotherapy (S-05) and adjunctive therapy to valproate and lithium (S-06) for the treatment of bipolar depression in adults
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	767631007 – Bipolar disorder, most recent episode depression (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Depressive episodes associated with bipolar I or II disorder (bipolar depression), as monotherapy and as adjunctive therapy with lithium or valproate
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	767631007 – Bipolar disorder, most recent episode depression (disorder)
Recommended Dosing Regimen	42 mg once daily orally

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OSE/DRISK	N/A

Signatures

See archived signatory memos for each discipline.

APPEARS THIS WAY
ON ORIGINAL

Glossary

AE	adverse event
AR	adverse reaction
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CGI-BP-S	Clinical Global Impression-Bipolar Severity
CMC	chemistry, manufacturing, and controls
CSR	clinical study report
CSS	Controlled Substance Staff
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EAS	efficacy analysis set
ECG	electrocardiogram
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISS	integrated summary of safety
ITT	intent to treat
LSM	least-squares mean
MADRS	Montgomery-Asberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MAR	missing at random
MINI	Mini International Neuropsychiatric Interview
mITT	modified intent to treat
MMRM	mixed-effects model for repeated measures
MNAR	missing not at random
NDA	new drug application
OLE	open label extension
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PBC	probenecid
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form
REMS	risk evaluation and mitigation strategy

SAE	serious adverse event
SAP	statistical analysis plan
SCID-5-CT	Structured Clinical Interview for DSM-5 Disorders –Clinical Trials Version
SDS	Sheehan Disability Scale
TEAE	treatment emergent adverse event
UGT	uridine 5'-diphospho-glucuronosyltransferases
VPA	valproate
YMRS	Young Mania Rating Scale

1 Executive Summary

1.1. Product Introduction

Lumateperone (ITI-007, trade name: Caplyta) is classified as an atypical antipsychotic and is indicated for the treatment of schizophrenia in adults. (b) (4)

Lumateperone appears to function as a serotonin 5HT2A and postsynaptic dopamine D2 receptor antagonist. In addition, lumateperone displays moderate binding affinity for the serotonin transporter (SERT).

For these supplemental new drug applications (sNDA 005 and 006), the Applicant is proposing that lumateperone be approved for the treatment of bipolar depression (as monotherapy and as adjunctive treatment to lithium or valproate). The proposed dosing regimen is 42 mg once daily by mouth. The application includes the results from three randomized, double-blind, placebo-controlled trials designed to evaluate the safety and efficacy of lumateperone for the treatment of bipolar depression, as well as one 6-month uncontrolled safety study.

Nomenclature: In some study reports, study drug doses were expressed as milligrams of lumateperone tosylate, a salt of lumateperone (also referred to by the Applicant as "ITI-007"). For the product label, drug doses are expressed as milligrams of lumateperone free base. To maintain consistency with the doses presented in the label, drug doses are expressed as milligrams of lumateperone free base throughout this document unless otherwise specified. To convert a quantity of the base to the equivalent quantity of the salt, the dose of the base is multiplied by 1.43 (e.g., 42 mg lumateperone free base = 60 mg lumateperone tosylate).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided results of three placebo-controlled clinical trials investigating the efficacy of lumateperone for the treatment of bipolar depression: Studies 401-A and 404 (monotherapy) and Study 402 (adjunctive therapy). Study 401-A was negative, but was likely a failed trial due to a relatively high placebo response rate (which is not an uncommon issue for psychiatric clinical trials conducted wholly in the United States). However, in alignment with FDA's pre-NDA meeting advice, we conclude that Studies 404 and 402 together can provide substantial evidence of effectiveness for lumateperone in the treatment of bipolar depression; also, the U.S. subgroup in the global studies had results consistent with the overall efficacy signal in those studies.

1.4 Benefit and Risk Assessment

Benefit-Risk Summary and Assessment

Lumateperone is an atypical antipsychotic drug that was approved by FDA for the treatment of schizophrenia on December 20, 2019 (NDA 209500). The Applicant has now submitted additional studies under Supplements 05 and 06 for the treatment of bipolar depression (as either monotherapy or adjunctive therapy to lithium or valproate). The phase 3 trials conducted for these supplements in adults were as follows:

- Study 401, Part A (monotherapy): 6 weeks of double-blind, fixed-dose treatment with either lumateperone 28 mg, 42 mg, or placebo, in 549 subjects with bipolar I or II disorder in the United States
- Study 404 (monotherapy): 6 weeks of double-blind, fixed-dose treatment with either lumateperone 42 mg or placebo, in 377 subjects with bipolar I or II disorder globally
- Study 402 (adjunctive therapy): 6 weeks of double-blind, fixed-dose treatment with either lumateperone 28 mg, 42 mg, or placebo after at least 28 days initial treatment and continuation with lithium or valproate, in 528 subjects with bipolar I or II disorder globally
- Study 401, Part B (monotherapy): 6 months of open-label treatment with lumateperone 42 mg in 188 subjects from Part A for long-term safety monitoring

The primary endpoint measure in all of the efficacy studies was change from baseline on the Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score, a well-established endpoint for the indication being studied. Study 401, Part A was not statistically significant on the primary endpoint for either dose arm versus placebo; of note, there was a high placebo response rate in this study conducted in the United States, which is an ongoing concern for U.S. psychiatric trials. Study 404 was statistically significant at $p<0.0001$ for a least-squares (LS) mean difference of -4.6 between drug and placebo. Study 402 was statistically significant at $p=0.0206$ with an LS mean difference of -2.4 between drug and placebo for the lumateperone 42-mg arm only. Prespecified secondary endpoints for Study 402 and Study 404 were also statistically significant on the Clinical Global Impression-Bipolar Disorder Severity (CGI-BP-S)-Depression Score and Total Score respectively (Study 402, $p=0.0082$ for 42 mg only; Study 404, $p<0.0001$).

Although U.S. Study 401 was not a statistically-significant positive study, and Studies 404 and 402 were not solely conducted in the United States (26% and 52% U.S., respectively), the U.S. subgroups in both of the positive studies nominally aligned with the overall results in exploratory analyses; hence, generalizing those study results to the U.S. population is acceptable. As per our agreement with the Applicant during the pre-NDA meeting, one positive study each in a monotherapy and an adjunctive therapy study would be sufficient for approval for both indications. Accordingly, the Applicant has met our evidentiary standard for effectiveness for the treatment of bipolar depression with lurasidone 42 mg for either monotherapy or adjunctive therapy to lithium or valproate.

In terms of safety, findings in the phase 3 studies were generally similar to those seen in the previous studies for schizophrenia. The most common adverse events (AEs; occurring >2% and more than placebo) during the placebo-controlled monotherapy studies were headache, somnolence, dizziness, nausea, dry mouth, diarrhea, vomiting, abdominal pain, and upper respiratory tract infection. The most common AE findings in the adjunctive Study 402 and the longer-term Study 401, Part B were very similar to these findings. Extrapyramidal symptoms did not occur at high rates on drug (around 1%) in the population with bipolar disorder in these studies and were comparable to placebo. Indices of lipid, glucose, prolactin, and weight gain were also largely unremarkable with only minor mean or outlier changes in both the short-term and long-term studies.

The benefits of lumateperone 42 mg appear to outweigh the risks for the treatment of bipolar depression, with substantial evidence of effectiveness and an acceptable safety profile in the submitted phase 3 studies. Lumateperone 42 mg will be approved for the treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression) as monotherapy or adjunctive therapy with lithium or valproate in adults

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Bipolar disorder is a serious mental illness leading to high morbidity, hospitalizations, and elevated suicide risk and is characterized by manic, hypomanic, and major depressive episodes (MDE). • Depression is the predominant psychopathology in bipolar disorder accounting for 70% of time in illness in bipolar I and 81% of time in illness in bipolar II disorder (Forte et al., 2015). • Intercurrent medical and psychiatric illness are common with bipolar depression,	Depressive episodes in patients with bipolar I and II are associated with significant morbidity and mortality.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	with a standardized mortality ratio for suicide that is 20-times the general population rate and higher than other psychiatric disorders.	
Current Treatment Options	• Medications that are effective for the acute manic episodes in bipolar disorder are often inadequate or possibly detrimental for the treatment of MDE in bipolar disorder. • Antidepressants that are helpful for the treatment of major depressive disorder (MDD) may induce manic symptoms in individuals with bipolar disorder, even for those on mood-stabilizing medications. • The only drugs with indications for the treatment of depressive episodes in bipolar disorder include the following second-generation antipsychotic drugs: cariprazine, lurasidone, olanzapine-fluoxetine, and quetiapine. • Common off-label medication choices include other mood-stabilizers (e.g., lithium, valproate, lamotrigine) and second-generation antipsychotics. • Psychosocial interventions, psychoeducation, and psychotherapy (e.g., cognitive behavioral therapy, family-focused therapy, interpersonal and social rhythm therapy) may be beneficial but are considered adjunctive to medication management.	There are few treatments with labeled indications for bipolar depression. Treatments can be effective but remain limited by common and often clinically concerning adverse reactions that affect morbidity and mortality in patients with bipolar depression. Additional effective treatments for bipolar depression remain an area of great need for patients with the condition.
Benefit	• The Applicant investigated two different indications: lumateperone as monotherapy treatment for bipolar depression (Study 401-A and Study 404), and as adjunctive to lithium or valproate (Study 402). All three clinical trials used the same primary endpoint of change from baseline to Day 43 in the MADRS total score. This primary endpoint is clinically relevant with a previous regulatory precedent for the same indications. • Study 401-A was a negative study. Neither lumateperone 28 mg nor lumateperone 42 mg was superior to placebo on the primary efficacy endpoint.	Substantial evidence of effectiveness for lumateperone 42 mg consists of two positive adequate and well-controlled studies for bipolar depression—one monotherapy and one adjunctive therapy to lithium and valproate.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• For Studies 402 and 404, the lumateperone 42 mg dose was statistically significantly superior to placebo on the primary endpoint and the secondary prespecified endpoint (Clinical Global Impression Scale-Bipolar Version-Severity (CGI-BP-S)-Depression score and the CGI-BP-S total score, respectively). • Only Study 401-A was conducted entirely in the United States. In Study 402, 52% of the study sites were U.S.-based and 26% were U.S.-based for Study 404. The U.S. and non-U.S. subgroups were consistent when comparing primary efficacy results for Studies 402 and 404. • The population demographics in Studies 402 and 404 were representative of the U.S. patient population, with the exception of low enrollment of people of Asian race and Hispanic ethnicity. • In Study 404, lumateperone 28 mg did not separate from placebo on the primary endpoint, which is consistent with findings in people with schizophrenia from the original NDA 209500 (lumateperone 42 mg was effective, whereas 28 mg was not). • In pre-NDA discussion, FDA agreed that Study 402 and Study 404 could be adequate to support both supplemental indications.	Study 401-A was a negative trial. It was the only clinical trial conducted entirely in the United States. Across studies, the magnitude of change on the primary endpoint was similar for the lumateperone groups but the placebo response was notably higher in Study 401-A compared to Study 402 and 404.
Risk and Risk Management	• No major or novel drug-specific adverse events (AE) were observed (i.e., non-class risk), including in the adjunctive study with lithium and valproate (indicating no unexpected drug interactions). • Rates of extrapyramidal symptoms (EPS) were low overall and similar to placebo in the short-term studies. Lipid, glucose, and weight changes were also largely minimal even in the 6-month open-label study. • Other mild to moderate AEs (such as EPS) are consistent with class-effect risks and can be monitored, treated, or prevented using clinical judgement or exclusion (e.g., pregnancy).	Lumateperone 42 mg demonstrated a safety profile comparable to that seen in prior phase 3 studies for patients with schizophrenia and for other drugs in its class. Bipolar-specific safety information will be added to the product label.

1.5 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that were submitted as part of the application include:			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		See Section 8.1
		x	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	Patient experience data was not submitted as part of this application.			

2 Therapeutic Context

2.1. Analysis of Condition

Bipolar disorder is a serious mental illness characterized by episodes of mania, hypomania, and depression. Bipolar I disorder is characterized by the presence of manic and major depressive episodes, and bipolar II is characterized by hypomanic and depressive episodes. The lifetime prevalence is about 1% for bipolar I disorder, 1.1% for bipolar II disorder, and 2.4% for sub-threshold bipolar disorder symptoms (Cerimele et al., 2014).

"Bipolar depression" refers to the major depressive episodes that occur in patients with a diagnosis of bipolar disorder. Depression is the predominant psychopathology in bipolar disorder accounting for 70% of the time in illness in bipolar I and 81% of time in illness in bipolar II disorder (Forte et al., 2015). In contrast to the euphoria and elevated mood described in manic episodes, bipolar depression is associated with low mood and energy, dysphoria, anhedonia, and psychomotor slowing and impairment. Compared with manic and hypomanic episodes, bipolar depressive episodes and their residual symptoms account for a greater proportion of long-term morbidity, impaired functioning, and risk of suicide (Simon et al., 2007); psychotic features such as delusions and hallucinations can accompany bipolar depressive episodes. Concomitant medical and psychiatric illness are common with bipolar depression, with a standardized mortality ratio for suicide that is 20 times the general population rate and higher than many other psychiatric disorders.

Medications that are effective for the acute manic episodes in bipolar disorder are often inadequate for the treatment of MDE in bipolar disorder. As described below, antidepressants that are helpful for the treatment of MDD may induce manic symptoms in individuals with bipolar disorder, even for those on mood-stabilizing medications. Drugs with indications for the treatment of depressive episodes in bipolar disorder include the following second-generation antipsychotic drugs, alone or in combination: cariprazine, lurasidone, olanzapine-fluoxetine, and quetiapine. Common off-label medication choices include other mood-stabilizers (e.g., lithium, valproate, lamotrigine) and other second-generation antipsychotics. Treatments can be effective but are limited by common and clinically concerning adverse reactions that affect morbidity and mortality in patients with bipolar depression, including EPS, tardive dyskinesia, weight gain, and metabolic syndrome.

2.2. Analysis of Current Treatment Options

The primary pharmacological treatments for bipolar depression are mood stabilizers (e.g., lithium, valproate, and lamotrigine) or antipsychotic drugs (e.g., lurasidone, quetiapine, and cariprazine).

Although treatment guidelines for bipolar depression suggest multiple mood stabilizers and antipsychotics as first-line treatments (Goodwin et al., 2016; Yatham et al., 2018; Yalin et al.,

2020), only four drugs are approved for the treatment of bipolar depression: quetiapine (Seroquel), olanzapine combined with fluoxetine (Symbyax), cariprazine (Vraylar), and lurasidone (Latuda). Notably, only lurasidone has indications for use in bipolar depression as monotherapy and as adjunctive treatment in patients with bipolar depression receiving lithium or valproate (See Table 1).

Antidepressant medications such as selective serotonin reuptake inhibitors (SSRIs) or bupropion are sometimes added to a primary mood stabilizing medication. However, there is lack of consensus about such use because antidepressants may result in destabilization of mood in patients with bipolar disorder and studies examining evidence of effectiveness are inconsistent (Goodwin et al., 2016).

Electroconvulsive therapy (ECT) is effective, but is associated with anesthesia risks and some short-term cognitive impairment.

Patients with bipolar depression may also be treated for comorbid psychiatric conditions and for iatrogenic adverse reactions (e.g., dystonia, parkinsonism, tardive dyskinesia, and akathisia). Treatments for these comorbid conditions and adverse reactions include anticholinergic drugs (e.g., benztropine, diphenhydramine), vesicular monoamine transporter 2 (VMAT2) inhibitors (e.g., deuterobenzene), beta-blockers (e.g., propranolol), benzodiazepines, and antidepressants.

Table 1: Summary of Treatment Armamentarium with Clinical Trial Data Relevant to Bipolar Depression

Product (s) Name	Relevant Indication	Year	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA-Approved Treatments						
Quetiapine	Bipolar disorder, depressive episodes	1997	Target dose of 300 mg/day	FDA approved[a]	Metabolic changes; long-term use requires lens examination for cataracts	—
Olanzapine combined with fluoxetine (Symbyax)	Acute Depressive Episodes Associated with Bipolar I Disorder	2003	Dose: 6 mg olanzapine with 25 mg fluoxetine to maximum of 12 mg/50 mg once daily	FDA approved[a]	Weight gain and metabolic disorders limit use; risk of inducing mania; concern for serotonin syndrome, orthostatic hypotension	Lower dose in patients predisposed to hypotensive reactions, hepatic impairment, or with potential for slowed metabolism

Product (s) Name	Relevant Indication	Year	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Lurasidone	Bipolar depression as monotherapy or adjunctive to lithium or valproate	2010	20 mg once daily (with meal); increase in increments of 20 mg to maximum dose of 120 mg	FDA approved[a]	Risk of metabolic changes, orthostatic hypotension	—
Cariprazine	Treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults	2015	Start at 1.5 mg daily, target 3 mg to 6 mg daily	FDA approved[a]	Risk of metabolic changes, orthostatic hypotension, risk of seizures in vulnerable patients	Late-occurring adverse reactions due to long half-life
Other Treatments without FDA Indications						
Olanzapine	N/A	N/A	5 mg once daily to maximum of 20 mg daily	Numerous clinical trials	Weight gain, sedation, and metabolic changes limit use	Considered "3rd line" due to weight gain
Valproate	N/A	N/A	250 mg twice daily; increased to therapeutic serum level	Suggested by small clinical trials[b]	Tolerability issues due to weight gain, nausea, vomiting, hair loss, easy bruising, and tremor	Avoid in women of childbearing age due to teratogenicity concerns
Lamotrigine	N/A	N/A	25 mg daily, titrated slowly over weeks to target dose	Inconsistent and modest effects in clinical trials[c]	Headache, nausea, dizziness, rash, somnolence, and pain are common. Risk of life-threatening cutaneous reaction.	Effect considered modest
Lithium	N/A	N/A	Dosing based on target serum concentrations	Limited and inconsistent clinical trial data support[d]	Dry mouth, nausea, tremor, thyroid dysfunction, renal dysfunction	Adverse reactions are common and can limit tolerability

Product (s) Name	Relevant Indication	Year	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Carbamazepine	N/A	N/A	Dosing based on serum concentrations	Clinical trial[e]	Concerns of rash, aplastic anemia, and liver toxicity limit use	Infrequently used in clinical settings

MaxDD= Maximum daily dose
[a] Determined by FDA to meet the standard of substantial evidence of effectiveness
[b] Bond DJ, Lam RW, Yatham LN. Divalproex sodium versus placebo in the treatment of acute bipolar depression: a systematic review and meta-analysis. J Affect Disord 2010; 124:228.
[c] Bowden CL, Asnis GM, Ginsberg LD, et al. Safety and tolerability of lamotrigine for bipolar disorder. Drug Saf 2004; 27:173.
[d] Zornberg GL, Pope HG Jr. Treatment of depression in bipolar disorder: new directions for research. J Clin Psychopharmacol 1993; 13:397.
[e] Durgam S, Earley W, Lipschitz A, et al. An 8-Week Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Cariprazine in Patients With Bipolar I Depression. Am J Psychiatry 2016; 173:271.
Source: Clinical Reviewer table generated from prescribing information and cited references

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

On December 20, 2019, FDA approved lumateperone 42 mg daily for the treatment of schizophrenia in adults. FDA only approved one dose, 42 mg daily, because lower doses of 14 mg and 28 mg and a higher dose of 84 mg did not separate from placebo on the primary endpoint.

Refer to Table 2 for the status of post-marketing requirements (PMR) outlined in the approval for NDA 209500.

Table 2: Status of Post-Marketing Requirements/Commitments under NDA 209500

PMR/ PMC	Summary	Status
3760-1	Conduct an open-label study to assess safety, tolerability, and PK of lumateperone in patients ages 13 to 17 with a diagnosis of schizophrenia	*Ongoing* - Final protocol submitted 04/29/2020 (IND 079690, SN:0155) - Study Completion: 10/2021 - Final Report Submission: 04/2022
3760-2	Conduct a randomized, doble-blind placebo-controlled efficacy and safety study in patients ages 13 to 17 with a diagnosis of schizophrenia	*Planned* - Final Protocol Submission: 12/2022 - Study Completion: 06/2027 - Final Report Submission: 12/2027
3760-3	Conduct an open label long-term safety study in patients ages 13 to 17 with a diagnosis of schizophrenia	*Planned* - Study Completion: 12/2027 - Final Report Submission: 06/2028
3760-4	Lactation study of lumateperone and metabolites in lactating women	*Planned* - Protocol submitted 12/4/2020 (IND 079690, SN:0171) - Study/Trial Completion: 06/2022 - Final Report Submission: 12/2022
3760-5	Conduct an in vivo drug-interaction study to measure the effect of UGT enzymes inhibition on the exposure of ITI-007 and its metabolites, including aniline metabolites IC201337 and IC201338	*Completed* - Study completed 12/2020. Final study report submitted 02/17/2021 (SN 0109) - Final protocol submitted 05/18/2020 (IND 079690, SN: 0156) - Study completed 12/2020 - Final study report submitted 02/17/2021 (NDA 209500, SN 0109)

PMR/ PMC	Summary	Status
3760-6	Conduct a standard in vitro drug-drug interaction assay, noting that lumateperone is extensively metabolized	*Completed* Study completed 12/2020. Final report submitted to FDA on 07/02/2021 (SN 0125)
3760-7	Conduct a placebo-controlled randomized withdrawal maintenance study in patients with schizophrenia	*Planned* - Final Protocol submitted 12/21/2020 (IND 079690, SN: 0172) - Study/Trial Completion: 12/2023 - Final Report Submission: 06/2024
3760-8	Develop new strengths of 10.5 mg and 21 mg of Caplyta to meet the need for dose adjustment in patients with moderate to severe hepatic impairment or in patients who are taking concomitant strong or moderate CYP3A4 inhibitors	*Planned* - Final Report Submission 12/2021

CY=Cytochrome; SN=Sequence number; UGT=Uridine 5'-Diphospho-GlucuronosylItransferases
Source: Clinical reviewer generated table based on the original NDA 209500 Multi-discipline Unireview archived 03/22/2019, the Applicant's investigator's brochure under IND 079690, and the Applicant's Annual Report under NDA 209500

3.2. Summary of Presubmission/Submission Regulatory Activity

Lumateperone is not marketed outside of the United States. The Applicant is (b) (4) (b) (4) The Applicant conducted the parent NDA studies under IND 079690, and the supplemental NDA studies under IND 126701.

- July 22, 2015, Pre-IND meeting: FDA agreed to the Applicant's preliminary plan to develop lumateperone for the treatment of depressive episodes in adults with bipolar I or bipolar II disorder, as monotherapy and as adjunctive treatment with lithium or valproate. The Applicant canceled the planned pre-IND meeting after receiving the Agency's preliminary comments

    - The Applicant initially proposed a sequential parallel comparison design (SPCD). FDA discouraged this approach and the Applicant ultimate selected a more traditional study design.

    - The clinical pharmacology team agreed with the plan to evaluate DDIs with valproate and lithium.

- November 3, 2015: The Applicant submitted the IND-opening protocol for Studies ITI-007-401 (monotherapy for bipolar depression) and ITI-007-402 (adjunctive therapy for bipolar

depression, with lithium or valproate).

  - April 25, 2018: The Applicant submitted an amendment to include a 6-month open-label extension to the studies. Consistent with requirements for the 1-year study ITI-007-303 under IND 079690, the Division required PK assessments for circulating level of aniline metabolites approximately every 2 weeks for the first 6 weeks of the open-label extension study.

- June 17, 2016: Under IND 079690, the Applicant submitted the 6-month repeat-dose toxicity study and the nonclinical reviewers recommended that the human plasma levels not exceed 1/10th of the exposures at the NOEL of 5 mg/kg/d in rats (consistent with previous recommendations from 2014).

- August 14, 2017: Applicant submitted Study ITI-007-404 (a phase 3 efficacy trial examining monotherapy treatment for bipolar depression), which was allowed to proceed with no clinical comments.

- March 21, May 13, June 22, September 17, and December 28, 2018: The statistical review team provided responses for Study 401-A as follows:

  - Asked the Applicant to submit details of the planned interim analyses for possible sample size adjustment to avoid inflating Type I error

  - Suggested removing the treatment-by-study site interaction analysis from the primary statistical plan because the analysis was exploratory

  - Provided guidance on analyzing the key secondary endpoint to avoid including too many covariates

  - Advised reconsidering the censoring approach for time-to-first response (original plan was to also censor patients who did not maintain response through 6 weeks)

  - Advised reconsidering the key secondary endpoint (time to response) because there is no well-established endpoint of time-to-response in labeling and similar information can be obtained by plotting the efficacy results by visit

  - Asked to state the estimand and limit missing data.

  The statistical reviewer comments for Study 402 (from November 14, 2019) and Study 404 (from December 28, 2018) were similar and included justifying the change to standard deviation (SD) in the sample size calculation, which increased the sample size; clarified expectations about sensitivity analyses.

- January 27, 2020: The Applicant submitted the phase 3 efficacy Study ITI-007-403 in response to lack of efficacy in Study 401. The Applicant later determined that they did not

need Study 403 to support their sNDA application and changed Study 403 to a proof-of-concept design (b) (4)

- March 10, 2020: iPSP submitted
  - The Applicant initially proposed an extrapolation approach. In the comments sent on July 5, 2020, FDA explained that we do not accept extrapolation for bipolar depression because we do not have a sufficient database to feel confident that efficacy in adults would predict efficacy in adolescents for bipolar depression.
  - In the Agreed iPSP for the supplemental bipolar indications, FDA agreed to a waiver of studies in patients younger than age 10, because the studies are highly impracticable due to the low prevalence and difficulty with diagnosis and to defer PK and efficacy studies in patients ages 10 to 17 years old so that the Applicant can first establish safety and efficacy in adults before exposing pediatric patients to lumateperone.
- May 13, 2020, Type B pre-NDA: The Applicant proposed to submit a supplemental new drug application (sNDA) for the indication of monotherapy treatment of MDE associated with bipolar I or bipolar II disorder, based on efficacy results from Study 404 and proposed to add the indication of adjunctive therapy with lithium or valproate for the treatment of depressive episodes associated with bipolar I or bipolar II disorder based on Study 402. FDA advised the Applicant to submit a second adequate and well-controlled study to substantiate the results of Study 404 and stated that "either Study 402 (adjunctive treatment to lithium or valproate) or Study 403 (monotherapy treatment), if positive, have the potential to provide evidence to substantiate the results of Study 404" in support of the proposed indication of treatment of bipolar depression. FDA also agreed to the Applicant's proposed structure for the integrated summaries of efficacy and safety. FDA noted the use of different formulations in the phase 3 studies and requested that the Applicant describe what effect(s) encapsulation would have on the drug release and absorption compared to the tablet itself (no encapsulation).

- December 16, 2020, Type C guidance meeting: FDA agreed to the proposed content and format of the planned bipolar depression and adjunctive therapy supplemental NDAs. FDA agreed that the final study reports for two phase 1 drug-drug interaction (DDI) studies may be submitted with the 120-Day Safety Update. There were no clinical or statistical comments.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Per the clinical inspection summary from October 12, 2021, the clinical sites of Drs. Hassman, Malik, Riesenberg, and Romain were inspected in support of this NDA and covered Protocols ITI-007-402 and ITI-007-404. According to OSI, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

4.2. Product Quality

Per the review from October 25, 2021, OPQ has no major concerns and recommends approval from a CMC perspective. They found the Applicant's biopharmaceutical data on bridging between lumateperone as three different formulations in the studies (over-encapsulated tablet, film-coated tablet, and the proposed 42-mg capsule) acceptable.

4.3. Clinical Microbiology

N/A

4.4. Devices and Companion Diagnostic Issues

N/A

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

There was no nonclinical information included in either Supplement 05 or Supplement 06. The Applicant's proposed dose of lumateperone 42 mg and chronic duration are supported by the current label. Further, there were no changes to the portions of the label that contained nonclinical information. Therefore, there were no items that needed to be reviewed from a nonclinical perspective.

APPEARS THIS WAY ON ORIGINAL

6 Clinical Pharmacology

6.1. Executive Summary

The clinical pharmacology development program for the bipolar depression indication included trials to evaluate:

1) Relative bioavailability of the overencapsulated tablet, which was used in the bipolar depression efficacy trials, to the commercial capsule formulation (Study ITI-007-019)
2) Food effect on the OE tablet (Study ITI-007-031) and capsule formulations (Study ITI-007-019)
3) Effect of uridine 5'-diphospho-glucuronosyltransferase (UGT) inhibitors probenecid (Study ITI-007-027) and valproate (Study ITI-007-028) on the PK of lumateperone. Study ITI-007-027 is also to fulfill PMR 3760-5 as outlined in the approval letter for lumateperone.

In addition to the phase 1 studies, the Applicant also performed population pharmacokinetic (PopPK) and population PK/pharmacodynamic (PK/PD) analyses for lumateperone in patients with bipolar depression receiving lumateperone as monotherapy or as adjunctive therapy. However, because PopPK related information was not included in the labelling for the proposed indication, no pharmacometric review was conducted for this supplement.

6.2. Summary of Clinical Pharmacology Assessment

The Office of Clinical Pharmacology (OCP)/Division of Neuropsychiatric Pharmacology (DNP) have reviewed the submission, and determined that from a clinical pharmacology perspective, the submitted data support approval of lumateperone 42 mg in the treatment of bipolar depression in adults. Additionally, OCP have determined that PMR 3760-5 has been fulfilled.

6.2.1. Pharmacology and Clinical Pharmacokinetics

Lumateperone is a serotonin 5-HT_{2A} receptor antagonist, a dopamine D_2 receptor pre-synaptic partial agonist and post-synaptic antagonist, a dopamine D_1 receptor-dependent modulator of glutamate, and a serotonin reuptake inhibitor. PK characteristics of lumateperone are described in the lumateperone label. Only new information provided in the supplements are discussed in the Sections below.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dose of lumateperone is 42 mg once daily. Dose titration is not required. Lumateperone could be administered with or without food, from a clinical pharmacology perspective.

Therapeutic Individualization

UGT Inhibitor
In vitro studies showed that multiple enzymes including UGT are involved in the metabolism of lumateperone. Coadministration of lumateperone 28 mg with a UGT inhibitor, probenecid, increased lumateperone Cmax about 9% and decreased AUC about 11%. Coadministration of lumateperone 28 mg with another broad-spectrum UGT enzyme inhibitor, valproate (VPA), decreased lumateperone Cmax about 33% and AUC 12%. Based on discussions with the clinical team, the magnitude of changes observed in lumateperone exposure in the presence of these two well-known broad spectrum UGT inhibitors are not clinically significant. Dosage adjustment of lumateperone is not necessary when it is administered concomitantly with a UGT inhibitor.

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

No new PK data are provided in this supplement; see the current label for lumateperone.

6.3.2. Clinical Pharmacology Questions

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the Applicant has demonstrated that the proposed dosing regimen of lumateperone 42 mg daily without titration for the treatment of bipolar depression (the same as approved for schizophrenia) is effective in Study ITI-007-404 (monotherapy study) and Study ITI-007-402 (adjunctive therapy with lithium and valproate). The primary analysis showed significant improvements in MADRS total score from baseline to Day 43 (primary endpoint) for lumateperone 42 mg versus placebo for both studies.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No new information to address this question is provided in this supplement. Dosing recommendations based on intrinsic factors are the same as the current lumateperone label.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food Effect
In the efficacy trial for the schizophrenia indication (original application), capsules (the current commercial formulation) were administered with food in the morning, and in the bipolar

depression efficacy trials, a clinical trial formulation, the over-encapsulated (OE) tablet, was administered in the evening with or without food.

The effect of food on the two formulations is summarized in Table 3. Study results showed that intake of high-fat, high-calorie food had similar effects on the two formulations: lumateperone mean C_{max} decreased about 25 to 33%, and mean AUC_{inf} increased about 9 to 19%.

Table 3: Summary Statistics of the Plasma PK Parameters of Lumateperone Following a Single Dose of 42 mg OE Tablet or Capsule Administration (Fed/Fasted, Geomean Ratio, 90%CI)

PK Parameters	42 mg OE Tablet	42 mg Capsule
C_{max}(ng/mL)	0.75 (0.51, 1.11)	0.67 (0.57, 0.802)
AUC_t (hr*ng/mL)	1.17 (0.95, 1.46)	1.07 (0.956, 1.202)
AUC_{inf} (hr*ng/mL)	1.19 (0.97, 1.47)	1.09 (0.97, 1.22)

Source: Table 7, Study 031 CSR; Table 1, Study 019 CSR Addendum

Given the magnitude of change observed in exposures and the high inter-subject PK variability (coefficients of variation 69 to 97% for steady state C_{max} and AUC, lumateperone label), either formulations of lumateperone can be administered with or without food, from a PK perspective.

The currently approved lumateperone label for the treatment of schizophrenia recommends lumateperone be administered with food. This recommendation was based on the following considerations: 1) lumateperone had been administered under fed conditions in the pivotal schizophrenia studies, per protocol specification; 2) the marginal decrease in C_{max} under fed conditions might result in fewer gastrointestinal (GI) effects, given that a higher incidence rate of GI effects was observed in the higher dose group (42 mg compared to 28 mg) in schizophrenia patients, though the differences were small (Table 4).

Table 4: Incidence (%) of Gastrointestinal Disorders in Clinical Trial

Program	Placebo	Lumateperone 28mg	Lumateperone 42 mg	Lumateperone 84 mg
Schizophrenia (capsule taken with food)	23.1	24.7	28.6	27.7
Bipolar depression (OE tablet taken without regard to food)	9.4	22.8	17.7	Not studied

Source: Table 2.7.4-8, Module 2.7.4: Summary of clinical findings e0005 NDA209500 (schizophrenia); Table 2.7.4-24, Module 2.7.4, Summary of clinical findings e0109 NDA209500 (bipolar depression)

To evaluate whether dosing without regard to food has an impact on GI adverse reactions, incidence rates of GI adverse reactions were compared between the patients with bipolar depression (drug was taken without regard to food), and patients with schizophrenia (drug was taken with food). As shown in Table 4, a lower incidence rate was reported in the patients with bipolar depression (drug was taken without regard to food), compared to in patients with schizophrenia (drug was taken with food), at both 28 mg and 42 mg dose levels, suggesting that taking lumateperone without regard to food did not increase the incidence rate of GI adverse

reactions compared to taking medication with food. However, the comparison is confounded by disease state: a 1.5-fold higher GI adverse reaction incidence rate in the placebo group was reported in patients with schizophrenia than in patients with bipolar depression.

When comparing GI adverse reactions between dose levels in the bipolar depression program, the incidence rate was numerically lower for the 42 mg dose group (17.7%) compared to the 28 mg dose group (22.8%), suggesting that 50% higher dose did not result in higher GI adverse reactions (Table 4). In the schizophrenia program, though a higher GI adverse reaction incidence rate was reported when dose was increased from 28 mg (24.7%) to 42 mg (28.6%), the incidence rate at 84 mg (27.7%) was lower than that at 42 mg (28.6%). The results seem to suggest a higher dose/exposure might not indicate a higher incidence of GI adverse reactions.

Based on the demonstrated PK similarity (exposure within BE limits, see discussion in the following question) between OE tablets and capsule formulations, similar magnitude of food effect on both formulations, high inter-subject PK variability for lumateperone, as well as the observed GI adverse reactions across doses in schizophrenia patients and bipolar patients, OCP recommends lumateperone can be administered with or without food in the updated label.

UGT Inhibitor

Valproate (VPA)
Compared to administration of lumateperone alone, coadministration of lumateperone 28 mg with VPA (pretreated once daily for 4 days), decreased lumateperone C_{max} about 33% and AUC 12% (Table 5). For measured metabolites, metabolite IC200161 exposure (C_{max} and AUC) was increased about 3 to 22%, while IC201308 and IC200131 exposures were decreased to a similar degree ~ 18 to 33%, in the presence of VPA. In general, the magnitude of changes seems to be small (the greatest change was ~33% decrease in IC200131 C_{max}). Given the small changes observed, dosage adjustment for lumateperone when used concomitantly with VPA is not considered necessary.

Probenecid (PBC)
Coadministration of lumateperone 28 mg with PBC 500 mg (pretreated once daily for 4 days), increased lumateperone C_{max} about 9% and decreased AUC 11% (Table 5). For measured metabolites, varying degrees of magnitude and direction of changes in the exposure were observed in the presence of PBC. Metabolite IC200161 exposure (C_{max} and AUC) was increased approximately 27 to 49%, IC200131 exposure (C_{max} and AUC) was decreased 30 to 37%, while IC201308 C_{max} was increased approximately 20% and AUC decreased approximately 5%. In general, the magnitude of changes observed in lumateperone and metabolites exposure seems to be small in the presence of PBC. Dosage adjustment for lumateperone when used concomitantly with PBC is not necessary.

Table 5: Geomean Ratio for Lumateperone and Metabolites in the Presence and Absence of UGT Inhibitor VPA or PBC

Geomean Ratio (T/R)	lumateperone		IC200161		IC201308		IC200131	
	VPA	PBC	VPA	PBC	VPA	PBC	VPA	PBC
Cmax	0.67	1.09	1.03	1.49	0.69	1.20	0.67	0.70
AUCinf	0.88	0.89	1.22	1.27	0.82	0.95	0.83	0.63

Source: Reviewer created; PK set 1 analysis was used for VPA (valproate, Study ITI-007-028); PBC: probenecid (Study ITI-007-027)

In the presence of UGT inhibitor (VPA or PBC), the two aniline metabolites of lumateperone, IC201337 and IC201338, which are associated with neuropathological changes observed in dogs, were found to be below levels of quantification (0.1 ng/mL)—the same as when no inhibitors were present.

In general, the exposure of lumateperone was not significantly different when administered alone or coadministered with PBC or VPA in the drug-drug interaction study. The observed changes in the exposures of lumateperone and metabolites are largely consistent with each other and do not seem to be clinically significant. The PK results suggest that when co-administered with broad-spectrum UGT enzyme inhibitors (for example, PBC or VPA), dose adjustment of lumateperone is unnecessary.

Can findings from clinical trial formulations be applied to commercial capsule formulation?

Yes, findings from overencapsulated tablets (used in efficacy trials) and film-coated tablets (used in the 6-month safety extension study) in the bipolar depression program can be applied to the commercial capsule formulation.

Overencapsulated Tablets versus Commercial Capsules
Appropriate bridging from overencapsulated tablets to the commercial capsule formulation is considered established.

The relative bioavailability of lumateperone overencapsulated tablets compared to the commercial capsule was evaluated in a clinical study under fasted conditions (Study ITI-007-019). Though the 90% CI of lumateperone AUC ratio falls within the BE limits of 80 to 125% (Table 6), the original statistical analysis showed that the 90% CI for geomean ratio of lumateperone C_{max} was statistically outside of the BE limits (0.886, 1.252). In a subsequent amendment to the sNDAs, the Applicant updated their statistical analysis by taking into account the effects of period and sequence of the study design, which was neglected in the original analysis. In the revised analysis, the 90% CI for geomean ratio of lumateperone C_{max} fell within the BE limits (0.880, 1.246).

Given the known large PK variability following lumateperone administration (coefficients of variation for C_{max} and AUC ranging from 68 to 97% at steady state), regardless of the statistical analysis (original or updated), the marginal difference observed in lumateperone exposure either administered as overencapsulated tablet or capsule, is not considered clinically

significant. The findings (i.e., efficacy results) from the overencapsulated tablets can be applied to the capsule formulation.

Table 6: Summary Statistics of the Plasma PK Parameters of Lumateperone and Metabolite IC200131, IC200161 and IC200565 (Capsule/Overencapsulated Tablet, Geomean Ratio, 90%CI) In the Original Analysis

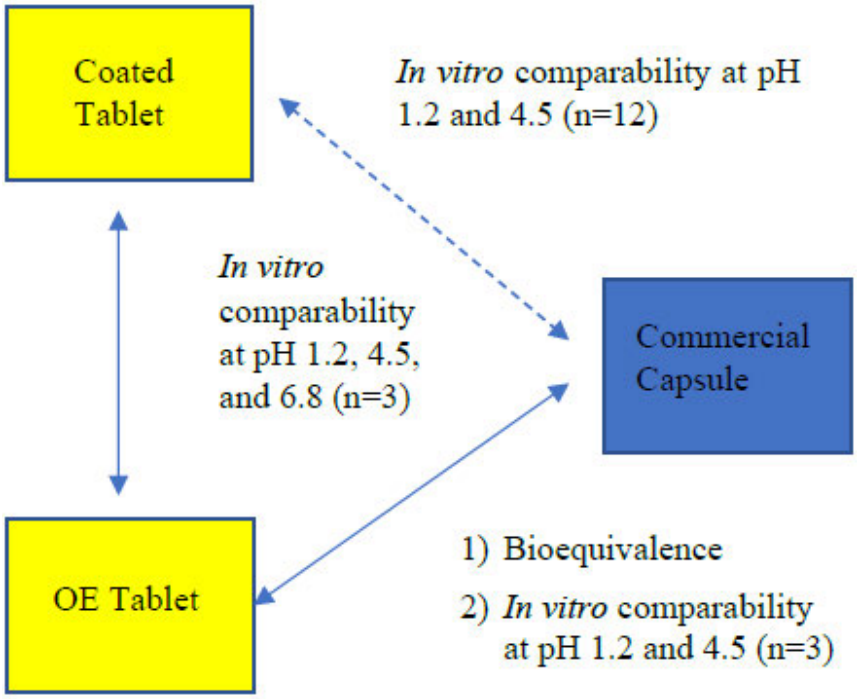
PK Parameters	lumateperone	IC200131	IC200161	IC201308
C_{max}(ng/mL)	1.053 (0.886, 1.252)	1.01 (0.88, 1.16)	0.99 (0.84, 1.17)	0.90 (0.78, 1.05)
AUC_t (hr*ng/mL)	1.01 (0.90, 1.13)	1.09 (0.96, 1.25)	0.98 (0.89, 1.07)	0.94 (0.84, 1.05)
AUC_{inf} (hr*ng/mL)	1.01 (0.91, 1.22)	1.08 (0.96, 1.21)	0.95 (0.87, 1.04)	0.95 (0.87, 1.05)

Source: Table 14, 15, 16, and 18 of Study ITI-007-019 CSR

Film-Coated Tablets versus Commercial Capsules

The relative bioavailability of lumateperone film-coated tablet compared to the commercial capsule was not evaluated in clinical trials. Rather, a three-way bridging approach as illustrated in the figure below was employed to establish the bridging. Per Biopharm recommendation, adequate bridging is considered established between the formulations. Refer to biopharm review for details.

Figure 1: Formulation Bridging Strategy



Source: Figure 1 response-information-request-21jul2021.pdf (e0128 submission)

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant's bipolar depression program consists of three phase 3, double-blind, randomized, placebo-controlled, clinical studies evaluating lumateperone as a treatment for MDEs associated with bipolar I or bipolar II disorder. The safety data were supplemented by results from a 6-month open label extension (OLE) study. For the safety review, we also considered results for studies conducted under IND 079690 and submitted under the original NDA (209500). See Table 7 for a list of clinical studies submitted by the Applicant in support of NDA 209500 S-05 and S-06 or submitted under the original NDA 209500 and used to support the review of safety.

Table 7: Summary of Clinical Studies Used in the Review of NDA 209500 S-05 and S-06

Study Name	NCT no.	Trial Design	Regimen/ Schedule (by mouth)	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Treated	Study Population	No. of Centers, Region
Controlled Studies to Support Efficacy and Safety for NDA 209500 S-05 and S-06								
ITI-007-401 Part A	NCT-0260-0494	R, DB, PC, MC	Luma 28 mg Luma 42 mg Placebo	Primary: Change from baseline to Day 43 in MADRS total score Secondary: Time to first sustained response[a]	6-weeks	Luma 28 mg: 180 Luma 42 mg: 184 Placebo: 185	(Monotherapy) Males and females ages 18 to 75 years; DSM-5 Bipolar I or II with MDE	53 U.S.
ITI-007-401 Part B	NCT-0260-0494	OLE	Luma 42 mg Placebo	Safety	Up to 6 months	Luma 42 mg: 127	(Monotherapy) Subjects from Part A	U.S. (rollover)

Study Name	NCT no.	Trial Design	Regimen/ Schedule (by mouth)	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Treated	Study Population	No. of Centers, Region
ITI-007-402	NCT-0260-0507	R, DB, PC, MC	Luma 28 mg Luma 42 mg Placebo	Primary: Change from baseline to Day 43 in MADRS total score Secondary: CFB to Day 43 in CGI-BP-S depression score	6 weeks	Luma 28 mg: 176 Luma 42 mg: 177 Placebo: 175	(Adjunctive) Males and females ages 18 to 75 years; DSM-5 Bipolar I or II with MDE	89 study centers: United States (46), Bulgaria (15), Russian Federation (13), Serbia (7), and Ukraine (8)U.S.
ITI-007-404	NCT-0324-9376	R, DB, PC, MC	Luma 42 mg Placebo	Primary: Change from baseline to Day 43 in MADRS total score Secondary: CFB to Day 43 in the CGI-BP-S total score	6 weeks	Luma 42 mg: 188 Placebo: 189	(Monotherapy) Males and females ages 18 to 75 years; DSM-5 Bipolar I or II with MDE	54 study centers: United States (14), Bulgaria (10), Colombia (3), Russian Federation (11), Serbia (5), and Ukraine (11)U.S.
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies, phase 3 studies completed under NDA 20950)								
Phase 3		Trial Design	Regimen/ once daily (by mouth)	Study Endpoints	Treatment Duration	No. of Patients Treated	Study Population	No. of Centers, Region
ITI-007-005	NCT-014-99563	R, DB, PC, efficacy with comparator	Luma 42 mg Luma 84 mg Placebo Risperidone 4 mg	Primary: change from baseline to Week 4 on PANSS total score	4 weeks	335	Adults with acute exacerbation of schizophrenia	8 U.S.
ITI-007-301	NCT-022-82761	R, DB, PC, efficacy, and safety	Luma 28 mg Luma 42 mg Placebo	Primary: change from baseline to Week 4 on PANSS total score	28 days	450	Adults with acute exacerbation of schizophrenia	12 U.S.

Study Name	NCT no.	Trial Design	Regimen/ Schedule (by mouth)	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Treated	Study Population	No. of Centers, Region
ITI-007-302	NCT-024-69155	Design: R, DB, PC, AC, efficacy, and safety with comparator	Luma 28 mg Luma 42 mg Placebo Risperidone 4 mg	Primary: change from baseline to Week 6 on PANSS total score	6 weeks	695	Adults with acute exacerbation of schizophrenia	13 U.S.
ITI-007-303	---	Open label	Luma 42 mg	Safety	Part 1: 6 weeks Part 2: 1 year	Part 1: 315 Part 2: 602	Patients with stable schizophrenia	40 U.S.

[a]Defined as the number of days from first dose of study medication to the earliest date the patient experienced a sustained ≥ 50% reduction from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score (i.e., the patient achieved responder status at ≥ 2 consecutive visits that continued to the last assessment).
AC=Active Control; CFB: CFB= Change from Baseline (CFB); CGI-BP-S= Clinical Global Impression Scale of Bipolar Disorder-Severity; CY= cytochrome; DB =Double Blind; Luma= lumateperone; MC=Multi-Center; MDE=Major Depressive Episode; OLE=Open-Label Extension; OL= Open Label; PC=Placebo Controlled; R=Randomized
Source: Clinical Reviewer generated from CSR for listed studies

7.2. Review Strategy

To assess efficacy, we reviewed the clinical study reports (CSRs) and submitted datasets for the Applicant's short-term phase 3 efficacy studies submitted in support of S-005 (monotherapy; Study 404 and Study 401-A) and S-006 (adjunctive; Study 402).

The assessment of safety included review of the Applicant's CSRs and submitted datasets from the short-term efficacy studies (Studies 401-A, 402, and 404) and the 6-month OLE study, Study 401-B. The results of the aforementioned studies with safety data were compared to the safety findings from the original NDA 209500 submission for the treatment of schizophrenia, as presented in the current lumateperone prescribing information (PI), the original review of NDA 209500 (March 22, 2019), and the corresponding CSRs for the primary efficacy studies, as relevant.

The Applicant did not submit data from their ongoing phase 3 trial, Study 403, so Study 403 was not considered in the review of efficacy or safety.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 401-A (Monotherapy)

Study Title for Study 401-A: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study with an Open-Label Extension to Assess the Efficacy and Safety of ITI-007 Monotherapy in the Treatment of Patients with Major Depressive Episodes Associated with Bipolar I or Bipolar II Disorder (Bipolar Depression).

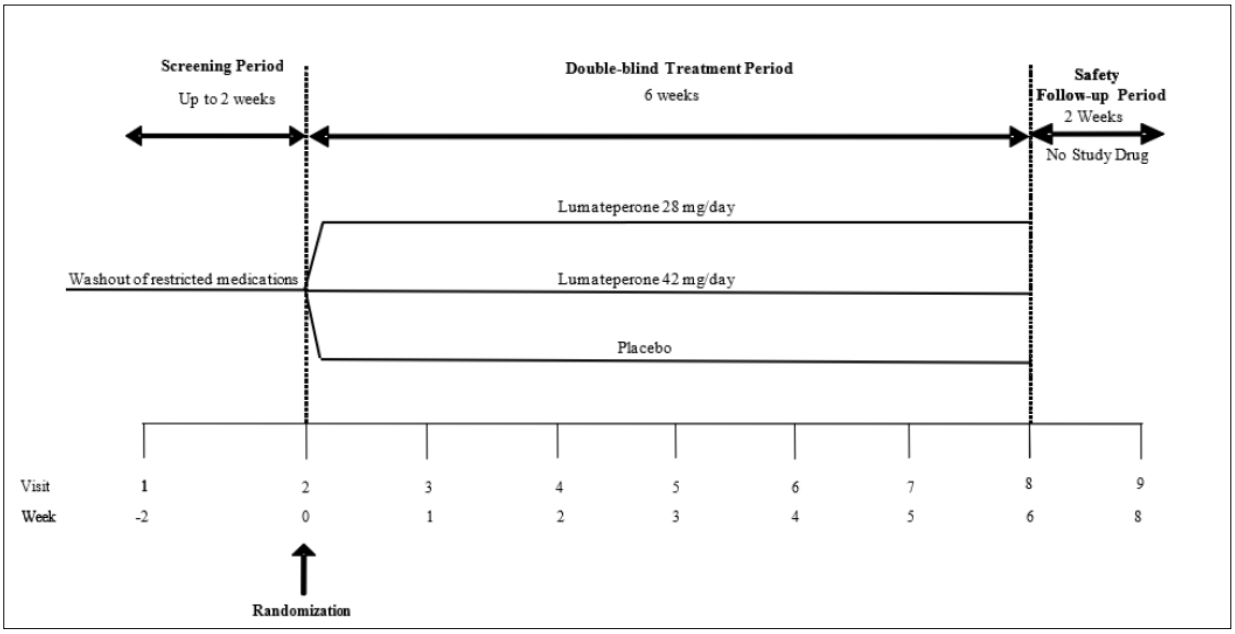
8.1.1.1. Trial Design for Study 401-A

A. Basic Study Design for Study 401-A

Study 401-A was a 6-week, phase 3, fixed-dose, randomized, double-blind, placebo-controlled multicenter study comparing the efficacy of lumateperone 28 and 42 mg to placebo. The Sponsor's study design was an acceptable approach to evaluating efficacy for a phase 3 clinical trial, and the design was similar to previous phase 3 programs for bipolar depression.

Study 401-A had three phases: A 2-week screening period, a 6-week double-blind treatment period, and a 2-week safety follow-up period. After washout of prior excluded medications, patients were randomized in a 1:1:1 ratio to either lumateperone 42 mg, lumateperone 28 mg, or placebo. See Figure 2 for the Applicant's Study 401-A Design Schema.

Figure 2: Study Design Schema for Study 401-A



Source: Applicant's information request submitted to FDA on September 9, 2021

B. Trial Location for Study 401-A

There were 53 study sites in the United States.

C. Choice of Control Group for Study 401-A

The Applicant used a placebo control group to establish efficacy, which is appropriate.

D. Diagnostic Criteria for Study 401-A

The diagnostic criteria used by the Applicant were based on instruments commonly used in clinical trials to determine diagnosis, symptom severity, and level of functioning. For diagnosis of bipolar disorder, the Applicant used the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria for bipolar I disorder or bipolar II disorder as confirmed by the Investigator or Applicant-approved expert rater by a Structured Clinical Interview for DSM-5 Disorders–Clinical Trials Version (SCID-5-CT) and met all of the following five criteria:

1) Onset of current MDE was at least within 2 weeks but not more than 6 months prior to screening

2) At least moderate severity, measured by MADRS total score ≥ 20 and corresponding to a CGI-BP-S score of ≥ 4 at screening and baseline

3) Verification of significant distress or impairment due to the current MDE

4) Lifetime history of 1 or more manic, mixed, or hypomanic episode

5) Young-Mania Rating Scale (YMRS) total score of ≤ 12, to assess manic symptoms.

The diagnostic criteria appear consistent with the Applicant's aim to restrict the population to bipolar depression.

E. Key Inclusion/Exclusion Criteria for Study 401-A

In addition to the inclusion criteria described above, patients were males and females ages 18 to 75 years old.

Key exclusion criteria included:

1) Experiencing a decrease in the rater administered MADRS total score of ≥25% between screening and baseline visits;
2) Significant risk of suicidal behavior at screening;
3) Comorbid psychiatric disorders (schizophrenia, psychotic disorder, psychosis not due to bipolar disorder; anxiety disorders, eating disorders, primary obsessive-compulsive disorder, personality disorder, moderate to severe substance use disorder; other psychiatric conditions of treatment focus);
4) Hospitalization for mania within 30 days or considered a rapid cycler or treatment-resistant);
5) Ongoing psychotherapy;
6) Other specified medical conditions (e.g., neurological, cardiovascular, or endocrine disorders) or abnormal laboratory, electrocardiographic, or vital sign values outside of pre-specified parameters;
7) Pregnant or breastfeeding women;
8) Use of prohibited medications.

The eligibility criteria appear consistent with the Applicant's aim to restrict the population to bipolar depression and limit confounders.

F. Dose Selection for Study 401-A

Study 401-A used two fixed doses: lumateperone 28 mg and 42 mg. ITI-007 40 mg and 60 mg described as the dosing in the study protocols refers to the tosylate salt (ITI-007 tosylate or lumateperone tosylate) and were equivalent to, respectively, 28 mg and 42 mg of the active base (lumateperone). ITI-007 was supplied as over-encapsulated tablets. The Applicant based the dose selection on the parent NDA dosing, which is acceptable.

G. Study Treatments for Study 401-A

Patients received lumateperone 28 mg, lumateperone 42 mg, or placebo orally once daily. Patients were instructed to self-administer the study drug between approximately 8:00 pm and 10:30 pm, and at approximately the same time each day whenever possible.

H. Assignment to Treatment for Study 401-A

Patients were randomly assigned to one of the following groups: lumateperone 28 mg, lumateperone 42 mg, or matching placebo. Unblinded biostatistics personnel used Statistical Analysis Software (SAS) to generate a permuted block randomization schedule (block size not specified), which was stratified by diagnosis of bipolar I or bipolar II.

I. Blinding for Study 401-A

Study 401-A was a double-blind study. Patients received a unique randomization number using an interactive web response system. Investigators were blinded to the patients' randomization outcome unless there was a medical emergency.

J. Dose Modification/Discontinuation for Study 401-A

The Applicant stated that titration was not necessary and therefore used a fixed-dose design. The dose could not be titrated or tapered.

K. Administrative Structure for Study 401-A

The Applicant listed all clinical study vendors, including personnel responsible for study oversight, statistical analyses, and CSR development. All of the listed vendors and primary Applicant personnel are located in the United States. except the [redacted] (b) (4) vendor [redacted] (b) (4) located in [redacted] (b) (4) (see Study 401 CSR for details).

L. Procedures and Schedule for Study 401-A

See Appendices for the Applicant's schedule of events for Study 401-A.

M. Dietary Restrictions/Instructions for Study 401-A

Patients were instructed to self-administer their study medication around the same time each evening. The study medication could be administered with or without food.

N. Concurrent Medications for Study 401-A

The Applicant required a wash-out of psychotropic drugs prior to study start. Patients were not permitted to start new psychotropic drugs during the study. Prohibited drugs include cannabis, alcohol, 5-HT_{2A}-receptor antagonist, or inverse agonist; or any strong or moderate cytochrome P450 3A4 inhibitor or inducer. The Applicant notes that patients could take sedatives daily for insomnia during the first 2 weeks of treatment. The Applicant monitored for and recorded all concomitant medications during the study.

O. Treatment Compliance for Study 401-A

The Applicant described using written instructions and tablet counts to monitor treatment compliance. The Applicant documented irregularities and discussed medication adherence with patients. Any patient who missed two doses of study medication per week in any 2 weeks of the study treatment period or who missed three or more doses of study medication in any single week were to be considered for early discontinuation.

P. Rescue Medication for Study 401-A

The Applicant noted that any concomitant medication deemed necessary for the welfare of the patient during the study could be given at the discretion of the Investigator.

Q. Subject Completion, Discontinuation, or Withdrawal

The Applicant defined treatment period completers as subjects who completed the 6-week On-Treatment Period and procedures ("study completers" also completed the End-of-Study assessments on Study Day 57 (±2) or directly rolled over to Part B).

The Applicant determined any discontinuation as premature when a patient who signed the informed the informed consent document ceased participation in the study, regardless of circumstances, before the completion of all study visits and procedures (e.g., noncompliance, pregnancy, withdrawal of consent). Patients who completed the double-blind treatment period in Part A but did not attend the safety-follow up visit were considered to have discontinued from the study.

R. Study Endpoints for Study 401-A

The primary endpoint was change from baseline to Day 43 in MADRS total score. There was no agreed upon secondary endpoint adjusted for multiplicity.

S. Statistical Analysis Plan for Study 401-A

The population for the primary endpoints was based on the intent to treat (ITT) analysis set. The Applicant described that all analyses using the ITT Set would classify subjects according to randomized treatment, regardless of the treatment received during the course of the study (note: the clinical study protocol refers to this population as the Efficacy Analysis Set (EAS)). The Applicant performed the primary efficacy analysis on an assumption of missing at random (MAR); they wished to evaluate the estimand as the effect of lumateperone compared to placebo if the treatment is administered for the planned study duration.

The primary endpoint was change from Baseline in rater-administered MADRS total score to Week 6 (Day 43), performed for the ITT Set and the Per Protocol (PP) Set (the ITT set without any major protocol deviations). The Applicant used mixed-effects model for repeated measures (MMRM) for the analysis of the primary efficacy endpoint. Estimates of model parameters were presented, as well as least-squares mean (LSM) estimates for change from baseline in MADRS score; standard errors and 95% confidence intervals (CI) for LSMs were presented by treatment group and time point. Contrast estimates (LSMs) for between-group comparisons (lumateperone 28 mg versus lumateperone 42 mg versus placebo), the corresponding standard errors, 95% CIs, effect sizes, and p-values werepresented for each visit.

There was an interim analysis plan for a potential stop for an efficacy claim as well as for a potential sample size increase. The stopping boundaries were based on the O'Brien-Fleming-type, which was derived from the Hwang-Shih-DeCani spending function with $\gamma = -4$. The two-sided nominal significance level for the interim analysis (stage 1) would be 0.0216 and for the final analysis (stage 2) it would be 0.0444. A weighted test statistic was pre-specified with the

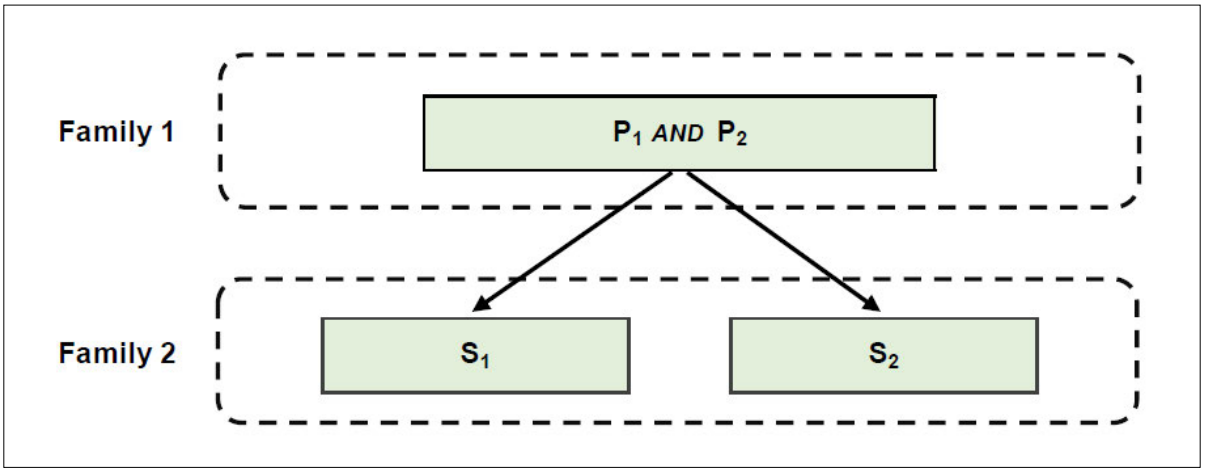
fixed weights (square root of 0.796 and square root of 0.204, respectively, for the two stages).

The Applicant pre-specified the secondary endpoint to be time to first sustained response. FDA did not agree to this prespecified endpoint and therefore it was not considered as a prespecified endpoint for the purpose of this review (see Statistical Reviewer's Comments, below).

The Applicant evaluated the efficacy of two doses of lumateperone compared to placebo for the primary and secondary endpoints based on three sources of multiplicity of this study (multiple data looks, multiple endpoints, and multiple dose-placebo comparisons).

At each stage (interim analysis and the final analysis), four hypotheses were grouped into two families based on the primary and secondary endpoints and for each dose (see Figure 3). A serial gatekeeping procedure was used to control the overall type I error rate in the strong sense across the primary and secondary efficacy endpoints, with the family of the primary endpoint hypotheses (family 1) serving as the gatekeeper for the secondary endpoint (family 2). The Applicant described that a Hochberg multiplicity adjustment would be applied within family 1, where two doses would be evaluated. For a strong control of overall type I error, the testing would not proceed to family 2 unless both doses demonstrate statistical significance in family 1.

Figure 3: Family-Based Approach to Multiple Comparisons for the Primary and Secondary Endpoint



Source: Applicant's Statistical Analysis Plan, Section 7.2 (p 19), Study 401

Statistical Reviewer's Comments: We had a concern with the proposed key secondary analysis of time to first sustained response and conveyed the following comments to the Applicant on their March 21, 2018 submission (Sequence No. 25).

According to the pre-specified plan, censored patients are (1) who do not experience at least 50% reduction from baseline in the rater administered MADRS total score, or do not maintain it through the end of the 6-week treatment, (2) patients who discontinue treatment, will be considered nonresponders and will be censored. Those censored patients due to efficacy might imply that the treatment is not effective, which makes censoring informative. Hence, the

underlying assumption required for a valid statistical analysis is violated.

In Seq No. 28, the Applicant responded:

> *We appreciate the Division's feedback and recommendation regarding the proposed key secondary endpoint in our bipolar depression trial (Study ITI-007-401). Given the imminent timing of the interim analysis in this trial, we would prefer not to amend the protocol and the SAP with new objectives and analysis plans prior to that time. However, we are conducting two other Phase 3 trials in this indication and will take your recommendation into consideration for our overall program.*

(b) (4)

T. Protocol Amendments for Study 401-A

The Applicant made several significant amendments to Study 401-A, including the following: adding a 6-month open-label extension (called Part B); doubling the number of study sites (from 30 to ~60); including some patients with psychotic symptoms if due to depressive episode at screening; permitted use of short-acting anxiolytic during Part B (up to lorazepam 6 mg weekly); and adding an external data monitoring committee.

The Applicant initially proposed an SPCD in their pre-IND briefing package. The FDA strongly discouraged the use of SPCD and the Applicant has decided not to use the SPCD trial design for this program. The Applicant's approach is consistent with the prespecified plan.

8.1.1.2. Study Results for Study 401-A

A. Compliance with Good Clinical Practices

The Applicant states that this clinical study complied with the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidance on General Considerations for Clinical Trials (ICH-E8; 62 FR 66113, December 17, 1997) and GCP (ICH-E6; 62 FR 25692, March 2018), as well as Code of Federal Regulations (CFR) Part 312. The Applicant states that the study protocol, informed consent form (ICF), information sheet advertisements, and amendments were approved by the IRBs/IECs at the study centers in conformance with 21 CFR part 56. The Applicant states that they conducted the studies under four U.S.-based Institutional Review Boards and in accordance with ICH good clinical practice (GCP).

B. Financial Disclosure for Study 401-A

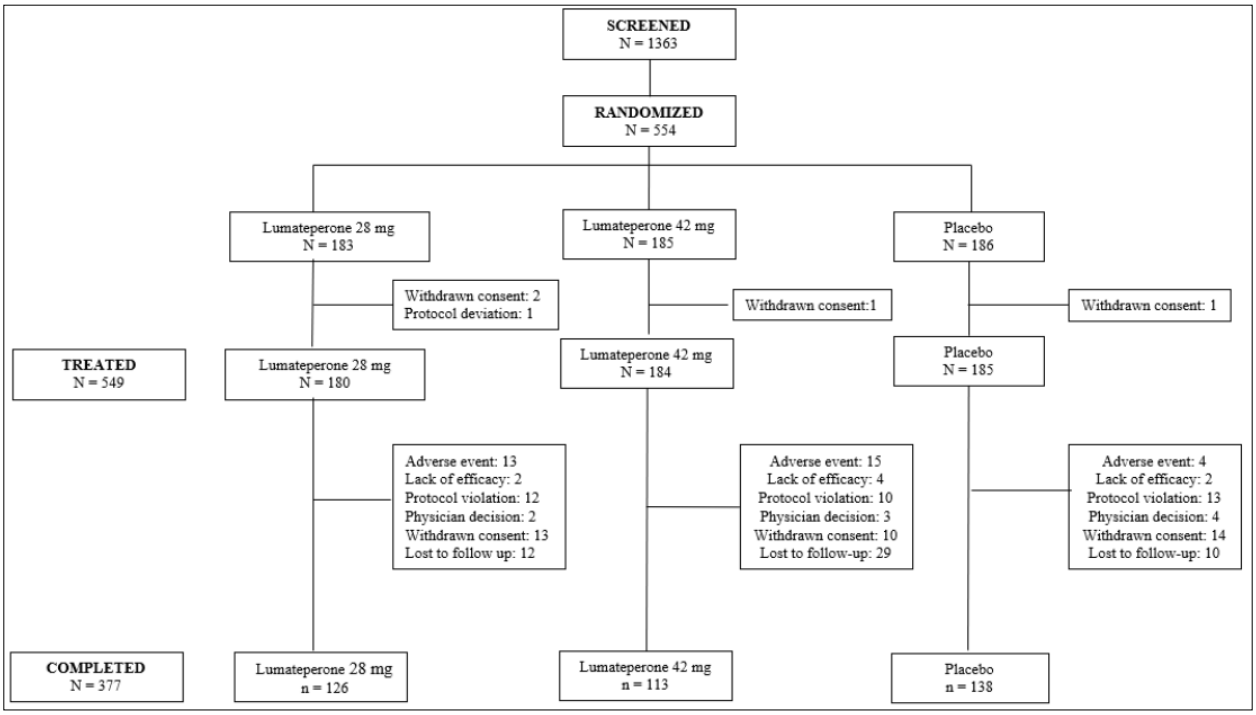
See Section 0.

C. Patient Disposition for Study 401-A

The Applicant states that 554 patients were randomized to either lumateperone 28 mg, 42 mg, or placebo. Of the randomized subjects, 68% of subjects completed the double-blind treatment

period (see Figure 4).

Figure 4: Patient Disposition Study 401-A



Source: Applicant's Figure 1, Study 401 CSR

The Applicant described that more subjects discontinued in the treatment group (29% for lumateperone 28 mg and 38% for lumateperone 42 mg) compared to placebo (25%). Of those that discontinued, 7.6% discontinued due to an AE (7.1% with lumateperone 28 mg; 8.1% with lumateperone 42 mg) compared to 2.2 % in the placebo group. The mean time to discontinuation was similar among groups (19.3 days with lumateperone 28 mg; 14.4 days with lumateperone 42 mg; 17.3 days with placebo). The lost-to-follow-up rate was highest for lumateperone 42 mg and more than double the rate seen with lumateperone 28 mg or placebo. The Applicant randomized five patients who did not receive study medication: four withdrew consent and there was one protocol violation. Of the 554 randomized subjects, the Applicant included 515 subjects in the ITT set (lumateperone 28 mg n=172; lumateperone 42 mg n=166; placebo n=177).

Clinical Reviewer Comment: The Applicant notes general adherence to the protocol for screening, randomizing, and determining the population of the ITT set (i.e., completed the baseline measures, received at least one dose of study drug, and completed at least one postbaseline MADRS); see the next section for rates of protocol deviations. Discontinuation (including due to AE) and lost-to-follow-up rates were considerably higher for the lumateperone 42-mg group compared to the other groups. Although the reasons for loss to follow up were not available, the subjects may have discontinued more frequently due to efficacy or tolerability issues at the higher dose.

D. Protocol Violations/Deviations for Study 401-A

The Applicant described protocol deviations for 27% of patients in the lumateperone 42-mg group, 26% of patients in the lumateperone 28-mg group, and for 29% of patients in the placebo group. See Table 8 for the Applicant's categories of protocol deviations by treatment group. The Applicant notes that two of the placebo subjects (subjects (b) (6) and (b) (6)) and received study drug (lumateperone) kits for 2 weeks of the study.

Table 8: Incidence of Patients with Major Protocol Deviations for Study 401-A – ITT Set

	Treatment Group			
Deviation Category	Lumateperone 28 mg N=172 n(%)	Lumateperone 42 mg N=166 n(%)	Placebo N=177 n(%)	Total N=515 n(%)
Patients with at least 1 major deviation	44 (25.6)	45 (27.1)	51 (28.8)	140 (27.2)
Informed consent	1 (0.6)	4 (2.4)	3 (1.7)	8 (1.6)
Eligibility criteria	5 (2.9)	7 (4.2)	10 (5.6)	22 (4.3)
Patients with ≥3 consecutive missed doses of study medication	11 (6.4)	12 (7.2)	6 (3.4)	29 (5.6)
Patients with overall compliance < 80% or > 120% or who took >2 doses of study medication per day	3 (1.7)	4 (2.4)	2 (1.1)	9 (1.7)
Patients dispensed wrong study medication kit[1]	0	0	2 (1.1)	2 (0.4)
Patients who took prohibited concomitant medication	17 (9.9)	11 (6.6)	15 (8.5)	43 (8.3)
Patients with positive UDS results[2]	15 (8.7)	19 (11.4)	26 (14.7)	60 (11.7)

UDS= Urine drug screen
[1]Two placebo subjects received study drug kits of lumateperone for 2 weeks total.
[2]Results excluded cannabis and benzodiazepines
Source: Study 401 CSR, Table 18

Clinical Reviewer Comment: In general, the Applicant's reports of major protocol deviations were similar across treatment groups. The Applicant describes that two placebo subjects received study drug for 2 of the 6 weeks of treatment. It is unlikely that this protocol deviation significantly affected the primary efficacy because the dosing was only for 2 of the 6 weeks, and only two subjects were involved out of 177.

We note that the placebo group had a higher number of positive UDS results compared to lumateperone 28 mg or 42 mg. The Applicant describes that not all tests were repeated, and we do not have quantitative data to help determine if substance use may have affected efficacy results in Study 401-A. Additionally, the Applicant states that they did not consider presence of benzodiazepines or cannabis as a positive UDS. Although zolpidem was a permitted medication during the first 2 weeks of treatment, it is not likely to result in a positive screen for benzodiazepines. Benzodiazepines were used as rescue medications during the trial. The Applicant did not provide a justification for not considering the presence of cannabis as a positive UDS. Therefore, it is not clear whether concomitant use of cannabis or benzodiazepines

influenced the outcome (i.e., whether higher rates of usage in the placebo group affected their results).

E. Table of Demographic Characteristics for Study 401-A

See Table 9. The majority of subjects were white, female, and non-Hispanic/Latino. The distribution of patients across ages, gender, race, and ethnicity was similar across treatment groups.

Table 9: Baseline Demographic Characteristics for Study 401-A (ITT Dataset)

Characteristic	Treatment Group		
	Lumateperone 28 mg (n = 172)	Lumateperone 42 mg (n = 166)	Placebo (n = 177)
Age			
Mean (SD)	41.2 (11.9)	43.0 (11.7)	42.5 (13.2)
Min, Max	18, 69	18, 71	18, 74
≤ 40 years, n (%)	78 (45.3)	69 (41.6)	74 (41.8)
> 40 years, n (%)	94 (54.7)	97 (58.4)	103 (58.2)
Gender, n (%)			
Male	69 (40.1)	66 (39.8)	69 (39.0)
Female	103 (59.9)	100 (60.2)	108 (61.0)
Race, n (%)			
White	95 (55.2)	94 (56.6)	93 (52.5)
Black or African American	73 (42.4)	66 (39.8)	77 (45.2)
Asian	1 (0.6)	2 (1.2)	3 (1.7)
American Indian or Alaska Native	0	2 (1.2)	1 (0.6)
Native Hawaiian or Other Pacific Islander	0	1 (0.6)	1 (0.6)
Multi-race	3 (1.7)	1 (0.6)	1 (0.6)
Not reported	0	0	1 (0.6)
Ethnicity, n (%)			
Hispanic or Latino	15 (8.7)	22 (13.3)	22 (12.4)
Non-Hispanic or Non-Latino	157 (91.3)	144 (86.8)	155 (87.6)

Source: Statistical Reviewer's Table from Applicant's Study 401-A database

Clinical Reviewer Comment: The baseline demographic characteristics suggest that the study population is only somewhat representative of the ethnicities in the U.S. adult population (i.e., 76% White, 13% Black or African American, 5.9% Asian; Source: https://www.census.gov/quickfacts/fact/table/U.S./PST045219, accessed October 15, 2021). Notably, Asian race is poorly represented, thus limiting the interpretation of findings by race subpopulation.

F. Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Approximately 88% of patients were coded as having a bipolar I diagnosis, and the remaining patients were coded as having a diagnosis of bipolar II disorder. The distribution of past-year hospitalization and number of lifetime MDEs was similar across treatment groups. However, the lumateperone 42-mg group had fewer patients with a history of psychiatric hospitalization, and as a group was slightly older at age of first bipolar diagnosis (see Table 10). Baseline MADRS, CGI-BP-S, Q-LES-Q-SF, and SDS scores were generally similar across treatment groups as were the respective subscale scores.

Table 10: Baseline Characteristics Study 401-A, Safety Set

Baseline Characteristic	Treatment Group		
	Lumateperone 28 mg (n = 180)	Lumateperone 42 mg (n = 184)	Placebo (n = 185)
Bipolar disorder diagnosis, Mean (SD)			
Bipolar I	158 (87.8)	162 (88.0)	163 (88.1)
Bipolar II	22 (12.2)	22 (12.0)	22 (11.9)
Age at first diagnosis of bipolar disorder			
Years, Mean (SD)	26.3 (10.51)	29.4 (11.19)	28.2 (11.86)
<22 years old, n, (%)	74 (41.1)	57 (31.0)	72 (38.9)
≥ 22 years old, n, (%)	106 (58.9)	127 (69.0)	113 (61.1)
Number of lifetime MDEs, n (%)			
≥ 1 to ≤ 9 episodes	85 (54.1)	90 (53.9)	80 (47.3)
≥ 10 to ≤ 20 episodes	61 (38.9)	65 (38.9)	71 (42.0)
> 20 episodes	11 (7.0)	12 (7.2)	18 (10.7)
Psychiatric hospitalization, n (%)			
Yes	112 (62.2)	101 (54.9)	117 (63.2)
No	68 (37.8)	83 (45.1)	68 (36.8)
BMI (kg/m^2), Mean (SD)	28.55 (4.493)	28.73 (4.299)	27.85 (4.576)
Lifetime hospitalizations, Mean (SD)	3.0 (2.86)	4.1 (6.92)	3.6 (3.12)
Hospitalized in the past year, n (%)			
Yes	12 (10.7)	12 (11.9)	12 (10.3)
No	100 (89.3)	89 (88.1)	105 (89.7)
MADRS total score			
Mean (SD)	35.8 (6.08)	35.9 (5.79)	34.7 (5.84)
Median (min, max)	36.0 (21, 53)	36.0 (20,50)	35.0 (20, 46)

Baseline Characteristic	Treatment Group		
	Lumateperone 28 mg (n = 180)	Lumateperone 42 mg (n = 184)	Placebo (n = 185)
CGI-BP-S total score, Mean (SD)	11.0 (1.28)	10.9 (1.40)	10.6 (1.24)
CGI-BP-S mania score, Mean (SD)	1.2 (0.47)	1.3 (0.55)	1.3 (0.53)
CGI-BP-S depression score, Mean (SD)	4.9 (0.61)	4.8 (0.63)	4.7 (0.58)
CGI-BP-S overall bipolar illness score, Mean (SD)	4.9 (0.61)	4.8 (0.63)	4.7 (0.58)
SDS total score, Mean (SD)	20.2 (6.22)	20.7 (6.81)	20.4 (5.56)
Q-LES-Q-SF percent score, Mean (SD)	34.2 (13.2)	35.2 (14.5)	37.0 (14.5)

BMI = body mass index; CGI-BP-S = Clinical Global Impression-Bipolar version - Severity; MDE: major depressive episode; max = maximum; min = minimum; MADRS = Montgomery-Åsberg Depression Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form; SDS = Sheehan Disability Scale.
Source: Clinical reviewer modified table from Applicant's Study 401-A CSR, Tables 14.1.3.1.2., 14.1.3.3.2., 14.1.3.4.2.

There were 92% of subjects who reported at least one medical condition at screening. Medical conditions across treatment groups were generally similar. Common medical diagnoses reported at screening (> 10% in all groups) were insomnia, anxiety, hypertension, drug sensitivity, and seasonal allergy (Source, study 401-A CSR, Table 14.1.4).

Clinical Reviewer Comment: The baseline characteristics were similar across groups, including baseline MADRS scores, baseline CGI-BP-S scores (total and sub scores), and the percentage of patients in each treatment group with bipolar I versus bipolar II disorder. Although there were differences in hospitalization history and age of first bipolar diagnosis, the differences did not cluster in one treatment group (i.e., no single treatment group appears to be more severe at baseline, based on these characteristics).

G. Treatment Compliance, Concomitant Medications, and Rescue Medication Use for Study 401-A

Treatment Compliance: The Applicant states that treatment compliance was approximately 97% across all treatment groups.

Prior/Concomitant Medications: Prior medication use was common (49%, 58%, and 53% of patients in the lumateperone 28-mg, lumateperone 42-mg, and placebo groups, respectively) and half of all patients continued taking prior medications during the double-blind treatment period; the most commonly continued prior medications were lisinopril, salbutamol, ibuprofen, omeprazole, amlodipine, and multivitamins.

The incidence of concomitant medication (initiated during the double-blind treatment period) was similar across groups (24% in the lumateperone 28-mg group, 21% in the lumateperone 42-mg group, and 20% in the placebo group). Most concomitant medications were used by two or

fewer patients, with the exception of ibuprofen, which was commonly used (>5% in each group), and hydrocodone/acetaminophen (Vicodin), which was used by three patients in the placebo group (source: Applicant's Study 401 CSR, Tables 14.1.5.1, 14.1.5.2, and 14.1.5.3). The Applicant reports rare use of psychiatric medications during the placebo-controlled phase of the study: four subjects received quetiapine (lumateperone 28 mg, n=2; lumateperone 42 mg, n=1; placebo, n=1); one subject in each lumateperone group received sertraline; one subject in the lumateperone group receive escitalopram; and two subjects received lorazepam (one in the lumateperone 28-mg group and one in the placebo group).

Zolpidem was a permitted concomitant medication during the first 2 weeks. The reported concomitant medication with zolpidem by group was lumateperone 28 mg, n=3; lumateperone 42 mg, n=4; and, placebo, n=5.

Rescue Medications: The use of rescue medications was similar between lumateperone 28 mg (2.8%) and lumateperone 42 mg (2.7%) and slightly higher in the placebo group (3.8%). The rescue medications listed by the Applicant were all benzodiazepines or sedative hypnotics.

Clinical Reviewer Comment: During the placebo-controlled phase of the study, the Applicant describes concomitant use of psychiatric medications (including zolpidem), but overall the numbers were low and similar across treatment groups and therefore is unlikely to have affected the overall efficacy results. The Applicant did not remove patients from the ITT set based on concomitant medication use or other protocol deviations.

H. Efficacy Results – Primary Endpoint for Study 401-A

The primary efficacy endpoint for this study was not met, see Table 11. The reduction from baseline in MADRS total score at Day 43 was not statistically significantly different between placebo and lumateperone 28-mg or 42-mg. Lumateperone 28 mg was numerically worse than placebo.

Table 11: Primary Efficacy Endpoint-Change from Baseline to Day 43 in MADRS Total Score—MMRM (ITT Set)

Statistic	Lumateperone 28 mg (n=172)	Lumateperone 42 mg (n=166)	Placebo (n=177)
n	172	166	177
Baseline, mean (SD)	35.9 (6.08)	35.9 (5.92)	34.7 (5.84)
Change from baseline to Day 43			
LS Mean (SE)[a]	-18.9 (1.11)	-20.7 (1.16)	-19.7 (1.11)
LS Mean Difference	0.9	-1.0	—
95% CI	(-1.83, 3.53)	(-3.73, 1.79)	—
Unadjusted p-value[b]	0.533	0.489	—

MADRS = Montgomery-Åsberg Depression Rating Scale; CI=confidence interval; LS=least squares; max=maximum; min=minimum; SD=standard deviation; SEM=standard error of the mean
[a] From a mixed-effects model for repeated measures analysis over all postbaseline visits, with the change from baseline in MADRS as the outcome, study visit, the bipolar disorder stratification variable, baseline MADRS total score, site (or pooled site), baseline MADRS total score-by-study visit interaction, treatment (lumateperone 28 mg, lumateperone 42 mg, placebo), and treatment-by-study visit interaction as covariates or factors. An unstructured covariance matrix was used to model the correlation among repeated measurements within patient.
[b]The unadjusted p-values were raw p-values, not adusted for multiple dose groups nor the interim analysis.
Source: Applicant's study 401-A CSR, Table 24 and Table 14.2.1.1

An unblinded interim analysis was performed on July 31, 2018 by an independent statistician and the results were presented to an independent Data Monitoring Committee. The interim analysis was conducted based on a total of 378 ITT patients. The results of this interim analysis showed no superior efficacy in either lumateperone dose at a significance level of 0.0216. Also, the interim analysis did not introduce any change to the originally planned sample size.

The Applicant examined efficacy by subgroup of bipolar I versus bipolar II disorder; results remained non-significant for lumateperone 28 mg or 42 mg compared to placebo.

Statistical Reviewer Comment: We could not verify the Applicant's adjusted p-values adjusting for the interim analysis and the multiple dose arms. The Applicant's unadjusted two-sided p-value for the 28-mg dose did not account for directional error because 28 mg did worse than placebo.

Clinical Reviewer Comment: Study 401-A cannot be used to support efficacy because the primary endpoint was not significant for lumateperone compared to placebo at either 28 mg or 42 mg. We note there was no general trend suggesting efficacy. We did not consider additional endpoints or subgroups because the Applicant did not establish efficacy on the primary endpoint. We note that the placebo response for Study 401-A was high compared to other studies with lumateperone; see Section 8.1.4 for a review of effectiveness across bipolar depression trials.

I. Efficacy Results – Secondary and other relevant endpoints for Study 401-A
As described above, no prespecified secondary endpoint was agreed upon; given that the primary endpoint was negative, there are no other relevant endpoints to discuss.

J. Data Quality and Integrity

See Section 4.1 for information regarding the OSI inspection of this trial. The Analysis Data Model (ADaM) and Study data Tabulation Model (SDTM) datasets were intact and evaluable using JMP programs for the clinical team and for evaluation by our Biometrics team.

K. Dose/Dose Response for Study 401-A

Study 401-A did not demonstrate efficacy at the primary endpoint for lumateperone 28 mg or 42 mg. There was no apparent dose response for efficacy on the primary endpoint (see Table 11). Numerically, the higher dose (lumateperone 42 mg) showed a greater change from baseline than the lower dose (lumateperone 28 mg), which may point towards potential dose response. However, we are unable to draw conclusions because the primary endpoint was not significant.

L. Durability of Response for Study 401-A

Study 401-A did not demonstrate efficacy at the primary endpoint so we could not fully assess the durability of response with this study.

M. Persistence of Effect for Study 401-A

Study 401-A did not demonstrate efficacy at the primary endpoint so we could not fully assess the persistence of effect with this study.

N. Additional Analyses Conducted on the Individual Trial

To explore reasons for lack of efficacy in this study, the Applicant conducted additional subgroup analyses comparing efficacy in subjects who continued on to Part B, the extension study, to those who opted not to continue onto Part B. We reviewed these data for each dose. Only one group separated from placebo: patients who enrolled in part B, lumateperone 42 mg.

Clinical Reviewer Comment: The Division considers study 401-A to be a negative trial.

8.1.2. Study 402 (Adjunctive)

Study Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Assess the Efficacy and Safety of ITI-007 Adjunctive to Lithium or Valproate in the Treatment of Patients with Major Depressive Episodes Associated with Bipolar I or Bipolar II Disorder (Bipolar Depression)

8.1.2.1. Trial Design for Study 402

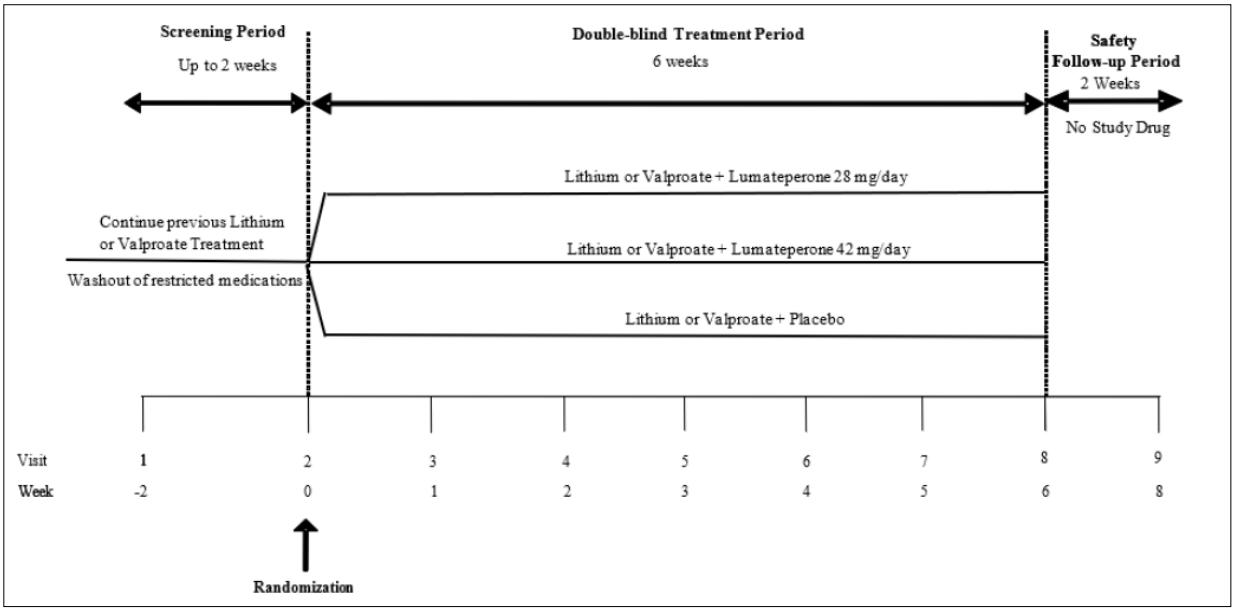
A. Basic Study Design for Study 402

Study 402 was a 6-week, phase 3, fixed-dose, randomized, double-blind, placebo-controlled, multi-center study comparing the efficacy of lumateperone 42 mg and lumateperone 28 mg, adjunctive to treatment with lithium or valproate, to placebo. All patients had bipolar depression with an inadequate response to their depression symptoms and were taking one of

the mood stabilizers lithium or valproate prior to enrollment (see Key Inclusion/Exclusion Criteria for Study 402, below). The study design, including duration, is similar to other programs for depressive episode as adjunctive therapy with lithium or valproate.

Study 402 had three phases: A 2-week screening period, a 6-week double-blind treatment period, and a 2-week safety follow-up period. After washout of prior excluded medications, patients were randomized in a 1:1:1 ratio to either lumateperone 28 mg, lumateperone 42 mg, or placebo (with stratification by baseline lithium or valproate treatment and bipolar I or II diagnosis). Study 402 had three phases: A 2-week screening period, a 6-week double-blind treatment period, and a 2-week safety follow-up period (see Figure 5).

Figure 5: Design Schematic for Study 402



Source: Applicant's information request submitted to FDA on September 9, 2021.

B. Trial Location for Study 402

There were 89 study centers: United States (46), Bulgaria (15), Russian Federation (13), Serbia (7), and Ukraine (8). Fifty-two percent of the study sites were U.S.-based and 48% were in non-U.S. locations which raises concerns about the applicability of the results to the U.S. population.

C. Choice of Control Group for Study 402

The Applicant utilized a placebo control group.

D. Diagnostic Criteria for Study 402

The diagnostic criteria used by the Applicant were based on instruments commonly used in clinical trials to determine diagnosis, symptom severity, and level of functioning. For diagnosis of bipolar disorder, the Applicant used the DSM-5 criteria for bipolar I disorder or bipolar II

disorder as confirmed by the Investigator or Applicant-approved expert site-based rater by a SCID-5-CT or by the Mini International Neuropsychiatric Interview (MINI; non-U.S. sites only).

E. Key Inclusion/Exclusion Criteria for Study 402

Key inclusion criteria include: age between 18 and 75 years; diagnostic criteria as described above; and, patients met all of the following:

1) Onset of current MDE was at least within 2 weeks but not more than 6 months prior to screening

2) At least moderate severity, measured by MADRS total score ≥ 20 and corresponding to a CGI-BP-S score of ≥ 4 at screening and baseline

3) Verification of significant distress or impairment due to the current MDE

4) Lifetime history of one or more manic, mixed, or hypomanic episode

5) YMRS total score of ≤ 12, to assess manic symptoms

6) A minimum of 28 days of treatment with either lithium (and 0.4 to 1.5 mEq/L blood level at screening) or valproate (minimum 25 μg/mL blood level at screening) and inadequate therapeutic response of depressive symptoms (confirmed by the treating health care provider or other reliable source). A re-test of lithium or valproate levels was not permitted; any patient who did not meet either of the two requirements was to be considered screen-failed.

The diagnostic criteria appear consistent with the Applicant's aim to restrict the population to bipolar depression.

Key exclusion criteria included:

1) Experiencing a decrease in the rater administered MADRS total score of ≥25% between screening and baseline visits

2) Significant risk of suicidal behavior at screening

3) Comorbid psychiatric disorders (schizophrenia, psychotic disorder, psychosis not due to bipolar disorder; anxiety disorders, eating disorders, primary obsessive-compulsive disorder, personality disorder, moderate to severe substance use disorder; other psychiatric conditions of treatment focus)

4) Hospitalization for mania within 30 days or considered a rapid cycler or treatment-resistant)

5) Ongoing psychotherapy

6) Other specified medical conditions (e.g., neurological, cardiovascular, or endocrine disorders) or abnormal laboratory, electrocardiographic, or vital sign values outside of pre-specified parameters

7) Pregnant or breastfeeding women

8) Use of prohibited medications.

The eligibility criteria appear consistent with the Applicant's aim to restrict the population to bipolar depression and limit confounders.

F. Dose Selection for Study 402

Similar to Study 401-A, Study 402 had two fixed doses: lumateperone 28 mg and 42 mg. The Applicant states that those two lumateperone doses, as adjunctive therapy with the mood stabilizers, lithium or valproate, were selected to deliver full occupancy of the cortical 5-HT_{2A} receptors (>85% occupancy). The study drug, ITI-007, was supplied as overencapsulated tablets.

G. Study Treatments for Study 402

Patients received lumateperone 28 mg, lumateperone 42 mg, or placebo orally once daily, adjunctive to ongoing lithium or valproate treatment for bipolar disorder. Patients were instructed to self-administer the study drug at night at approximately the same time each day whenever possible.

H. Assignment to Treatment for Study 402

Patients were randomly assigned to one of the following groups: lumateperone 28 mg, lumateperone 42 mg, or placebo (as adjunct to lithium or valproate). Unblinded biostatistics personnel used SAS to generate a permuted block randomization schedule (block size not specified), which was stratified by diagnosis of bipolar I or bipolar II.

I. Blinding for Study 402

Patients received a unique randomization number using an interactive web response system. Investigators were blinded to the patients' randomization outcome unless there was a medical emergency.

J. Dose Modification, Dose Discontinuation for Study 402

The Applicant stated that previous studies had no evidence of a need for drug titration; therefore, the Applicant employed a fixed-dose design. The dose could not be titrated or tapered.

K. Administrative Structure for Study 402

The Applicant listed all clinical study vendors, including personnel responsible for study

oversight, statistical analyses, and CSR development. All of the listed vendors and primary Applicant personnel are located in the United States, except the (b) (4) vendor (b) (4) located in (b) (4) (see Table 6-1 and 6-2 from the Study 402 CSR for details).

L. Procedures and Schedule for Study 402
See the Appendices for the Applicant's schedule of events for Study 402.

M. Dietary Restrictions/Instructions for Study 402
Patients were instructed to self-administer their study medication around the same time each evening. The study medication could be administered with or without food.

N. Concurrent Medications for Study 402
The Applicant required a wash-out of psychotropic drugs prior to study start. Patients were not permitted to start new psychotropic drugs during the study. Prohibited drugs include cannabis, alcohol, 5-HT_{2A}-receptor antagonist or inverse agonist; or any strong or moderate cytochrome P450 3A4 inhibitor or inducer. The exceptions were zolpidem, zolpidem CR, and lorazepam, which were permitted for no more than three times per week and were allowed only during the screening period and within the first 2 weeks of the double-blind treatment period. Comparatively, Study 401-A did not permit the use of lorazepam. The Applicant monitored for and recorded all concomitant medications during the study.

O. Treatment Compliance for Study 402
The Applicant describes using written instructions and tablet counts to monitor treatment compliance. The Applicant documented irregularities and discussed medication adherence with patients. Any patient who missed two doses of study medication per week in any 2 weeks of the study treatment period or who missed three or more doses of study medication in any single week were to be considered for early discontinuation.

P. Rescue Medication for Study 402
The Applicant notes that any concomitant medication deemed necessary for the welfare of the patient during the study could be given at the discretion of the Investigator.

Q. Subject Completion, Discontinuation, or Withdrawal for Study 402
The Applicant defined treatment period completers as subjects who completed the 6-week On-Treatment Period and procedures ("study completers" also completed the End-of-Study assessments on Study Day 57 (±2) or directly rolled over to Part B).

The Applicant determined discontinuation as premature when a patient who signed the ICF ceased participation in the study, regardless of circumstances, before the completion of all study visits and procedures (e.g., noncompliance, pregnancy, withdrawal of consent). Patients who withdrew prematurely would be seen for an early termination visit (within 1 week of early

termination, when possible) and would be asked to return to the clinic for a safety follow-up visit 2 weeks following withdrawal.

R. Study Endpoints for Study 402

The primary endpoint was change from Baseline to Day 43 in MADRS total score, which is the same primary endpoint as Study 401-A and 404. The secondary endpoint adjusted for multiplicity was the change from Baseline to Day 43 in CGI-BP-S depression score. A previous development program for adjunctive treatment of bipolar depression used these same primary and secondary endpoints.

S. Statistical Analysis Plan for Study 402

The treatment effect on the primary efficacy endpoint of change from Baseline to Day 43 in MADRS total score was evaluated using a mixed-effect model repeated measures (MMRM) method. The model included the change from Baseline at each pre-specified time point in the rater-administered MADRS total score as the response variable; visit, treatment group, pooled site, and the stratification variables (first-line treatment (lithium or valproate) and bipolar disorder type at Screening (I or II)), and the interaction term for treatment group-by-visit as fixed effects; and the baseline MADRS total score and the interaction term of baseline MADRS-by-visit as covariates. An unstructured covariance matrix was used to model the correlation among repeated measurements within patient.

The key secondary efficacy endpoint was change from Baseline to Day 43 in CGI-BP-S depression score. The analysis of the change from Baseline in CGI-BP-S depression score at Day 43 was evaluated using the MMRM model similar to the one for the primary efficacy endpoint with the difference of including the baseline CGI-BP-S depression score as the covariate variable instead of the baseline MADRS total score. A prespecified, fixed-sequence (hierarchical) gatekeeping procedure was used to control the overall type I error rate.

The primary and key secondary efficacy endpoints were tested in the following order:

1) Lumateperone 42 mg versus placebo comparison of change from baseline in MADRS total score at Day 43

2) Lumateperone 42 mg versus placebo comparison of change from baseline in CGI-BP-S Depression score at Day 43

3) Lumateperone 28 mg versus placebo comparison of change from baseline in MADRS total score at Day 43

4) Lumateperone 28 mg versus placebo comparison of change from baseline in CGI-BP-S Depression score at Day 43

All tests were performed at the 0.05 level. Once one hypothesis failed to achieve statistical

significance, all subsequent tests had their p-values reported as nominal significance levels.

The blinded sample size recalculation was performed after approximately 52% of the desired number of patients had been randomized and completed up to Day 43 of study treatment. The Applicant prespecified that sample size would be recalculated based on whether the estimated pooled SD from all available subjects at sample size re-assessment was considerably larger than the assumed pooled standard deviation in the sample size calculation (SD=7.5).

Sensitivity analyses of the primary efficacy endpoint were performed using the pattern mixture models (PMM) approach. Spaghetti plots of the primary endpoint for patients who discontinued versus completers were presented by reason of discontinuations to inform on imputations of the potential plausible values of the missing data in the PMM. Additional PMM sensitivity analysis was also performed and reported based on various assumptions of the missing data.

Exploratory subgroup analyses were also conducted in primary endpoint on the ITT.

T. Protocol Amendments for Study 402
Significant amendments included changing the statistical plan to adjust the secondary endpoint of change in CGI-BP-S-Depression score for multiplicity (changing it to a prespecified secondary efficacy endpoint).

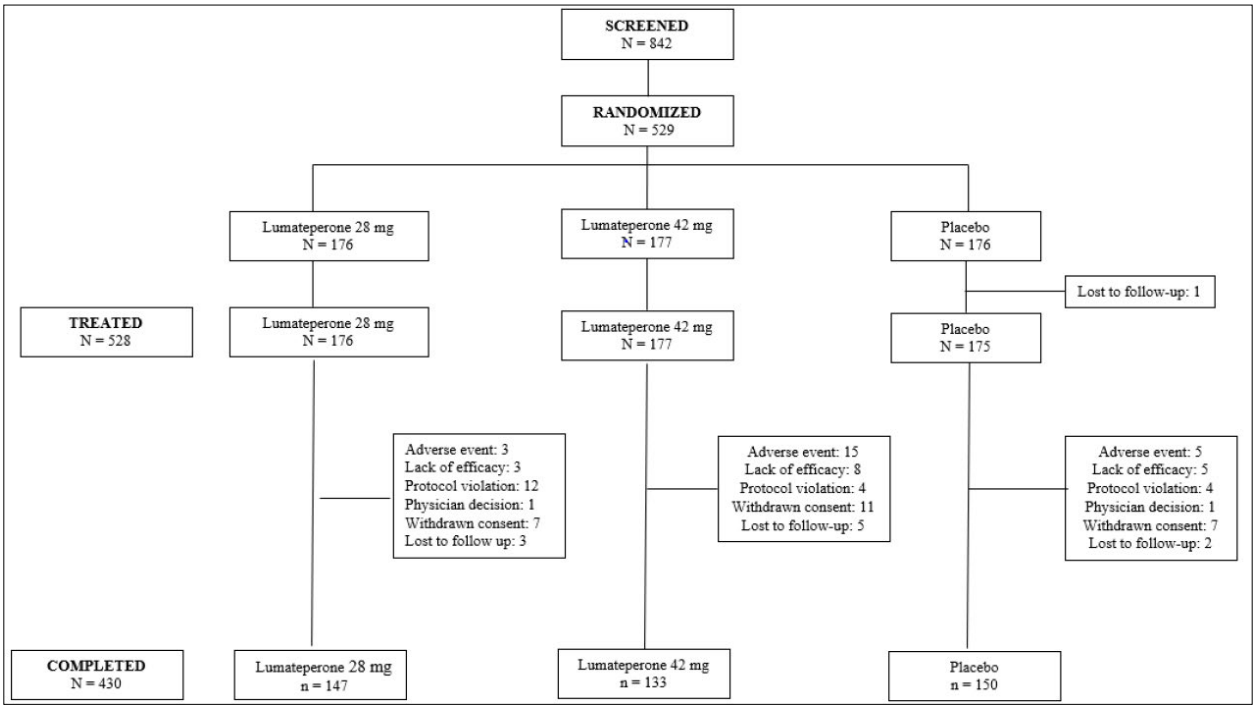
8.1.2.2. Study Results for Study 402

A. Compliance with Good Clinical Practices for Study 402:
The Applicant states that they conducted Study 402 in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that this clinical study complied with the ICH Guidance on General Considerations for Clinical Trials (ICH-E8; 62 FR 66113, December 17, 1997) and GCP (ICH-E6; 62 FR 25692, March 2018), as well as CFR Part 312. The Applicant states that the study protocol, ICF, information sheet advertisements, and amendments were approved by the IRBs/IECs at the study centers in conformance with 21 CFR part 56.

B. Financial Disclosure
See Section 0.

C. Patient Disposition for Study 402
The Applicant states that 529 patients were randomized to lumateperone 28 mg (176 patients), lumateperone 42 mg (177 patients), and to placebo (176 patients). Approximately 81% of patients completed the double-blind treatment. See Figure 5 for the disposition of patients.

Figure 6: Patient Disposition Study 402



Source: Applicant's study 402 CSR Figure 10-1.

D. Protocol Violations/Deviations for Study 402

A deviation from the protocol was defined as an unintended or unanticipated departure from the planned procedures or processes and that a significant deviation occured when there was nonadherence to the protocol by the patient or Investigator that resulted in a significant, additional risk to the patient (e.g., nonadherence to the eligibility criteria). The Applicant prespecified that deviations would lead to the patient being withdrawn from the study and that they would document deviations and inform their IRB.

E. Demographic Characteristics for Study 402

See Table 12 for the demographic characteristics for Study 402.

Table 12: Baseline Demographic Characteristics for Study 402

Disposition (All Subjects Enrolled Set)			
Number screened, n	842		
	Lumateperone 28 mg	Lumateperone 42 mg	Placebo
Number randomized, n	176	177	176
Number treated, n	147 (83.5)	133 (75.1)	150 (85.2)
Number completed, n (%)	29 (16.5)	44 (24.9)	25 (14.2)
Number discontinued, n (%)	3 (1.7)	15 (8.5)	5 (2.8)
Adverse event	3 (1.7)	8 (4.5)	5 (2.8)
Lack of efficacy	3 (1.7)	5 (2.8)	2 (1.1)
Protocol violation	12 (6.8)	4 (2.3)	4 (2.3)
Physician decision	1 (0.6)	0	1 (0.6)
Withdrawal of consent	7 (4.0)	11 (6.2)	7 (4.0)
Other	0	1 (0.6)	1 (0.6)
Demographics and Baseline Characteristics (ITT Set)			
	Lumateperone 28 mg (n=171)	Lumateperone 42 mg (n=174)	Placebo (n=174)
Gender, n (%)			
Male	74 (43.3)	67 (38.5)	76 (43.7)
Female	97 (56.7)	107 (61.5)	98 (56.3)
Age, mean (SD)	43.99 (13.60)	44.60 (12.56)	45.14 (12.97)
Race, n (%)			
White	148 (86.6)	155 (89.1)	156 (89.7)
Black or African American	22 (12.9)	18 (10.4)	14 (8.1)
Asian	0	0	3 (1.7)
Other	0	0	1 (0.6)
Multi-race	1 (0.6)	1 (0.6)	0
Ethnicity, n (%)			
Hispanic or Latino	10 (5.9)	13 (7.5)	10 (5.8)
Non-Hispanic or Non-Latino	159 (93.0)	161 (92.5)	164 (94.3)
Not reported	1 (0.6)	0	0
Unknown	1 (0.6)	0	0

Source: Disposition (All Subjects Enrolled Set) was Applicant's Table 10-1. Demographics and Baseline Characteristics (ITT Set) was calculated by statistical reviewer.

Clinical Reviewer Comment: The baseline demographics were generally consistent across treatment groups and consistent with Study 401-A, which was conducted only in the United States. Similar to the other phase 3 studies, individuals identifying as non-Hispanic and White were over-represented and Asian race was poorly represented, thus limiting the interpretability

of subgroup efficacy analyses by race.

F. Other Baseline Characteristics for Study 402

The Applicant states that 62 to 67% of patients reported medical history conditions at screening. The most common medical history conditions were hypertension (10%, 11%, 13%) and insomnia (12%, 11%, 9.7%) in the lumateperone 28-mg group, lumateperone 42-mg group, and placebo group, respectively. The most common prior medications (≥ 10% in any treatment group) were quetiapine (12% in the lumateperone 28-mg group, 8.5% in the lumateperone 42-mg group, and 11% in the placebo group) and escitalopram (7.4% in the lumateperone 28- mg group, 9.6% in the lumateperone 42-mg group, and 10.9% in the placebo group).

See Table 13 for select baseline assessment characteristics by group.

Table 13: Selected Baseline Assessments – Study 402 – Safety Analysis Set

Baseline Assessment Characteristic	Treatment Group		
	Lumateperone 28 mg (n=176)	Lumateperone 42 mg (n=177)	Placebo (n=175)
Bipolar disorder diagnosis, Mean (SD)			
Bipolar I	146 (83.0)	148 (83.6)	146 (83.4)
Bipolar II	30 (17.0)	29 (16.4)	29 (16.6)
Concomitant lithium or valproate therapy, n (%)			
Lithium	50 (28.4)	51 (28.8)	50 (28.6)
Valproate	126 (71.6)	126 (71.2)	125 (71.4)
Age at first diagnosis of bipolar disorder			
Years, Mean (SD)	32.4 (11.39)	32.3 (11.40)	32.1 (11.66)
<22 years old, n (%)	32 (18.2)	32 (18.1)	41 (23.4)
≥ 22 years old, n (%)	144 (81.8)	145 (81.9)	134 (76.6)
Number of lifetime MDEs, n (%)			
≥ 1 to ≤ 9 episodes	145 (87.3)	140 (80.5)	143 (85.1)
≥ 10 to ≤ 20 episodes	18 (10.8)	28 (16.1)	22 (13.1)
> 20 episodes	3 (1.8)	6 (3.4)	3 (1.8)
Psychiatric hospitalization, n (%)			
Yes	115 (65.3)	131 (74.0)	118 (67.4)
No	61 (34.7)	46 (26.0)	57 (32.6)
BMI (kg/m^2), Mean (SD)	26.03 (4.327)	26.95 (4.197)	26.54 (4.139)
Lifetime hospitalizations, Mean (SD)	3.3 (3.33)	3.9 (3.44)	3.8 (3.65)
Hospitalized in the past year, n (%)			
Yes	27 (23.5)	34 (26.0)	22 (18.6)
No	88 (76.5)	97 (74.0)	96 (81.4)

Baseline Assessment Characteristic	Treatment Group		
	Lumateperone 28 mg (n=176)	Lumateperone 42 mg (n=177)	Placebo (n=175)
MADRS total score			
Mean (SD)	32.5 (5.55)	32.3 (4.96)	32.2 (5.23)
Median (min, max)	32.0 (20, 51)	32.0 (24, 46)	32.0 (22, 49)
CGI-BP-S mania score			
CGI-BP-S mania score, Mean (SD)	1.1 (0.26)	1.1 (0.38)	1.1 (0.29)
CGI-BP-S depression score, Mean (SD)	4.7 (0.56)	4.7 (0.59)	4.6 (0.54)
CGI-BP-S overall bipolar illness score, Mean (SD)	4.7 (0.56)	4.7 (0.59)	4.6 (0.54)
SDS total score, Mean (SD)	22.2 (4.76)	21.2 (7.42)	20.5 (7.26)
Q-LES-Q-SF percent score, Mean (SD)	36.30 (12.02)	22.7 (18.4)	17.4 (16.6)
WHO-5 Well-being Index percent score, Mean (SD)	19.0 (16.1)	22.7 (18.4)	17.4 (16.6)

CGI-BP-S = Clinical Global Impression-Bipolar version - Severity; MADRS = Montgomery-Åsberg Depression Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form.
Source: Modified from Study 402 CSR, Table 14.1.3.1.2, safety analysis set

Clinical Reviewer Comment: The baseline characteristics were generally similar across treatment groups. I noted that some baseline characteristics were highest for lumateperone 42 mg (e.g., higher number of lifetime episodes, past year hospitalizations) possibly reflecting a more chronic or severe history of illness in the lumateperone 42-mg group.

G. Treatment Compliance, Concomitant Medications, and Rescue Medication Use for Study 402:

Treatment compliance: The Applicant reported that treatment compliance was 99.5% across all treatment groups.

Prior Medications: The most common prior medications (≥ 10% in any treatment group) were quetiapine (12% in the lumateperone 28 mg group, 8.5% in the lumateperone 42 mg group, and 11% in the placebo group) and escitalopram (7.4% in the lumateperone 28 mg group, 9.6% in the lumateperone 42 mg group, and 11% in the placebo group).

Concomitant Medications: Concomitant medication use was similar across groups (lumateperone 28 mg (12%), lumateperone 42 mg (10%), and placebo (13%)). The most common concomitant medication was ibuprofen (taken by six patients (3.4%) in the

lumateperone 28-mg group and four patients (2.3%) in the placebo group), followed by levothyroxine, lisinopril, atorvastatin, acetylsalicylic acid, salbutamol, and levonorgestrel.

Zolpidem was permitted during the first 2 weeks of the treatment period. The Applicant reported few uses of concomitant sedative medications (e.g., four or fewer patients in the lumateperone groups and six patients in the placebo group). Few patients endorsed concomitant lorazepam: four in the lumateperone 28-mg group, one in the lumateperone 42-mg group, and three in the placebo group.

The concomitant use of lithium or valproate therapy was similar across treatment groups (see Table 14 for details, including blood levels of lithium and valproate at the end of treatment assessment).

Table 14: Concomitant Lithium and Valproate Concentrations on End of Treatment

Concentration	Treatment Group		
	Lumateperone 28 mg (n = 176)	Lumateperone 42 mg (n = 177)	Placebo (n = 175)
Lithium, n (%)	50 (28.6)	51 (28.8)	50 (28.6)
mEQ/L, Mean (SD)	0.56 (0.283)	0.65 (0.267)	0.62 (0.330)
Valproate, n (%)	126 (71.4)	126 (71.2)	125 (71.4)
µg/mL, Mean (SD)	60.78 (26.375)	62.26 (26.682)	62.37 (28.164)

Source: Applicant's study 402 CSR, Table 11-6.

Rescue medication use: For Study 402, rescue medication use was more common among individuals in the placebo group (4.0%) compared to lumateperone 28 mg (5.1%) and lumateperone 42 mg (2.3%). The only rescue medications listed by the Applicant were zolpidem for insomnia (used by two patients in the placebo group and three patients in the lumateperone group) and benzodiazepines (used by five placebo patients, seven patients receiving lumateperone 28 mg, and four patients receiving lumateperone 42 mg source: Applicant's response to information request dated October 28, 2021, Table B1.2).

Clinical Reviewer Comment: The rate of lithium and valproate use was similar across groups due to stratification during randomization. The blood levels of lithium and valproate at the end of treatment were also highly similar; therefore the effect of lithium or valproate was likely similar across groups. The Applicant permitted sedative-hypnotics the first 2 treatment weeks, but the use of sedative-hypnotics was limited and similar across groups and likely did not affect the primary efficacy endpoint. Few subjects used rescue medications, but use was higher in the placebo group and lumateperone 28-mg group compared to the lumateperone 42-mg group, possibly suggesting greater efficacy in the lumateperone 42-mg group (i.e., less need for rescue medication in the lumateperone 42-mg group compared to other treatment arms).

H. Efficacy Results – Primary Endpoint for Study 402

Lumateperone 42 mg as adjunctive therapy to lithium or valproate showed significant improvement in depression symptoms versus placebo based on the primary endpoint of change from Baseline to Day 43 in MADRS total score (p = 0.0206). Lumateperone 28 mg showed a trend for improvement in MADRS total score versus placebo at Day 43 that did not reach statistical significance (p = 0.0994); see Table 15.

Table 15: Primary Efficacy Endpoint for Study 402-Change from Baseline to Day 43 in MADRS Total Score—MMRM[a] (ITT Set)

Statistic	Lumateperone 28 mg (n = 171)	Lumateperone 42 mg (n = 174)	Placebo (n = 174)
Baseline, mean (SD)	32.3 (5.54)	32.2 (4.98)	32.1 (5.21)
Change from baseline to Day 43			
LS Mean (SE)	-16.2 (0.79)	-16.9 (0.81)	-14.5 (0.79)
LS Mean Difference (SE)	-1.7 (1.01)	-2.4 (1.03)	—
95% CI	(-3.65, 0.32)	(-4.42, -0.37)	—
p-value	0.0994	0.0206	—

MADRS = Montgomery-Åsberg Depression Rating Scale; CI=confidence interval; LS=least squares; max=maximum; min=minimum; SD=standard deviation; SEM=standard error of the mean

[a] From a mixed-effects model for repeated measures analysis over all postbaseline visits, with the change from baseline in MADRS total score as the outcome, study visit, the bipolar disorder stratification variable, baseline MADRS total score as a covariate, site (or pooled site), baseline MADRS total score-by-study visit interaction, treatment (lumateperone 28 mg, lumateperone 42 mg, placebo), and treatment-by-study visit interaction. An unstructured covariance matrix was used to model the correlation among repeated measurements within patient.

Source: Study 402 CSR, Table 11-7, confirmed by statistical reviewer

Clinical Reviewer Comment: On the primary endpoint, lumateperone 28 mg failed to separate from placebo, whereas lumateperone 42 mg was statistically significantly superior to placebo. The negative findings for lumateperone 28 mg are consistent with the original NDA 209500 clinical trials for schizophrenia.

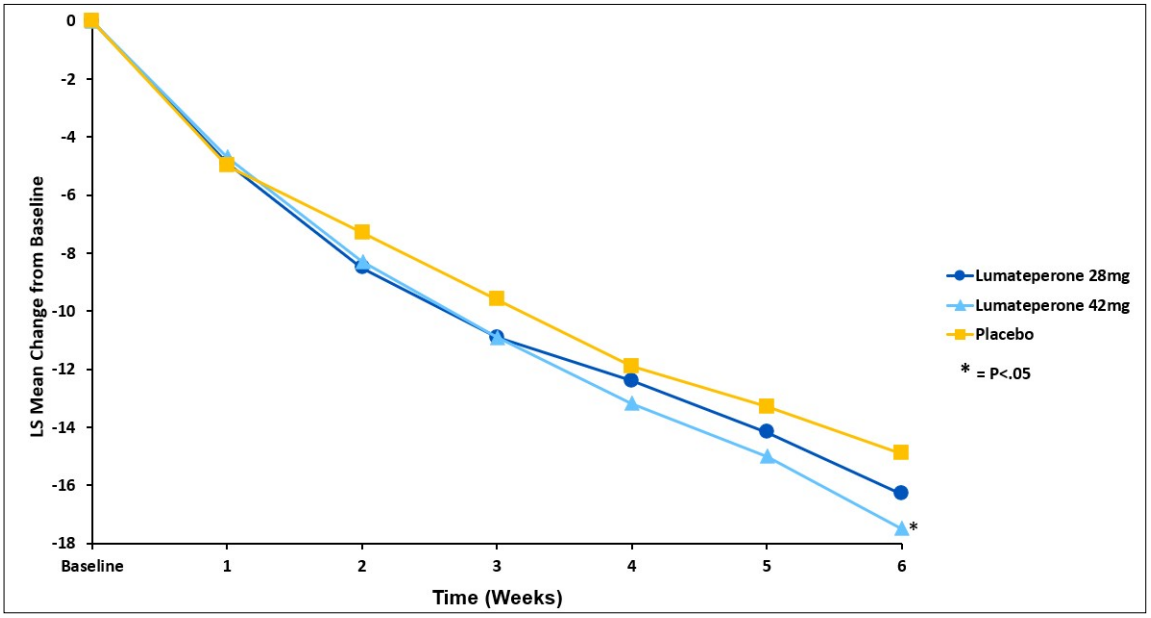
The Applicant's by-visit analysis of change from baseline in MADRS total score did not demonstrate a difference for either dose group at earlier weeks at nominal significance level of 0.05 (see Table 16). Figure 7 displays the mean improvement from Baseline for each treatment group over the 6 weeks. It appears that lumateperone 42 mg may have started separating from placebo at Day 15—although this was not statistically significant.

Table 16: Change from Baseline in MADRS Total Score by Visit for Study 402 - MMRM[a] (ITT Set)

Statistic	Lumateperone 28 mg (n = 171)	Lumateperone 42 mg (n = 174)	Placebo (n = 174)
Baseline, mean (SD)	32.3 (5.54)	32.2 (4.96)	32.1 (5.21)
Change from baseline to:			
Day 8 LS mean (SE)	-5.0 (0.59)	-4.7 (0.59)	-4.9 (0.60)
LSMD (95% CI)	-0.1 (-1.47, 1.27)	0.2 (-1.21, 1.53)	—
p-value	0.8852	0.8211	—
Day 15 LS mean (SE)	-8.6 (0.66)	-8.4 (0.66)	-7.3 (0.67)
LSMD (95% CI)	-1.3 (-2.91, 0.28)	-1.1 (-2.67, 0.54)	—
p-value	0.1057	0.1919	—
Day 22 LS mean (SE)	-10.9 (0.71)	-11.0 (0.72)	-9.5 (0.72)
LSMD (95% CI)	-1.4 (-3.16, 0.38)	-1.5 (-3.25, 0.33)	—
p-value	0.1228	0.1087	—
Day 29 LS mean (SE)	-12.4 (0.74)	-13.0 (0.75)	-11.7 (0.74)
LSMD (95% CI)	-0.7 (-2.55, 1.12)	-1.4 (-3.22, 0.50)	—
p-value	0.4435	0.1524	—
Day 36 LS mean (SE)	-14.2 (0.74)	-15.0 (0.76)	-13.2 (0.75)
LSMD (95% CI)	-1.1 (-2.92, 0.78)	-1.9 (-3.73, 0.03)	—
p-value	0.2561	0.0533	—
Day 43 LS mean (SE)	-16.2 (0.79)	-16.9 (0.81)	-14.5 (0.79)
LSMD (95% CI)	-1.7 (-3.65, 0.32)	-2.4 (-4.42, -0.37)	—
p-value	0.0994	0.0206	—

MADRS = Montgomery-Åsberg Depression Rating Scale; CI=confidence interval; LS=least squares; max=maximum; min=minimum; SD=standard deviation; SEM=standard error of the mean
[a]Same as the primary statistical model
Source: Table 14 2.4.1.1 in CSR, confirmed by statistical reviewer

Figure 7: Change in MADRS Total Score Over Time for Study 402—MMRM (ITT Set)



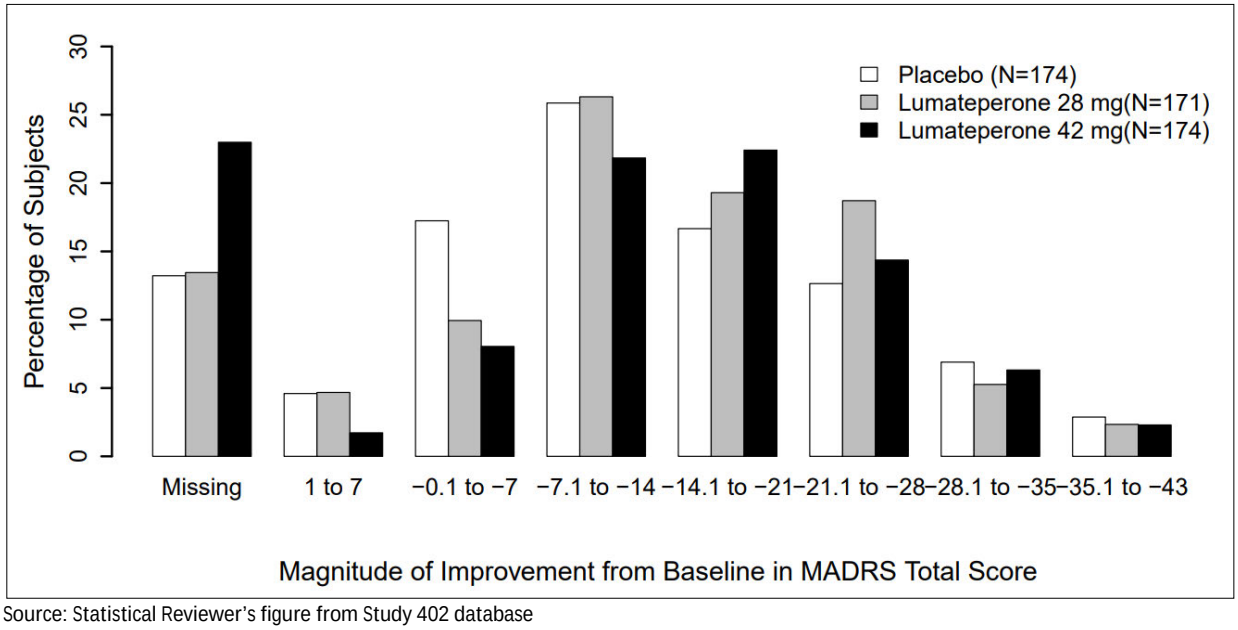
Source: Study 402 CSR, Figure 11-4

The change from Baseline to Day 43 in MADRS total score – the primary efficacy variable – was reviewed in a blinded fashion based on data retrieved on November 19, 2019. The MMRM as specified in the SAP (based on pseudo-treatment assignment using permutation method) was employed to assess the blinded standard deviation of the change from baseline in MADRS total score. The estimated SD obtained based on the interim data was 10.5.

Assuming this SD would stay the same in the final analysis, the study would have 83% statistical power based on the planned 520 patients in total (173 per group) to detect a treatment difference as low as 3.3 units. Based on the same sample size and the estimated interim SD of 10.5, the study had at least 97% power if the true treatment difference is -4.6 units. The originally planned sample size of the study of 520 randomized patients was considered to have adequate statistical power and, therefore, was retained.

Figure 7 shows the percentages of subjects with different magnitudes of improvement on the primary endpoint in the lumateperone 28 mg, lumateperone 42 mg, and placebo groups. A patient could have one of three types of response: symptom improvement (i.e., a lower MADRS Total Score at Day 43 than Baseline), worsening, or dropout of the study. The lumateperone 42-mg group (black bars) had fewer patients with worsening MADRS Total Score or no change in MADRS Total Score compared to placebo (light gray bar) or lumateperone 28 mg (gray bars). However, the lumateperone 42-mg arm had the greatest percentage of dropouts and did not have a greater proportion of patients showing improvement compared to the other groups in most of magnitudes of improvement.

Figure 8: Histogram of the Magnitude of Improvement from Baseline in MADRS Total Score at Day 43, Study 402



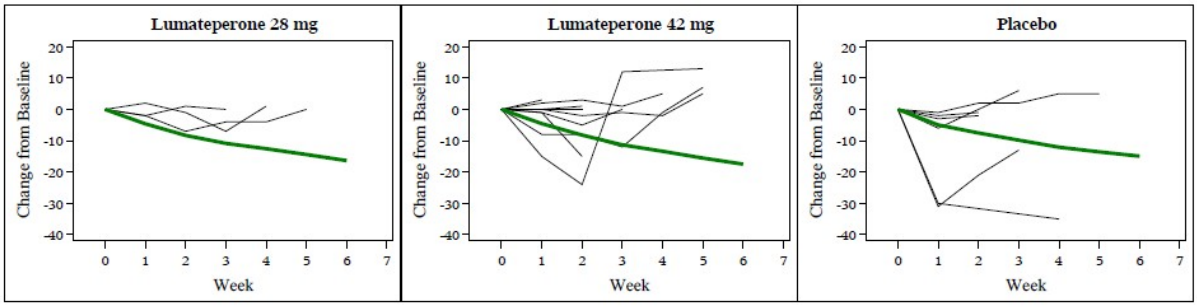
Source: Statistical Reviewer's figure from Study 402 database

Sensitivity Analysis of Primary Efficacy Endpoint for Study 402

The Applicant investigated the patterns of the missing data and their impact on the primary efficacy results based on following spaghetti plots for discontinued patients, as presented below:

Discontinuation due to lack of efficacy: Figure 9 displays the spaghetti plot for each treatment group for the change from Baseline in MADRS total score over time for patients who discontinued treatment due to lack of efficacy versus the mean response for completers. The figure also includes those patients who self-reported lack of efficacy as their reason for withdrawal of their consent. The majority of patients who discontinued based on this lack of efficacy criterion had their efficacy response not improve or worsen before discontinuation and, frequently, to a level worse than the mean response of the completers.

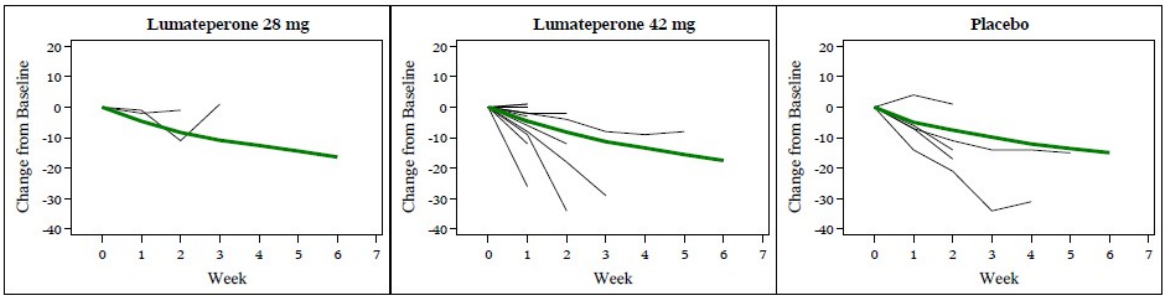
Figure 9: Change from Baseline Over Time in MADRS Total Score: Discontinuations Due to Lack of Efficacy versus All Completers (ITT Set), Study 302[a, b]



[a] Completers are defined as patients with non-missing change from baseline to Day 43 in MADRS total score.
[b] The thick green line is the mean change from baseline in MADRS total score based on Completers. Each thin line is the change from baseline in MADRS total score for individual patient discontinued due to lack of efficacy (including self-reported lack of efficacy).
Source: Study 302 CSR, Figure 11-1

Discontinuation due to AE: Figure 10 presents the spaghetti plot for each treatment group for the change from baseline in MADRS total score over time for patients who discontinued treatment due to an AE versus the mean response for completers. The majority of patients who discontinued due to an AE in the lumateperone 42-mg group had their efficacy response improved before discontinuation at a frequency similar to the mean response of the completers.

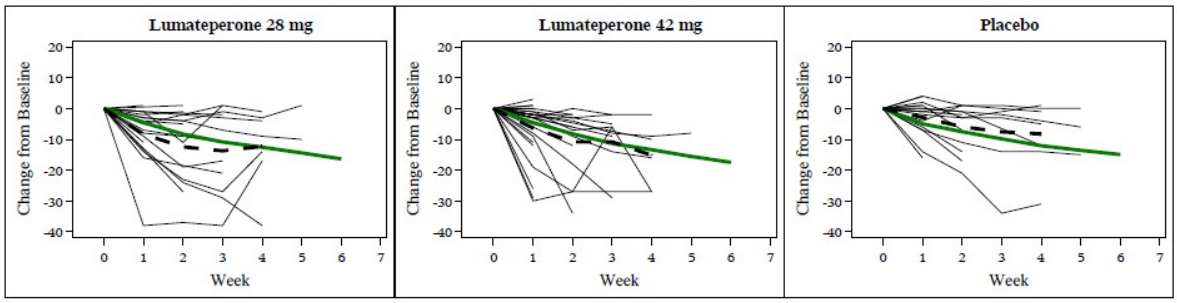
Figure 10: Change from Baseline Over Time in MADRS Total Score: Discontinuations Due to Adverse Events versus All Completers (ITT Set)[a, b]



[a] Completers are defined as patients with non-missing change from baseline to Day 43 in MADRS total score.
[b] The thick green line is the mean change from baseline in MADRS total score based on Completers. Each thin line is the change from baseline in MADRS total score for individual patient discontinued due to AEs.
Source: Study 302 CSR, Figure 11-2

Discontinuation due to any other reason other than lack of efficacy: Figure 11 presents the spaghetti plot for the change from baseline in MADRS total score over time for patients who discontinued treatment due to any reason other than lack of efficacy versus the mean response for completers. The mean response by time point is displayed for those discontinued due to reasons other than lack of efficacy except at Week 5 due to the very few patients with such data. As shown in Figure 11, patients who discontinued due to reasons other than lack of efficacy in the lumateperone 42-mg group had their efficacy response improve before discontinuation at a frequency similar or slightly better than the mean response of the completers. On the other hand, patients in the placebo group who discontinued due to reasons other than lack of efficacy had their efficacy response improved before discontinuation at a frequency lower than the mean response of the completers.

Figure 11: Change from Baseline Over Time in MADRS Total Score: Discontinuations Due to Reasons Other Than Lack of Efficacy versus All Completers (ITT Set)[a, b, c]



[a] Completers are defined as patients with non-missing change from Baseline to Day 43 in MADRS total score.
[b] The thick green line is the mean change from Baseline in MADRS total score based on Completers. Each thin line is the change from Baseline in MADRS total score for individual patient discontinued due to reasons other than lack of efficacy or self-reported lack of efficacy.
[c] The thick dashed lines are the mean change from baseline in MADRS total score based on patients discontinued due to reasons other than lack of efficacy or self-reported lack of efficacy.
Source: Study 402, Figure 11-3

Following the review of the spaghetti plots, the Applicant concluded that results obtained from the primary MMRM analysis are robust with respect to the MAR assumption as supported by the patterns of missing data. That can be observed through the MAR assumption because the missing data patterns does not favor lumateperone 42 mg in the primary MMRM analysis versus placebo as supported by the following two points: nearly equal numbers of patients discontinued due to lack of efficacy in both lumateperone 42-mg group (nine patients) and placebo group (seven patients); and those who discontinued due to reasons other than lack of efficacy appear to be MAR in the lumateperone 42-mg group while the MAR assumption for the missing data in the placebo group appears to consider better responses than would be expected. In addition, the majority of patients who discontinued due to AE in the lumateperone 42-mg group had their efficacy response improved before discontinuation at a frequency similar to the mean response of the completers. These data suggest that the missing patient-level responses likely follow the trajectory of the mean responses of the completers after their last observed response as assumed by MAR in the primary MMRM analysis.

The Applicant compared the change from Baseline to Day 43 in MADRS total score between lumateperone 42 mg and placebo using the PMM sensitivity analyses, which relied on a multiple imputation method for discontinuation based on the reasons for discontinuation (lack of efficacy as missing not at random (MNAR)) and other missing data as MAR in the set of all randomized patients with baseline MADRS total score. This approach was implemented by imputing missing data first under the MAR assumption in each treatment group using multiple imputation and then adding a pre-defined $\Delta 1=0$, 4, 8, 12 to each imputed value in the placebo group and adding a different pre-defined $\Delta 2$ to each imputed value in the active treatment groups, then varying $\Delta 1$ and $\Delta 2$ over an enclosure of a plausible range of values. For each value of $\Delta 1$, the value of $\Delta 2$ was calculated as $\Delta 1 + k2 \times LSMD$, where k2=0, 0.2, 0.4, 0.6, 0.8 and 1, and LSMD are the least squares mean differences between the active treatment group and placebo based on the primary MMRM primary analysis. It is important to note that if k2=0, then $\Delta 2=\Delta 1$, and if k2=1, then $\Delta 2=\Delta 1+$ LSMD; therefore, the considered range for $\Delta 2$ is from $\Delta 1$ to $\Delta 1+$ LSMD. A total of 24 combinations of shifts were added to the imputed values. The applicant concluded that the results of these analyses supported the robustness of the statistically significant improvement demonstrated by lumateperone 42 mg compared with placebo in change from Baseline to Day 43 in MADRS total score (see Table 17).

Table 17: Change from Baseline to Day 43 in MADRS Total Score, Pattern-Mixture Model Analysis—MMRM (Sensitivity Set), Study 402

Lumateperone 28 mg (n=176)				Lumateperone 42 mg (n=177)				Placebo (n=175)	
Shift	LS Mean	LSMD (95% CI)	p-value	Shift	LS Mean	LSMD (95% CI)	p-value	Shift	LS Mean
Common Shift to Missing Data Due to LOE in All Treatment Groups									
0	-16.20	-1.55 (-3.550, 0.440)	0.1266	0	-16.95	-2.30 (-4.325, -0.284)	0.0254	0	-14.65
4	-16.13	-1.66 (-3.684, 0.370)	0.1091	4	-16.75	-2.27 (-4.323, -0.218)	0.0302	4	-14.48
8	-16.06	-1.76 (-3.830, 0.312)	0.0960	8	-16.54	-2.24 (-4.331, -0.139)	0.0366	8	-14.30
12	-15.99	-1.86 (-3.986, 0.266)	0.0863	12	-16.33	-2.20 (-4.350, -0.050)	0.0450	12	-14.13
Common Shift (and Additional Shift to Lumateperone Treatment Groups) to Missing Data Due to Drop-Out of LOE in All Treatment Groups									
1.668	-16.18	-1.52 (-3.533, 0.485)	0.1371	2.392	-16.84	-2.18 (-4.217, -0.148)	0.0355	0	-14.65
5.668	-16.11	-1.63 (-3.671, 0.420)	0.1193	6.392	-16.63	-2.15 (-4.218, -0.077)	0.0421	4	-14.48
9.668	-16.04	-1.73 (-3.821, 0.366)	0.1057	10.392	-16.42	-2.11 (-4.230, 0.005)	0.0506	8	-14.31
13.668	-15.96	-1.83 (-3.981, 0.322)	0.0956	14.392	-16.21	-2.08 (-4.253, 0.098)	0.0613	12	-14.14

Source: Study 402, Table 11-10; confirmed by statistical reviewer

The subgroup analyses presented in this section are all exploratory. The main objective of the exploratory subgroup analysis is to assess consistency across subgroups with respect to the primary analysis results. Because of the exploratory purpose of the subgroup analyses in Table 18, those p-values are not presented here. The observed magnitudes of treatment effect do not appear to differ largely from their counterparts in all the subgroups.

Table 18: Subgroup Analysis for Study 402 Primary Endpoint, Change from Baseline to Day 43 in MADRS Total Score—MMRM (ITT Set)

Subgroup	Lumateperone 28 mg (n = 171)	Lumateperone 42 mg (n = 174)	Placebo (n = 174)
Region			
U.S., n	54	55	55
LS Mean (SE)	-16.7 (1.40)	-19.2 (1.46)	-16.5 (1.36)
LSMD (95% CI)	-0.2 (-3.89, 3.48)	-2.7 (-6.46, 1.10)	—
Non-U.S., n	117	119	119
LS Mean (SE)	-15.5 (0.92)	-15.6 (0.94)	-13.5 (0.92)
LSMD (95% CI)	-2.0 (-4.36, 0.45)	-2.1 (-4.50, 0.38)	—
Age group[a]			
Age ≤ 40 years, n	69	59	59
LS Mean	-15.8 (1.21)	-16.1 (1.39)	-14.7 (1.30)
LSMD (95% CI)	-1.1 (-4.48, 2.25)	-1.4 (-4.98, 2.21)	—
Age > 40 years, n	102	115	115
LS Mean (SE)	-16.4 (1.00)	-17.3 (0.96)	-14.5 (0.94)
LSMD (95% CI)	-2.0 (-4.49, 0.53)	-2.9 (-5.30, -0.40)	—
Sex			
Male, n	74	67	76
LS Mean (SE)	-15.8 (1.14)	-17.3 (1.25)	-13.6 (1.13)
LSMD (95% CI)	-2.3 (-5.30, 0.77)	-3.8 (-6.91, -0.61)	—
Female, n	97	107	98
LS Mean (SE)	-16.6 (1.03)	-16.8 (1.01)	-15.4 (1.02)
LSMD (95% CI)	-1.2 (-3.81, 1.51)	-1.4 (-4.01, 1.31)	—
Race			
White, n	149	156	156
LS Mean (SE)	-16.7 (0.84)	-17.0 (0.85)	-15.2 (0.83)
LSMD (95% CI)	-1.5 (-3.62, 0.59)	-1.8 (-3.93, 0.31)	—
Non-white, n	22	18	18
LS Mean (SE)	-12.4 (2.27)	-15.0 (2.68)	-8.9 (2.37)
LSMD (95% CI)	-3.4 (-9.54, 2.67)	-6.1 (-12.82, 0.65)	—

CI = confidence interval; LSMD = least squares mean difference; n = number of patients in the subgroup category with a baseline and 1 postbaseline assessment.
Note: Exploratory analyses of demographic subgroups were analyzed using the MMRM method similar to the one specified for the primary analysis. The subgroup, subgroup-by-treatment interaction, subgroup-by-visit interaction, and subgroup-by-treatment-by-visit interaction were included in the model. An unstructured covariance matrix was used to model the correlation among repeated measurements within patient.
[a] 20 subjects are greater than 65 years old in the ITT dataset.
Source: Study 402 CSR, Table 11-20; confirmed by statistical reviewer

Clinical Reviewer Comment: Based on the subgroup analyses, patients with bipolar I disorder had higher change from baseline MADRS scores compared to those with bipolar II for lumateperone 42 mg. Patients from the United States had a higher change from baseline compared to those from outside the United States.

I. Data Quality and Integrity for Study 402

See Section 4.1 for information regarding the OSI inspection of this trial. The ADaM and SDTM datasets were intact and evaluable using JMP programs for the clinical team and for evaluation by our biometrics team.

J. Efficacy Results – Secondary and Other Relevant Endpoints for Study 402

The prespecified secondary efficacy objective of this study was met: lumateperone 42 mg demonstrated statistically significant improvement in the change from Baseline to Day 43 in CGI-BP-S depression score (LS mean difference versuss placebo= -0.3; p = 0.0082) compared with placebo (see Table 19). The prespecified secondary efficacy results for the lumateperone 28 mg were considered descriptive based on the pre-specified hierarchical testing order, because the primary objective for the 28-mg dose was not met.

Table 19: Change from Baseline to Day 43 in CGI-BP-S Depression Score, Study 402—MMRM[a] (ITT Set)

Statistic	Lumateperone 28 mg (n = 171)	Lumateperone 42 mg (n = 174)	Placebo (n = 174)
n	171	174	174
Baseline, mean (SD)	4.7 (0.57)	4.7 (0.60)	4.6 (0.54)
Change from baseline to Day 43			
LS Mean (SE)	-1.7 (0.09)	-1.8 (0.10)	-1.5 (0.09)
LS Mean Difference[a]	-0.3	-0.3	—
95% CI	(-0.50, -0.01)	(-0.59, -0.09)	—
p-value	0.0400	0.0082	—

GI-BP-S = Clinical Global Impression Scale of Bipolar Illness–Severity of Illness; CI=confidence interval; LS=least squares; max=maximum; min=minimum; SD=standard deviation; SEM=standard error of the mean

[a] From a mixed-effects model for repeated measures analysis over all postbaseline visits, with the change from baseline in CGI-BP-S Depression Score as the outcome, study visit, the bipolar disorder stratification variable, baseline CGI-BP-S Depression Score as a covariate, site (or pooled site), baseline CGI-BP-S Depression Score -by-study visit interaction, treatment (lumateperone 28 mg, lumateperone 42 mg, placebo), and treatment-by-study visit interaction. An unstructured covariance matrix was used to model the correlation among repeated measurements within patient.

Source: Study 402, Table 11-11; confirmed by statistical reviewer

Clinical Reviewer Comment: The prespecified secondary endpoint was statistically significantly superior to placebo for lumateperone 42 mg but could not be considered for lumateperone 28 mg because of hierarchical testing order. The results of the prespecified secondary endpoint analyses further supports the efficacy of lumateperone for the proposed indication and target population.

K. Dose/Dose Response for Study 402

The LS mean change from Baseline to Day 43 for the primary and prespecified secondary endpoint for lumateperone 42 mg was very slightly higher than lumateperone 28 mg, which was slightly higher than placebo, suggesting the possibility of a dose response for lumateperone. This small dose response was noted for five of the six visits when looking at the primary endpoint, see Table 16.

The small differences in efficacy between lumateperone 28 mg and 42 mg begin around Week

4, suggesting a possible dose response (see also). However, these findings are considered exploratory.

L. Durability of Response for Study 402

There are no efficacy data to review beyond the 6-week period for Study 402. Figure 7 plots the change from Baseline in MADRS total score by visit for the ITT. Although the endpoints before Week 6 are not adjusted for multiplicity, results suggest a gradual and consistent reduction in symptoms over the course of the 6-week period; this trend could potentially continue, but for what period of time is unknown given the study design.

M. Persistence of Effect for Study 402

The Applicant did not administer the primary efficacy measure after 6 weeks, and therefore the persistence of effect cannot be determined using results from Study 402. Based on naturalistic studies (e.g., Suppes et al., 2007) and clinical experience with drugs from the same class, a gradual reduction of symptoms would be expected.

N. Additional Analyses Conducted on the Individual Trial for Study 402

Study 402 was conducted, in part, during the COVID-19 pandemic. Therefore, the Applicant amended their protocol to pre-specify an analysis of the primary efficacy endpoint based on the subset of patients who were randomized on or before January 30, 2020. The Applicant's results suggest that both lumateperone 28 mg (n=139) and lumateperone 42 mg (n=141) separated from placebo (n=142) in subjects randomized before the pandemic (Table 20), but results were not significant for those who were randomized after January 30, 2020 (Table 21), suggesting a possible impact of the COVID-19 pandemic on the study results.

Table 20: Change from Baseline to Day 43 in MADRS Total Score for Patients Randomized On or Before 30 Jan 2020—MMRM (ITT Set)

Statistic	Lumateperone 28 mg N=139	Lumateperone 42mg N=141	Placebo N=142
Baseline, mean (SD)	32.6 (5.56)	32.5 (5.26)	32.4 (5.48)
Change from baseline to day 43			
LS mean (SE)	-16.1 (0.92)	-17.3 (0.93)	-13.8 (0.91)
LS mean difference	-2.3	-3.5	
Effect Size	-0.26	-0.38	
95% CI	(-4.59, -0.04)	(-5.78, -1.15)	
p-value	0.0465	0.0035	

Source: Study 402 CSR, Table 11-8

Table 21: Change from Baseline to Day 43 in MADRS Total Score for Patients Randomized After 30 Jan 2020—MMRM (ITT Set)

Statistic	Lumateperone 28 mg N=32	Lumateperone 42mg N=33	Placebo N=32
Baseline, mean (SD)	31.0 (5.34)	31.3 (3.41)	30.8 (3.58)
Change from baseline to day 43			
LS mean (SE)	-14.9 (1.49)	-13.7 (1.52)	-16.5 (1.65)
LS mean difference	1.6	2.8	
95% CI	(-1.98, 5.11)	(-0.61, 6.24)	
p-value	0.3837	0.1057	

Source: Study 402 CSR, Table 11-9

The Applicant conducted analyses on numerous secondary and exploratory endpoints that were not controlled for type I error. We note that the subgroup analyses were conducted using ANCOVA with LOCF, ITT set. The FDA and others discourage the LOCF imputation method[1] (even for sensitivity analyses) because it is based on a very strong assumption about missing data and each missing outcome is imputed once only. Although the results from these exploratory analyses cannot demonstrate the efficacy of lumateperone, we observed that the measures generally indicated an improvement in symptoms that is consistent with the primary and prespecified secondary endpoint outcomes. For example, the LS mean change from Baseline to Day 43 in MADRS total score (ANCOVA with LOCF, ITT set) was similar in the lumateperone group for males versus females, age of onset (below age 22 versus 22 or greater), lifetime episodes of bipolar disorder (1 to 9 versus 10 to 20 episodes), age (40 or less versus greater than age 40), and Hispanic versus not Hispanic (Source, Study 402 CSR, Table 14.2.4.3.2).

For race, White race was higher (-16.9) compared to non-White race (-13.5). However, the subgroup results for non-White race were too small to draw any conclusions.

Notably, the placebo response on the primary endpoint was very different in the U.S. population (-37, SE 10) compared to the non-U.S. population (-11, SE 1), which is consistent with the findings in Study 402.

8.1.3. Study 404 (Monotherapy)

Study Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Assess the Efficacy and Safety of Lumateperone Monotherapy in the Treatment of Patients with

[1] "The prevention and treatment of missing data in clinical trials" (https://www.nap.edu/catalog/12955/the-prevention-and-treatment-of-missing-data-in-clinical-trials)

Major Depressive Episodes Associated with Bipolar I or Bipolar II Disorder (Bipolar Depression)
Conducted Globally

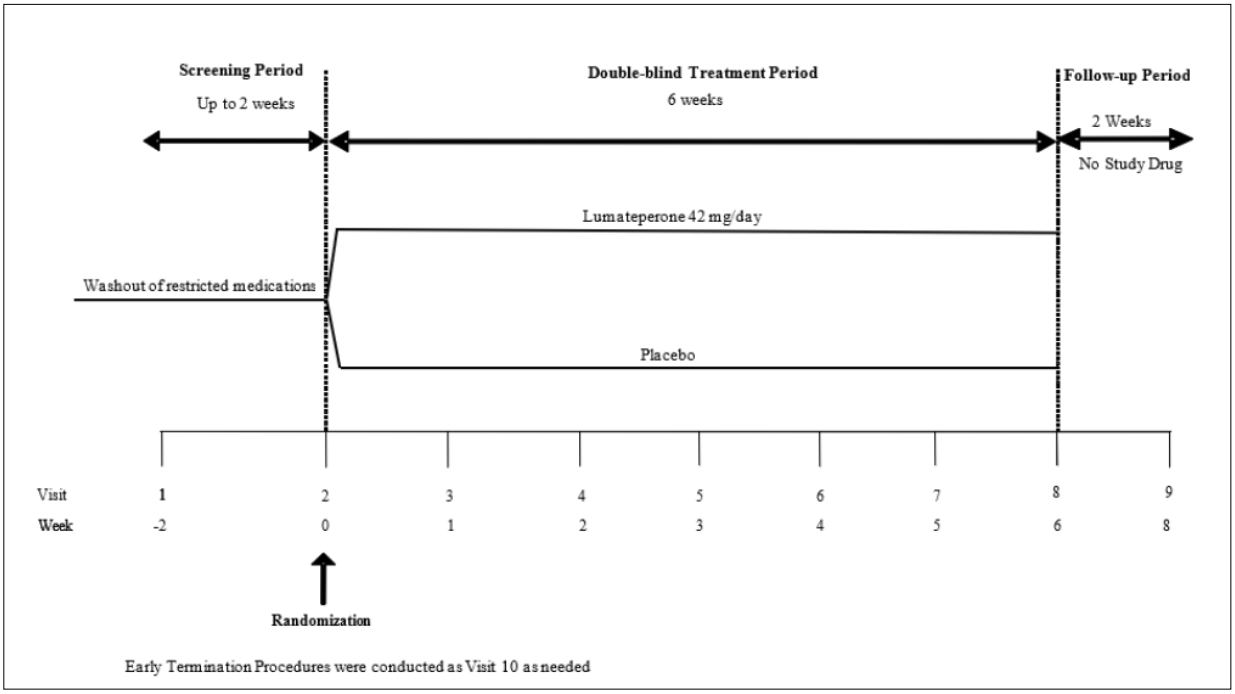
8.1.3.1. Trial Design of Study 404 (Monotherapy)

A. Basic Study Design

Study 404 was a 6-week, phase 3, fixed-dose, randomized, double-blind, placebo-controlled multi-center study comparing the efficacy of lumateperone 28 mg and lumateperone 42 mg to placebo.

Similar to Study 401-A and 402, Study 404 had three phases: A 2-week screening period, a 6-week double-blind treatment period, and a 2-week safety follow-up period. After washout of prior, excluded medications, patients were randomized in a 1:1 ratio to either lumateperone 42 mg or placebo (see Figure 12). There is precedent from a prior development program for a 6-week duration clinical trial for bipolar depression monotherapy.

Figure 12: Study Design for Study 404



Source: Applicant's response to FDA information request, submitted September 9, 2021

B. Trial Location of Study 404

There were 54 study sites: United States (14), Bulgaria (10), Colombia (3), Russian Federation (11), Serbia (5), and Ukraine (11). Almost 75% of the study sites were outside of the United States, thus raising concerns about the applicability of the results to the U.S. population.

C. Choice of Control Group of Study 404

The Applicant utilized a placebo control group, stating it was necessary to establish efficacy.

D. Diagnostic Criteria and Key Inclusion Exclusion Criteria for Study 404

The diagnostic criteria used by the Applicant was similar to Study 401-A. For diagnosis of bipolar disorder, the Applicant used the DSM-5 criteria for bipolar I disorder or bipolar II disorder as confirmed by the investigator or Applicant-approved expert site-based rater by the MINI (non-U.S. sites only). Note, Study 404 is the only clinical trial under review that did not use the SCID-5-CT as part of the diagnostic criteria for the U.S. sites. However, the MINI and SCID-5-CT should provide similar results, because they are both based on the DSM-5 criteria.

Additionally, patients met all of the following five criteria:

1) Onset of current MDE was at least within 2 weeks but not more than 6 months prior to screening
2) At least moderate severity, measured by MADRS total score ≥ 20 and corresponding to a CGI-BP-S score of ≥ 4 at screening and baseline
3) Verification of significant distress or impairment due to the current MDE
4) Lifetime history of one or more manic, mixed, or hypomanic episode
5) YMRS total score of ≤ 12, to assess manic symptoms

Key Inclusion/Exclusion criteria:

1) Experiencing a decrease in the rater administered MADRS total score of ≥25% between screening and baseline visits
2) Significant risk of suicidal behavior at screening
3) Comorbid psychiatric disorders (schizophrenia, psychotic disorder, psychosis not due to bipolar disorder; anxiety disorders, eating disorders, primary obsessive-compulsive disorder, personality disorder, moderate to severe substance use disorder; other psychiatric conditions of treatment focus)
4) Hospitalization for mania within 30 days or considered a rapid cycler or treatment-resistant)
5) Ongoing psychotherapy
6) Other specified medical conditions (e.g., neurological, cardiovascular, or endocrine disorders) or abnormal laboratory, electrocardiographic, or vital sign values outside of pre-specified parameters
7) Pregnant or breastfeeding women

8) Use of prohibited medications. The eligibility criteria appear consistent with the Applicant's aim to restrict the population to bipolar depression and limit confounders

E. Dose Selection of Study 404

The only study drug dose was lumateperone 42 mg. The Applicant states that they selected the 42-mg dose to deliver full occupancy of the cortical 5-HT_{2A} receptors (>85% occupancy) with modest striatal D2 receptor occupancy and SERT occupancy. The Applicant did not explain why they did not include a lumateperone 28-mg treatment arm, which would have been consistent with Study 401-A and Study 402. However, this choice is acceptable because other trials of lumateperone did not demonstrate an effect for the 28-mg dose.

F. Study Treatments of Study 404

ITI-007 60-mg tablet (equivalent to 42 mg of the active moiety lumateperone), or placebo (matched to ITI-007 60-mg tablet), self-administered orally once every evening, between approximately 8:00 pm and 10:30 pm, and at approximately the same time each day whenever possible.

G. Assignment to Treatment of Study 404

After washout of prior, excluded medications, patients were randomized in a 1:1 ratio to either lumateperone 42 mg or placebo.

H. Blinding of Study 404

Patients received a unique randomization number using an interactive voice/web response system. Investigators were blinded to the patients' randomization outcome unless there was a medical emergency.

I. Dose Modification/Discontinuation of Study 404

There was a single dose available, and titration or tapering was not permitted.

J. Administrative Structure of Study 404

The Applicant listed all clinical study vendors, including personnel responsible for study oversight, statistical analyses, and CSR development. All of the listed vendors and primary Applicant personnel are located in the United States (see Table 6-1 and 6-2 from the Study 404 CSR for details).

K. Procedures and Schedule of Study 404

See the Appendices Section for the Applicant's schedule of events for Study 404.

L. Dietary Restrictions/Instructions of Study 404

Patients were instructed to self-administer their study medication around the same time each evening. The study medication could be administered with or without food.

M. Concurrent Medications of Study 404

Similar to Study 401-A and Study 402, the Applicant required a wash-out of psychotropic drugs prior to study start. Patients were not permitted to start new psychotropic drugs during the study. Prohibited drugs included cannabis, alcohol, 5-HT_{2A}-receptor antagonist, or inverse agonist; or any strong or moderate cytochrome P450 3A4 inhibitor or inducer. The exceptions were zolpidem, zolpidem CR, and lorazepam, which were permitted no more than three times per week and were allowed only during the screening period and within the first 2 weeks of the double-blind treatment period. Notably, Study 401-A did not permit the use of lorazepam. The Applicant monitored for and recorded all concomitant medications during the study.

N. Treatment Compliance of Study 404

The Applicant describes using written instructions and tablet counts to monitor treatment compliance. The Applicant documented irregularities and discussed medication adherence with patients. Any patient who missed two doses of study medication per week in any 2 weeks of the study treatment period or who missed three or more doses of study medication in any single week were to be considered for early discontinuation.

O. Rescue Medication of Study 404

Rescue medications of benzodiazepines were allowed.

P. Subject Completion, Discontinuation, or Withdrawal of Study 404

The All Subjects Randomized Set contained all patients who signed the informed consent and were randomized to study medication. The ITT set contained all randomized patients who received at least one dose of study medication and had a valid baseline (pre-dose) measurement and at least one valid post-baseline measurement of MADRS total score.

The Applicant determined a discontinuation as premature when a patient who signed the ICF ceased participation in the study, regardless of circumstances, before the completion of all study visits and procedures (e.g., noncompliance, pregnancy, withdrawal of consent). Patients who withdrew prematurely were asked to return for the end-of-study assessments. The Applicant did not replace patients who prematurely discontinued.

Q. Study Endpoints of Study 404

The primary endpoint was change from Baseline to Day 43 in MADRS total score, which is the same primary endpoint as Study 401-A and 404. The secondary endpoint adjusted for multiplicity was the change from Baseline to Day 43 in CGI-BP-S total score (by comparison, the prespecified secondary endpoint in Study 402 was CGI-BP-S depression score).

R. Statistical Analysis Plan of Study 404

The primary efficacy endpoint of change from Baseline in MADRS total score at Day 43 was analyzed using the MMRM method. The model included the change from baseline at each pre-specified time point as the response variable; study visit, bipolar disorder stratification variable at screening (bipolar I or bipolar II), treatment (lumateperone or placebo) and site (or pooled site) as factors; and baseline MADRS total score as covariate and interaction terms for baseline MADRS total score-by-study visit and treatment-by-study visit. The subject term was included in

the model as a random effect while all other terms were considered fixed effects. An unstructured covariance matrix was used to model the correlation among repeated measurements within patient.

The prespecified secondary efficacy endpoint of change from Baseline to Day 43 in CGI-BP-S total score was analyzed using the MMRM where the change from baseline to each pre-specified time point in CGI-BP-S total score is the response variable; study visit, bipolar disorder stratification variable at screening (bipolar I or bipolar II), treatment (lumateperone or placebo) and site (or pooled site) as factors; baseline CGI-BP-S total score as covariate and interaction terms for baseline CGI-BP-S total score-by-study visit and treatment-by-study visit. The subject term was included in the model as a random effect while all other terms were considered fixed effects. An unstructured covariance matrix was used to model the correlation among repeated measurements within subject.

A fixed-sequence (hierarchical) gatekeeping strategy was applied to control the overall type I error rate (familywise error rate) in the strong sense across the primary and key secondary efficacy endpoints at a 2-sided $\alpha = 0.05$ and included the following steps: Step 1: perform Test 1 (analysis of the primary efficacy endpoint) at the full 2-sided $\alpha = 0.05$, and, Step 2: perform Test 2 (analysis of the key secondary efficacy endpoint) at the full 2-sided $\alpha = 0.05$ if Test 1 is significant.

A number of sensitivity analyses of the primary efficacy endpoint were performed to assess the impact of assumptions about unobserved missing data patterns on the primary inferences in the trial, including a Pattern-Mixture Model and Copy Reference Sensitivity Analyses of MMRM Approach, and also the sensitivity analysis based on ANCOVA with LOCF method.

Exploratory subgroup analyses were also conducted in primary endpoint on the ITT.

S. Protocol Amendments of Study 404

The only significant protocol amendment involved increasing the sample size from 250 to 350 after blinded sample size re-estimation.

Following an estimated pooled standard deviation of 8.82 for change from Baseline to Day 43 in MADRS total score through a blinded review of data extracted on September 6, 2018, the total sample size was increased to 350 for total number of patients randomized. This sample size was based on an assumed pooled standard deviation of 9.0 and approximately 324 evaluable patients (162/treatment group) that would provide at least 90% statistical power to detect a treatment difference of 3.5 points between lumateperone and placebo on the change from Baseline to Day 43 in MADRS total score, at a 2-sided significance level of 0.05. Also, based on the sample size of 350 patients, the study has approximately 85% statistical power to detect a treatment difference of 3.0 points under these same assumptions.

8.1.3.2. Study Results of Study 404

A. Compliance with Good Clinical Practices

The Applicant states that they conducted Study 404 in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that this clinical study complied with the ICH Guidance on General Considerations for Clinical Trials (ICH-E8; 62 FR 66113, December 17, 1997) and GCP (ICH-E6; 62 FR 25692, March 2018), as well as CFR Part 312. The Applicant states that the study protocol, informed ICF, information sheet advertisements, and amendments were approved by the IRBs/IECs at the study centers in conformance with 21 CFR part 56.

B. Financial Disclosure
See Section 0.

C. Patient Disposition of Study 404
The Applicant states that 381 patients were randomized to either lumateperone 42 mg or placebo (see Figure 13) and that 87% completed the study. The primary reasons for discontinuing the study were adverse events (5.8% in the lumateperone group and 2.6% in the placebo group) and lack of efficacy (1% in the lumateperone group and 2.1% in the placebo group). In the placebo group, 4.7% withdrew consent compared to 1.6% in the lumateperone group.

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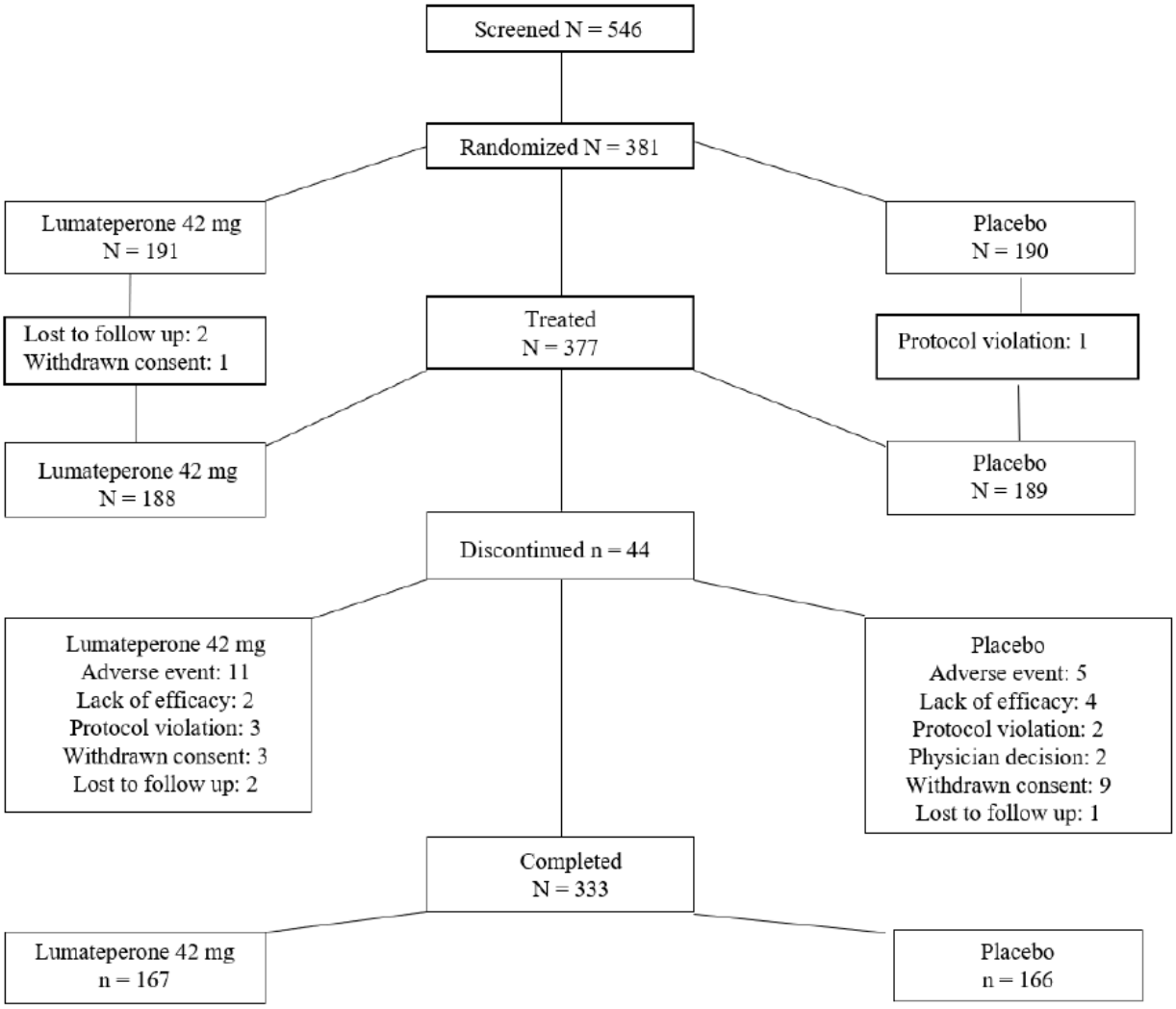
Figure 13: Patient Disposition for Study 404



Source: Study 404 CSR, Figure 10-1

Clinical Reviewer Comment: More patients discontinued due to an AE in the study drug group compared to placebo, and more placebo subjects discontinued due to lack of efficacy; these findings are consistent with the study drug demonstrating efficacy.

D. Protocol Violations/Deviations for Study 404

The Applicant reported major protocol deviations in 12% of patients (12% in the lumateperone group and 13% in the placebo group). The most common reasons were positive UDS results (5.9% of subjects) and taking concomitant medications (4% of subjects). Three subjects received an incorrect drug kit: two placebo subjects ((b) (6) and (b) (6)) received an incorrect study drug kit; one lumateperone patient (subject (b) (6)) received a kit labeled as placebo but upon checking, the kit contained lumateperone 42 mg (i.e., the kit was mislabeled).

E. Demographic Characteristics for Study 404
See Table 22 for the baseline demographic characteristics for by treatment group for Study 404.

Table 22: Demographic Characteristics for Study 404 (ITT set)

Characteristic	Treatment Group	
	Lumateperone 42 mg (n = 188)	Placebo (n = 188)
Age		
Mean (SD)	45.7 (14.09)	44.1 (12.90)
Min, Max	18, 72	18, 72
≤ 40 years, n (%)	70 (37.2)	79 (42.0)
> 40 years, n (%)	118 (62.8)	109 (58.0)
Gender, n (%)		
Male	89 (47.3)	69 (36.7)
Female	99 (52.7)	119 (63.3)
Race, n (%)		
White	173 (92.0)	170 (90.4)
Black or African American	14 (7.4)	15 (8.0)
Asian	1 (0.5)	0
Other	0	3 (1.6)
Ethnicity, n (%)		
Hispanic or Latino	18 (9.6)	21 (11.1)
Non-Hispanic or Non-Latino	170 (90.4)	168 (88.9)

Source: Statistical Reviewer's table, generated from the Applicant's Study 404 database

Clinical Reviewer Comment: The two study groups were generally similar on age, race, and ethnicity. The placebo group had a higher percentage of females than the lumateperone group. Most of the subjects identified as White with only one subject identifying as Asian. The non-white representation in Study 404 is poor and not representative of the U.S. population. This may be in part because the study was primarily conducted outside the United States.

F. Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)
A total of 39% of patients reported medical history conditions at screening. The most common (≥ 10% incidence in either treatment group) medical history conditions were hypertension (15% and 17%) and insomnia (7.4% and 11%) in the lumateperone and placebo groups, respectively (See Table 23).

Table 23: Selected Baseline Assessments – Study 404

	Treatment Group	
Baseline Assessment Characteristic	Lumateperone 42 mg (n = 188)	Placebo (n = 189)
Bipolar disorder diagnosis, n (%)		
Bipolar I	150 (79.8)	151 (79.9)
Bipolar II	38 (20.2)	38 (20.1)
Age at first diagnosis of bipolar disorder		
Years, Mean (SD)	33.2 (11.97)	32.0 (11.50)
<22 years old, n (%)	39 (20.7)	38 (20.1)
≥ 22 years old, n (%)	149 (79.3)	151 (79.9)
Number of lifetime MDEs, n (%)		
Mean (SD)	5.2 (3.77)	5.5 (4.36)
≥ 1 to ≤ 9 episodes (n, %)	166 (88.3)	168 (88.9)
≥ 10 to ≤ 20 episodes	21 (11.2)	19 (10.1)
> 20 episodes	(0.5)	2 (1.1)
Psychiatric hospitalization, n (%)		
Yes	115 (61.2)	122 (64.6)
No	73 (38.8)	67 (35.4)
BMI (kg/m^2), Mean (SD)	26.7 (4.27)	27.5 (4.16)
Lifetime hospitalizations, Mean (SD)	4.0 (4.47)	4.1 (4.16)
Hospitalized in the past year, n, (%)		
Yes	25 (21.7)	23 (18.9)
No	90 (78.3)	99 (81.1)
MADRS total score		
Mean (SD)	30.8 (4.92)	30.2 (4.65)
Median (min, max)	31.0 (20, 50)	30.0 (20, 40)
CGI-BP-S total score, Mean (SD)	10.3 (1.12)	3.5 (1.21)
CGI-BP-S mania score, Mean (SD)	1.1 (0.25)	10.2 (1.08)
CGI-BP-S depression score, Mean (SD)	4.6 (0.56)	1.1 (0.28)
CGI-BP-S overall bipolar illness score, Mean (SD)	4.6 (0.55)	4.5 (0.52)
Q-LES-Q-SF percent score, Mean (SD)	37.0 (12.53)	38.6 (12.25)

BMI = body mass index; CGI-BP-S = Clinical Global Impression-Bipolar version - Severity; MDE: major depressive episode; max = maximum; min = minimum; MADRS = Montgomery-Åsberg Depression Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form.
Source: Modified from Study 404 CSR, Tables 14.1.3.3.2. and 14.1.3.4.2., Safety Analysis Set

Clinical Reviewer Comment: The baseline scores were similar across the two treatment groups, including for the primary and prespecified secondary endpoint measures. However, there were notably more males in the lumateperone group compared to placebo. Therefore, we examined the exploratory subgroup analysis of the efficacy endpoints by sex to help understand if there is a difference in treatment effect by sex (see Additional Analyses Conducted on the Individual Trial for Study 404).

G. Treatment Compliance, Concomitant Medications, and Rescue Medication Use for Study 404

Treatment Compliance: The Applicant states that treatment compliance was 100%.

Prior and Concomitant Medications: Approximately 56% of patients in both treatment groups reported prior medications at screening. The most common prior medication (≥ 10% in either treatment group) reported by patients was quetiapine (10% in the lumateperone group and 9.5% in the placebo group). The proportions of other prior medications taken by patients were generally similar between both treatment groups.

During the treatment phase, approximately 25% of patients in the lumateperone group and 28% of patients in the placebo group continued taking their prior medications during the double-blind treatment period (lisinopril was the most common: 5.3% in the lumateperone group and 2.6% in the placebo group). The incidence of concomitant medications initiated by patients during the double-blind treatment period was similar between the lumateperone (12%) and placebo groups (13%). The most common newly initiated concomitant medications were ibuprofen (taken by nine patients (4.8%) in the lumateperone group and four patients (2.1%) in the placebo group) and zopiclone (taken by four patients in the placebo group and one patient in the lumateperone group); other concomitant medications were used by no more than two patients.

Sedative-hypnotics were permitted during the first 2 weeks of treatment, but use was only reported in three subjects in the lumateperone group and six patients in the placebo group.

Rescue Medications: For Study 404, 2.1% of lumateperone patients took rescue medications, compared to 5.3% of placebo patients. All of the listed rescue medications were benzodiazepines or sedative hypnotic drugs (Source: Applicant's response to information request dated October 28, 2021, Table B1.1.2).

Clinical Reviewer Comment: Concomitant medication use was common during the study. However, the pattern of use was similar in both groups and seems unlikely to have influenced efficacy outcomes in favor of one treatment group.

H. Data Quality and Integrity

See Section 4.1 for information regarding the OSI inspection of this trial. The ADaM and SDTM datasets were intact and evaluable using JMP programs for the clinical team and for evaluation by the biometrics team.

I. Efficacy Results – Primary Endpoint for Study 404:

The primary efficacy objective of this study was met: lumateperone demonstrated statistically significant improvement in change from Baseline in MADRS total score at Day 43 ($p < 0.0001$) compared with placebo (see Table 24).

Table 24: Primary Efficacy Endpoint for Study 404-Change from Baseline to Day 43 in MADRS Total Score (ITT Set)

Statistic	Lumateperone 42 mg (N=188)	Placebo (N=188)
n	169	166
Baseline, mean (SD)	30.7 (4.74)	30.2 (4.68)
Change from baseline to Day 43:		
LS mean (SE)	–16.70 (0.693)	–12.12 (0.677)
LS Mean Difference[a]	-4.585	—
95% CI	(-6.344, -2.826)	—
Adjusted p-value	< 0.0001[a]	—

MADRS = Montgomery-Åsberg Depression Rating Scale; CI = confidence interval; LS = least squares; max = maximum; min = minimum; SD = standard deviation; SEM = standard error of the mean

[a] From a mixed-effects model for repeated measures analysis over all postbaseline visits, with the change from baseline in MADRS as the outcome, study visit, the bipolar disorder stratification variable, baseline MADRS total score as a covariate, site (or pooled site), baseline MADRS total score-by-study visit interaction, treatment (lumateperone 42 mg and placebo), and treatment-by-study visit interaction. An unstructured covariance matrix was used to model the correlation among repeated measurements within patient data.

Source: Study 404 CSR, Table 11-6, confirmed by statistical reviewer

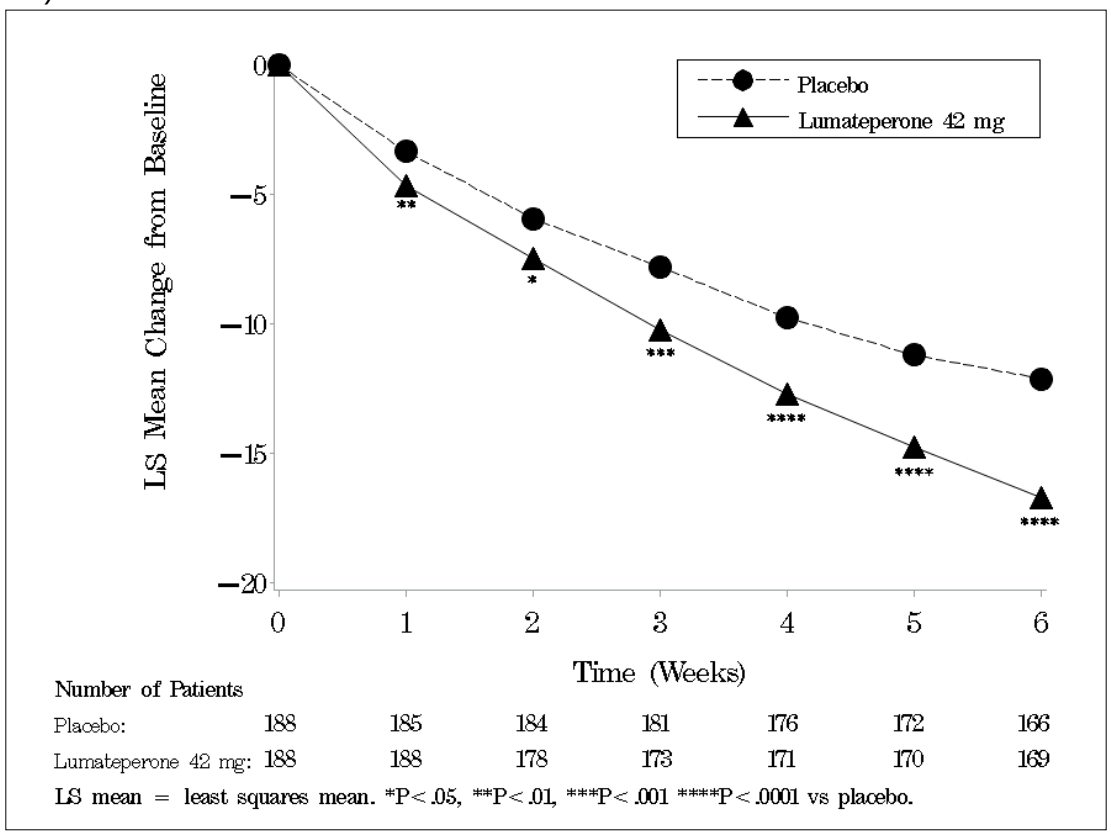
Analysis of by-visit postbaseline changes in MADRS total score suggested that at the nominal significance level of 0.05 lumateperone had statistically significant improvement compared with placebo beginning on Day 8 and was sustained through Day 43 compared with placebo (Table 25), but these findings are considered descriptive because these comparisons were not included in the multiplicity adjustment.

Table 25: Change from Baseline in MADRS Total Score by Visit for Study 404—MMRM (ITT Set)

Statistic	Lumateperone 42 mg (n=188)	Placebo (n=188)
Baseline, mean (SD)	30.8 (4.92)	30.3 (4.65)
Change from baseline to:		
Day 8 mean (SD)	-4.4 (5.75)	-3.6 (6.03)
LS Mean Difference (95% CI)	-1.3 (-2.27, -0.31)	—
p-value	0.010	—
Day 15 mean (SD)	-7.2 (7.12)	-6.2 (7.51)
LS Mean Difference (95% CI)	-1.5 (-2.74, -0.34)	—
p-value	0.012	—
Day 22 mean (SD)	-9.6 (7.51)	-8.1 (8.40)
LS Mean Difference (95% CI)	-2.4 (-3.81, -1.04)	—
p-value	<0.001	—
Day 29 mean (SD)	-12.1 (7.69)	-10.1 (9.00)
LS Mean Difference (95% CI)	-2.9 (-4.37, -1.50)	—
p-value	<0.001	—
Day 36 mean (SD)	-14.2 (8.16)	-11.6 (9.63)
LS Mean Difference (95% CI)	-3.5 (-5.13, -1.94)	—
p-value	<0.001	—
Day 43 mean (SD)	-16.2 (8.67)	-13.0 (10.22)
LS Mean Difference (95% CI)	-4.6 (-6.34, -2.83)	—
p-value	<0.001	—

Source: Study 404 CSR, Table 14.2.3.1.1, confirmed by statistical reviewer

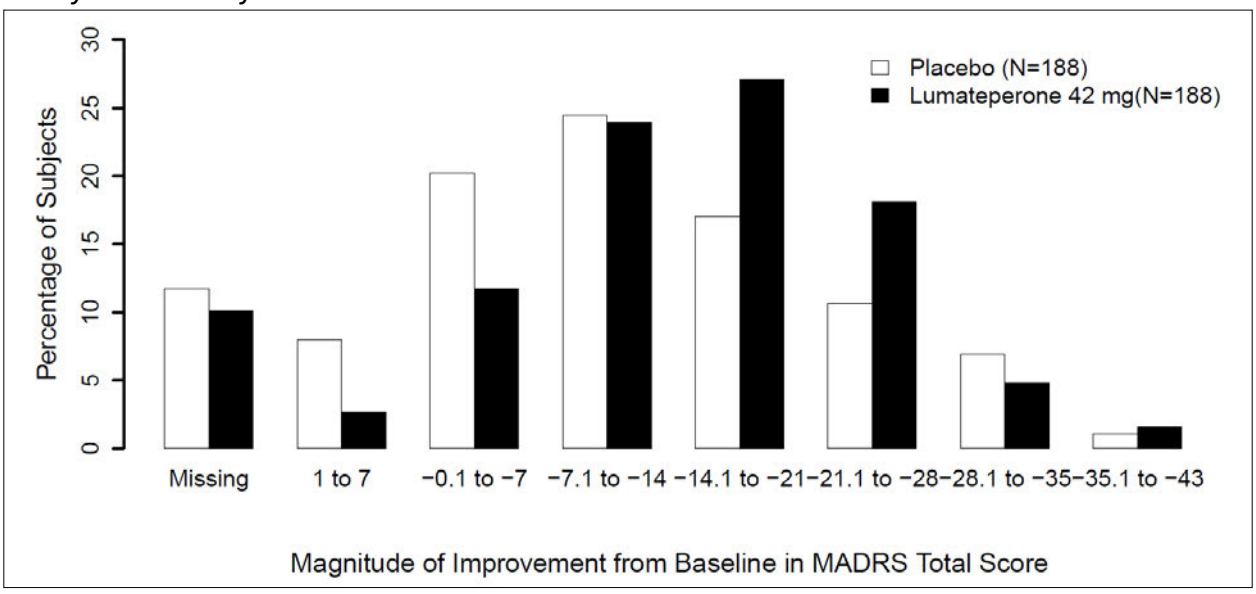
Figure 14: By-visit Postbaseline Reduction in MADRS Total Score for Study 404 —MMRM (ITT Set)



Source: Study 404, Figure 11-1

Figure 15 shows the percentages of subjects with different magnitudes of improvement on the primary endpoint in the lumateperone 42-mg and placebo groups. A patient can have one of three types of response: symptom improvement (measured as a negative change at Day 43 in MADRS Total Score), worsening, or dropout out of the study. Dropout rates are similar among the 42-mg and placebo groups. The response distributions of 42-mg group are shifted towards greater magnitude of improvement in MADRS Total Score compared to the placebo arm's response distribution based on thehistogram of the magnitude of improvement from Baseline to Week 6 in MADRS Total Score.

Figure 15: Histogram of the Magnitude of Improvement from Baseline in MADRS Total Score at Day 43 for Study 404



Source: Statistical Reviewer's Analysis based on Study 404 database

Sensitivity Analyses

Sensitivity analyses were performed to assess the impact of assumptions about MAR patients who prematurely discontinued on the study's primary inferences. The Applicant first analyzed change at Day 43 MADRS total score comparisons with placebo using the pattern mixture model (PMM) with worsening shifts up to 16.59 units to lumateperone 42 mg and shifts up to 12 units to placebo. They investigated three patterns based on discontinuation reasons including lack of efficacy; lack of efficacy and AEs as MNAR and other missing data as MAR; and all discontinuations as MNAR. Under each level of shifts, 100 imputations using a monotone regression imputation method were generated. Each of imputed data was analyzed using an MMRM model with the change from baseline at each pre-specified timepoint as the response variable and study visit, bipolar disorder stratification variable, baseline MADRS total score, site (or pooled site), baseline MADRS total score-by-study visit interaction, treatment and treatment-by-study visit interaction, assuming an unstructured covariance matrix. Statistical significance at all levels of shifts were observed in these analyses ($p < 0.001$ at all imputations).

The Applicant also performed the sensitivity analysis based on PMM-copy reference with worsening shifts up to 12 units to both treatment groups for discontinuation reasons including lack of efficacy; lack of efficacy and AEs as MNAR and other missing data as MAR; and all discontinuations as MNAR. Under each level of shifts, 100 imputations using a monotone regression imputation method were generated. Each of imputed data was analyzed used the same model as that in the PMM sensitivity analysis. Statistical significance at all levels of shifts were observed in these analyses with $p < 0.001$ at all imputations.

Additionally, the Applicant performed a sensitivity analysis based on an ANCOVA with LOCF method. Single value imputation approaches such as LOCF are discouraged. Nevertheless, the results support the primary analysis conclusion.

Subgroup Analysis

The Applicant conducted exploratory subgroup analyses for lumateperone 42 mg compared to placebo for the change from Baseline to Day 43 in MADRS Total Score – MMRM. The results were generally consistent across subgroups with respect to the primary analysis results except for the non-White subgroup, which consisted of very few patients (see Table 26).

Table 26: Change from Baseline to Day 43 in MADRS Total Score in Subgroups—MMRM (ITT Set), Study 404[a, b]

Subgroup	Lumateperone 28 (n = 188)	Placebo (n = 188)
Region		
U.S., n	51	58
LS Mean (SE)	-18.6 (2.26)	-15.2 (2.08)
LSMD (95% CI)	-3.4 (-6.83, -0.02)	—
Non-U.S., n	137	130
LS Mean (SE)	-16.1 (0.98)	-11.0 (1.00)
LSMD (95% CI)	-5.2 (-7.25, -3.09)	—
Age group[c]		
Age ≤ 40 years, n	58	71
LS Mean	-16.0 (1.12)	-11.7 (1.01)
LSMD (95% CI)	-4.3 (-7.17,-1.42)	—
Age > 40 years, n	111	95
LS Mean (SE)	-17.0 (0.84)	-12.4 (0.87)
LSMD (95% CI)	-4.6 (-6.87,-2.40)	—
Sex		
Male, n	85	67
LS Mean (SE)	-15.9 (0.96)	-11.5 (1.05)
LSMD (95% CI)	-4.4 (-7.11,-1.72)	—
Female, n	84	99
LS Mean (SE)	-17.4 (0.94)	-12.5 (0.84)
LSMD (95% CI)	-5.0 (-7.32,-2.59)	—

Subgroup	Lumateperone 28 (n = 188)	Placebo (n = 188)
Race		
White, n	158	150
LS Mean (SE)	-16.9 (0.71)	-12.0 (0.70)
LSMD (95% CI)	-4.9 (-6.72,-3.06)	—
Non-white, n	11	16
LS Mean (SE)	-13.5 (2.61)	-13.2 (2.13)
LSMD (95% CI)	-0.4 (-6.73,6.03)	—

Abbreviations: MADRS = Montgomery-Åsberg Depression Rating Scale; MMRM = Mixed Effects Model for Repeated Measures; LS = Least Squares; SE = Standard Error; CI = Confidence Interval; n = number of subjects with data.
[a] Baseline is defined as the last non-missing pre-treatment measurement.
[b] LS Means, standard errors, and confidence intervals are based on an MMRM model with the change from baseline at each pre-specified timepoint as the response variable and study visit, bipolar disorder stratification variable at screening (bipolar I or bipolar II), treatment (lumateperone or placebo) and site (or pooled site) as factors, baseline MADRS total score and subgroup as covariates and interaction terms for baseline MADRS total score-by-study visit, treatment-by-study visit, treatment-by subgroup, subgroup-by-visit and treatment-by-subgroup-by-visit, assuming an unstructured covariance matrix.
[c] 22 subjects are greater than 65 years old in the ITT dataset.
Source: Study 404 CSR, Table 14.2.4.3.1, confirmed by statistical reviewer

Clinical Reviewer Comment: The U.S.-only group was 30% of the total number of patients and thus had lower power to detect an effect. See Section 8.1.4 for additional discussion.

J. Efficacy Results – Secondary and Other Relevant Endpoints for Study 404

The key secondary efficacy endpoint of this study was met: lumateperone demonstrated statistically significant improvement in CGI-BP-S total score at Day 43 ($p < 0.0001$) compared with placebo. Statistically significant difference in change from Baseline to Day 43 in CGI-BP-S total score between lumateperone and placebo was also observed in the PP Set. The observed effect size was also similar to that observed in the ITT Set (see Table 27).

Table 27: Change from Baseline to Day 43 in CGI-BP-S Total Score (ITT Set) for Study 404[a]

Statistic	Lumateperone 42 mg (n=188)	Placebo (n=188)
n[b]	169	166
Baseline, mean (SD)	10.3 (1.10)	10.2 (1.07)
Change from baseline to Day 43		
LS Mean (SE)	-3.48 (0.170)	-2.54 (0.167)
LS Mean Difference (95% CI)	-0.939 (-1.373, -0.505)	—
p-value	< 0.0001*	—

[a] Change from baseline to Day 43 in CGI-BP-S score was analyzed using the MMRM where the change from baseline to each pre-specified time point in CGI-BP-S total score is the response variable; study visit, bipolar disorder stratification variable at screening (bipolar I or bipolar II), treatment (lumateperone or placebo) and site (or pooled site) as factors; baseline CGI-BP-S total score as covariate and interaction terms for baseline CGI-BP-S total score-by-study visit and treatment-by-study visit. An unstructured covariance matrix was used to model the correlation among repeated measurements within patient.
[b] n = number of patients with data
* Actual p-value= 0.00002743
Source: Study 404, Table 11-8, confirmed by statistical reviewer

Clinical Reviewer Comment: The Applicant states that treatment compliance was 100%, which is high for a clinical trial of 6 weeks' duration. See Section 8.1.5, Integrated Assessment of Effectiveness, for additional discussion.

K. Dose/Dose Response for Study 404

Dose response cannot be assessed in Study 404 because only there was only one active treatment arm (lumateperone 42 mg).

L. Durability of Response for Study 404

Figure 14 plots the primary endpoint during each week of the study and suggests that the improvement in MADRS continues across 6 weeks. Study 404 did not measure the effect beyond 6 weeks. While the study was not designed to determine if lumateperone statistically separated from placebo during Weeks 1 through 5, the figure shows a numerical trend towards increasing improvement each week on drug versus placebo, suggesting durability of response.

M. Persistence of Effect for Study 404

The Applicant did not administer the primary efficacy measure after 6 weeks, and therefore the persistence of effect (effect after the treatment stops) cannot be determined using results from study 404.

N. Additional Analyses Conducted on the Individual Trial for Study 404

The Applicant conducted analyses on numerous secondary and exploratory endpoints that were not controlled for type I error. Although the results cannot be considered to demonstrate efficacy of lumateperone, the measures generally indicated an improvement in symptoms that is consistent with the primary and key secondary endpoint outcomes. For example, the LS mean change from baseline to Day 43 in MADRS total score (ANCOVA with LOCF, ITT set) was similar in outcome for the lumateperone group for males versus females, age of onset (below age 22 versus 22 or greater), lifetime episodes of bipolar disorder (1 to 9 versus 10 to 20 episodes), age (40 or less versus greater than age 40), Hispanic versus not Hispanic (Source, Applicant's Study 404 CSR, Table 14.2.4.3.2).

For race, improvement based on the primary efficacy measure was higher in White race (-16.9) compared to non-White race (-13.5). However, the subgroup results for non-White race were too small to draw conclusions.

Notably, the placebo response on the primary endpoint was very different in the U.S. population (-37, SE 10) compared to the non-U.S. population (-11, SE 1), which is consistent with the findings in Study 402.

8.1.4. Assessment of Efficacy Across Trials

The Applicant conducted three clinical trials to examine the efficacy of lumateperone compared to placebo, Studies 401-A, 402, and 404. The trials were essentially identical on key design

variables and used the same primary endpoint and statistical approach. The most notable differences among the studies are as follows: 1) Study 401-A was conducted only in the United States, and Studies 402 and 404 were conducted primarily outside of the United States; 2) Study 404 only tested one dose of lumateperone (42 mg) while the other studies tested two doses (28 and 42 mg); and, 3) subjects in Study 402 all were receiving lithium or valproate, and the lumateperone was added as an adjunctive medication.

Comparing all three studies, the majority of patients were female (approximately 53 to 63%). The mean age was 42 years in Study 401-A and 45 years in Study 404 and Study 402. The majority of patients were White (53 to 57% for Study 401-A and 87 to 92% in Studies 404 and 402). In Studies 402 and 404, White race was over-represented whereas Asian race was poorly represented, with only four patients identifying as Asian. The study demographics were not consistent with the most recent U.S. census data *(e.g., 76% White, 13% Black or African American, 5.9% Asian; Source: https://www.census.gov/quickfacts/fact/table/U.S./PST045219, accessed October 15, 2021)* and, therefore, the Applicant did not achieve a patient population that completely reflects the U.S. treatment population with regard to non-White and non-Black race groups. However, a non-representative sample is not uncommon in pharmaceutical clinical trials, especially those conducted mostly outside of North America.

Results demonstrate statistically significant separations from placebo on the primary and prespecified secondary endpoints for Study 402 (adjunctive bipolar depression indication) and Study 404 (monotherapy bipolar indication), but not for Study 401-A (monotherapy). We note that the primary endpoint of change from Baseline to Day 43 in MADRS score had a larger placebo response for Study 401-A (-19.7, SE 1.11) compared to Study 402 (-14.5, SE 0.79) or 404 (–12.12, SE 0.677). Conversely, the degree of numerical improvement for the 42-mg arm in Study 401-A was similar to the other two studies; if Studies 402 or 404 had the same placebo response as Study 401-A, none of the studies would have reached statistical significance. There are known issues with high placebo response in U.S. psychiatric clinical trials for multiple indications (Khin et al., 2012); additionally, we note that the placebo response was much higher in the U.S. subpopulation for the primary endpoint, compared to the non-U.S. population for Study 404 (-37 U.S. versus -11 non-U.S.), which further supports the role of the placebo response in Study 401-A's lack of efficacy.

We noted several other possibilities for differences in efficacy across trials. For example, the dropout rate was higher in Study 401-A (29% for lumateperone 28 mg, 38% for lumateperone 42 mg, and 25% for placebo) compared to Study 402 (16% for lumateperone 28 mg, 25% for lumateperone 42 mg, and 14% for placebo) and Study 404 (11% for lumateperone 42 mg, and 12% for placebo), thus making the total N for Study 401-A lower than the other studies, especially for lumateperone 42 mg. Additionally, given that the study drug efficacy was not substantially different from placebo until Week 6, it is possible that there is a different level of tolerance for AEs and "waiting for effect" in the United States compared to other countries in Studies 402 and 404. Additionally, baseline MADRS total scores in Study 401-A were higher in all treatment groups (range, 34.7 to 35.8) relative to patients in Studies 402 (range 32.2 to 32.5)

and 404 (range 30.2 to 30.8). A lower baseline MADRS may be expected for Study 402 since patients were receiving valproate or lithium, which may benefit depressive symptoms independently. However, it is unclear why the baseline MADRS scores were so much lower in Study 404, or what effect having a higher MADRS score had on the placebo or efficacy results in Study 401-A. The treatment compliance across studies was greater than 97%, so compliance is not likely an issue for the differences in efficacy across studies.

Also, analyses for the U.S. versus non-U.S. subgroups in Study 402 and 404 suggested improvement in the lumateperone group compared to placebo. Additionally, in Study 402, patients from the United States had greater improvement compared to those from outside the United States. In conjunction with the overall statistically significant efficacy results for those two studies, these findings suggest that applicability to the U.S. population may be inferred from Studies 402 and 404 (although minority representation remains less than ideal).

Primary Endpoints Across Trials: The primary endpoint demonstrated statistically significantly superior effect for lumateperone 42 mg compared to placebo in Studies 402 and 404 but not Study 401-A. Lumateperone 28 mg failed to separate from placebo in any of the bipolar depression trials. See above for discussion about the discrepancies between Studies 402 and 404 compared to 401-A.

Secondary and Other Endpoints Across Trials: The secondary endpoints that were prespecified and controlled for type I error demonstrated statistically significant improvement for lumateperone 42 mg in Studies 402 and 404. Other secondary endpoints and exploratory endpoints suggested a trend in improvement for lumateperone 42 mg.

Subpopulations Across Trials: For Studies 402 and 404, improvement in the primary endpoint of change from Baseline to Day 43 in MADRS remained when we considered the subpopulations of diagnosis of bipolar I versus bipolar II or U.S. versus non-U.S. populations.

There were some differences in outcome when the primary efficacy measure was examined by race. However, the subpopulations were too small to draw conclusions about differences in efficacy by race.

Additional Efficacy Considerations: The PI for lumateperone states that patients should take lumateperone with food. However, the patients in the bipolar depression program were permitted to take lumateperone 42 mg with or without food. Based on previous PK studies, we know that the C_{max} is reduced when lumateperone is taken with food; however, the AEs were generally consistent in both the schizophrenia and bipolar depression programs. Therefore, we feel it is appropriate to update the lumateperone label to reflect that the drug may be taken with or without food.

8.1.5. Integrated Assessment of Effectiveness

The Applicant submitted evidence of effectiveness of two positive adequate and well-controlled studies for the indication of treatment of bipolar depression (for both monotherapy and adjunctive therapy) with lumateperone at the 42-mg dose.

Although Study 401-A is considered a negative study, Studies 402 and 404 demonstrate evidence of effectiveness for bipolar disorder for lumateperone 42 mg. The primary and prespecified secondary endpoint efficacy results are generally supported by other secondary and exploratory endpoints in Studies 402 and 404. The benefit appears to be clinically meaningful based on the change from baseline reported for the primary and key secondary measures, all of which are well-established measures for observing relevant symptom differences in these conditions.

Lumateperone 28 mg did not meet evidence of effectiveness, a finding that is consistent with previous clinical trials in patients with schizophrenia.

8.2. Review of Safety

8.2.1. Safety Review Approach

As described in the previous sections, the NDA 209500 efficacy supplements 005 and 006 included three phase 3 placebo-controlled efficacy and safety trials evaluating lumateperone for the treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression). Studies 401-A and 404 evaluated lumateperone 28 mg and 42 mg as monotherapy treatment and Study 402 evaluated lumateperone 42 mg as adjunctive treatment. In addition, patients in Study 401-A could enroll in the 6-month open-label (OLE) Study 401-B, which evaluated lumateperone 42 mg.

FDA previously conducted a review of safety as part of the NDA 209500 submission (indication is for the treatment of schizophrenia, lumateperone 42 mg dose only). Therefore, this safety review for supplements 05 and 06 focuses on evaluating lumateperone in a new population of patients (bipolar depression, as monotherapy and as adjunctive treatment) and comparing the new safety results to the established safety profile of lumateperone 42 mg in patients with schizophrenia.

Our safety evaluation is based on the Summary of Clinical Safety (SCS) that presents analysis of safety data for three groups:

- Group 1: “Pooled Monotherapy” group, includes Study 404 and Study 401-Part A
- Group 2: Study 402 (adjunctive therapy study)
- Group 3: OLE Study 401-Part B

For this safety review, we primarily considered Groups 1 and 2, because these groups contain safety data from the primary efficacy studies and, therefore, directly represent the population of interest and allows for comparison of study drug with placebo-controlled data. It was important to review Groups 1 and 2 separately at times because all subjects in Group 2 were also receiving concomitant lithium or valproate, thus may experience adverse reactions associated with those medications.

For ease of reading we will hereafter refer to the Applicant's Group 1 as the "Pooled Monotherapy" group, Group 2 as "Study 402," and, Group 3 as "OLE Study 401-B."

When relevant, we reviewed the Applicant's CSRs, statistical analysis plans, and safety datasets from the individual studies. When comparing results of the aforementioned studies with safety data from patients with schizophrenia, we reviewed findings and conclusions from the original NDA 209500 submission, safety data as presented in the lumateperone prescribing information, and the phase 3 efficacy studies from the original NDA 209500 (Studies 301, 302, and 005).

The Applicant did not submit unblinded data from their ongoing phase 3 trial, Study 403, so Study 403 was not considered in the review of efficacy or safety.

The Applicant's assessment of safety included physical examination, AE reporting, vital sign measurements, electrocardiograms (ECG), laboratory studies, the Columbia-Suicide Severity Rating Scale (C-SSRS) to assess for suicidal ideation or behavior (see Appendices for the Applicant's schedule of events by study).

8.2.2. Review of the Safety Database

Overall Exposure

The Applicant reports a total of 2664 patients have been exposed to at least one dose of lumateperone (for a total of 319.6 patient-years exposure): 1715 patients from the schizophrenia clinical studies and 949 patients from the completed bipolar depression clinical studies. In addition, a total of 69 subjects were exposed to lumateperone in the phase 1 studies supporting the bipolar depression program. Table 28 describes the exposures by dose and population and compared with placebo.

Table 28: Safety Population, Size and Denominators

Safety Database for the Study Drug Lumateperone				
Clinical Trial Groups	Placebo (n=549)	Lumateperone 28 mg (n=356)	Lumateperone 42mg (n=633)	Pooled exposure lumateperone (14 mg, 28 mg, 42 mg, and 84 mg)
Controlled trials conducted for bipolar I or II	549	356	633	949
Controlled trials conducted for schizophrenia	412	150	1310	1715
Total controlled trials, bipolar or schizophrenia	961	506	1943	2664

Source: Clinical Reviewer generated table using data from the Applicant's Summary of Clinical Safety (SCS) and the NDA 209500 Original Unireview

Adequacy of the Safety Database

The size of the safety database is adequate and meets ICH E1A exposure guidelines. The exposure is adequate for the appropriate doses, duration of treatment, patient demographics, and disease characteristics for bipolar disorder in the United States.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Note: The Applicant's approach to measuring and reporting safety was essentially identical for all the phase 3 bipolar depression clinical trials.

A. Issues Regarding Data Integrity and Submission Quality

The JumpStart team reviewed the Applicant's submitted databases and found numerous small errors for each clinical trial. We sent an information request to the Applicant, who replied with appropriately updated databases. None of the errors would have had a meaningful effect on the safety review. Additionally, the OSI site inspection resulted in no action indicated.

The clinical reviewer reviewed each AE reported in the clinical trials and did not find any data quality issues or inconsistencies. The reviewer randomly compared several narrative summaries with AE reports and the data appeared consistent. The reviewer reanalyzed some of the Applicant's safety datasets to check concurrence on findings and did not find any notable inconsistencies.

B. Categorization of Adverse Events

The Applicant elicited AEs during study visits (see Appendices for the Applicant's schedule of events by study).

The Applicant coded AEs using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary. The Applicant defined treatment emergent adverse events (TEAEs) as AEs that started or worsened in severity on or after the first dose of study medication and on or before the date of last dose of study medication plus one day for Studies 401-A, 402, and 404. For Study 401, AEs with an onset date after the last dose of study medication plus one day but before the start of Part B were labeled as "Follow-up Adverse Event." AE data listings included all AEs, TEAEs and non-TEAEs.

For coding, the Applicant mapped multiple reports of events within each patient to a common MedDRA preferred term (PT) and system organ class (SOC) were condensed into a single AE for incidence counts. The clinical reviewer reviewed each AE reported in the Applicant's AE databases for studies 401-A, 402, and 404. The translations from verbatim to preferred terms were consistent and the reviewer did not observe any errors or omissions and therefore did not recode the Applicant's safety database.

The Applicant used a similar approach to lumping preferred terms into categories for each study; see Table 29 for an example. The Applicant's approach was consistent and appeared appropriate and justified.

Table 29: Applicant's Approach to Categorizing Preferred Terms

Category	Applicable Preferred Terms
Euphoria	Euphoric mood; elevated mood; feeling abnormal; feeling drunk; feeling of relaxation; dizziness; thinking abnormal; hallucination; inappropriate affect
Impaired attention, cognition, and mood	Somnolence; sedation; mood disorders and disturbances
Dissociative/psychotic	Psychosis; aggression; confusion and disorientation
Other related terms	Drug tolerance; habituation; drug withdrawal syndrome; substance-related disorders

Source: Study 401 CSR, Table 12.

C. Routine Clinical Tests

See Appendices for the Applicant's schedule of events by study to see the schedule for obtaining laboratory samples. The Applicant collected chemistry (including metabolic labs), hematology (including liver safety labs), and urinalysis. The Applicant prespecified low, normal, and high laboratory ranges and presented shift tables and outlier criteria.

The Applicant prespecified normal and outlier parameter criteria for the ECG evaluations and vital signs.

Other safety assessments include clinical scales to measure mania, EPS, suicide, and physical exams. See Appendices and below for additional details.

8.2.4. Safety Results

A. Deaths

There were no deaths reported for any patients receiving lumateperone during the treatment period. However, there was one death for a placebo patient, after the treatment period.

B. Serious Adverse Events

In the Pooled Monotherapy group (Studies 401-A and 404), the Applicant reports serious adverse events (SAEs) for one patient (0.3%) in the placebo group (aggression) and one patient in the lumateperone 42-mg group (mania) and five patients (2.8%) in the lumateperone 28-mg group (one post-operative anemia, one procedural hemorrhage, one asthma, and four psychiatric). Source: Applicant's ISS Table 6.2.2.1. The reviewer reviewed the narrative summaries of the psychiatric-related SAEs in the lumateperone group. The Applicant did not associate any of the SAEs with the study drug.

Serious Adverse Events, Pooled Monotherapy Group Studies:

- Patient (b) (6) (43-year-old female) receiving lumateperone 28 mg in Study 401-A had an SAE of mania on Study Day 9 and was hospitalized and discontinued from the study. The AE reportedly resolved by Day 15 and the event was considered possibly related to study drug.

- Patient (b) (6) (43-year-old female) receiving lumateperone 28 mg in Study 401-A was hospitalized after an incident of sexual and physical abuse and was discontinued from the study.

- Patient (b) (6) (26-year-old female) receiving lumateperone 28 mg in Study 401-A with a history of anxiety, experienced an SAE of panic attack requiring hospitalization and discontinuation of study drug.

- Patient (b) (6) (68-year-old male) receiving lumateperone 42 mg in Study 404 had an acute manic episode that began on Study Day 21 and resolved on Study Day 71.

Serious Adverse Events, Study 402 (adjunctive):

- One patient in the lumateperone group had an SAE coded as "toxicity of various agents." Patient (b) (6) a 37-year-old white male diagnosed with bipolar I disorder, visited the emergency room due to feeling unwell and was found to have a lithium level of 1.5 mEq/L. The patient was discharged the next day with a lithium level of 0.5 mEq/L. The investigators state that the AE was considered unlikely due to the study drug.

Other:

Across all phase 3 bipolar depression studies, there was only one SAE in the placebo group

(exacerbation of depressive symptoms). After the end of treatment period, the Applicant reported ten additional SAEs for the Pooled Monotherapy group and two SAEs for Study 402. The reviewer reviewed the summary reports and did not observe a pattern suggesting rebound effects or discontinuation syndromes.

Clinical Reviewer Comment: The reported SAEs were more common in the lumateperone treatment group compared to placebo. The SAEs appeared be unlikely due to the study drug or were within the expected range of AEs that are associated with lumateperone or other drugs in the class. Risk of harm from these AEs can be mitigated by psychoeducation and adequate monitoring from the prescribing physician.

C. Dropouts and/or Discontinuations Due to Adverse Effects

See Table 30 for a list of AEs associated with treatment discontinuation in the Pooled Monotherapy group. The most common AEs associated with discontinuation in the pooled lumateperone group were four reports each of suicidal ideation, headache, and nausea (See Table 30 for percentages). The Applicant provided narratives for the patients who discontinued due to an AE; see below for additional narrative reviews.

See Table 31 for a list of AEs associated with treatment discontinuation in Study 402. The most common AEs associated with discontinuation in all lumateperone patients in Study 402 were dizziness, nausea, and vomiting (see Table 31 for percentages).

When considering Study 401-B OLE, the most common AEs associated with discontinuation in the lumateperone 42-mg group were three patients with irritability (2.4%) and two patients with nausea (1.6%).

Table 30: Incidence of Adverse Events Associated with Treatment Discontinuation—Pooled Monotherapy Group (Studies 401-A and 404)

System Organ Class Preferred Term	Placebo N=374 n(%)	Lumateperone 28 mg N=180 n(%)	Lumateperone 42 mg N=372 n(%)	Pooled Lumateperone N=552 n(%)
Number of patients with ≥1 AE leading to treatment discontinuation	8 (2.1)	14 (7.8)	26 (7.0)	40 (7.2)
Psychiatric Disorders				
Suicidal ideation	0	1 (0.6)	3 (0.8)	4 (0.7)
Mania	2 (0.5)	1 (0.6)	2 (0.5)	3 (0.5)
Hypomania	0	1 (0.6)	2 (0.5)	3 (0.5)
Depression	0	0	2 (0.5)	2 (0.4)
Insomnia	0	0	2 (0.5)	2 (0.4)
Agitation	0	0	1 (0.3)	1 (0.2)
Confusional state	0	0	1 (0.3)	1 (0.2)
Psychomotor retardation	0	0	1 (0.3)	1 (0.2)
Panic attack	0	1 (0.6)	0	1 (0.2)
Anxiety	1 (0.3)	0	0	0
Aggression	1 (0.3)	0	0	0

System Organ Class Preferred Term	Placebo N=374 n(%)	Lumateperone 28 mg N=180 n(%)	Lumateperone 42 mg N=372 n(%)	Pooled Lumateperone N=552 n(%)
Nervous system disorders				
Headache	1 (0.3)	1 (0.6)	3 (0.8)	4 (0.7)
Migraine	0	3 (1.7)	0	3 (0.5)
Somnolence	0	1 (0.6)	1 (0.3)	2 (0.4)
Dizziness	0	0	1 (0.3)	1 (0.2)
Sedation	0	0	1 (0.3)	1 (0.2)
Akathisia	1 (0.3)	0	0	0
Gastrointestinal disorders				
Nausea	0	1 (0.6)	3 (0.8)	4 (0.7)
Vomiting	0	1 (0.6)	1 (0.3)	2 (0.4)
Diarrhea	0	0	1 (0.3)	1 (0.2)
Reproductive system and breast disorders				
Priapism[1]	0	0	1 (0.6)	1 (0.4)
Investigations				
aPTT abnormal	0	1 (0.6)	0	1 (0.2)
aPTT prolonged	1 (0.3)	0	0	0
Cardiac disorders				
Atrial fibrillation	0	1 (0.6)	0	1 (0.2)
Respiratory, thoracic, and mediastinal disorders				
Asthma	0	1 (0.6)	0	1 (0.2)
Skin and subcutaneous tissue disorders				
Pruritis generalized	1 (0.3)	0	0	0

Source: Applicant's Summary of Clinical Safety, Table 2.7.4-41

Table 31: Incidence of Adverse Events Associated with Treatment Discontinuation—Study 402 Adjunctive Therapy (Safety Analysis Set)

System Organ Class Preferred Term	Placebo N=175 n(%)	Lumateperone 28 mg N=176 n(%)	Lumateperone 42 mg N=177 n(%)	Pooled Lumateperone N=353 n(%)
Number of patients with AE leading to discontinuation	5 (2.9)	3 (1.7)	15 (8.5)	18 (5.1)
Nervous system disorders				
Dizziness	0	0	2 (1.1)	2 (0.6)
Burning sensation	0	0	1 (0.6)	1 (0.3)
Extrapyramidal disorder	0	0	1 (0.6)	1 (0.3)
Headache	0	0	1 (0.6)	1 (0.3)
Mental impairment	0	0	1 (0.6)	1 (0.3)
Sedation	0	0	1 (0.6)	1 (0.3)
Somnolence	0	0	1 (0.6)	1 (0.3)
Ataxia	0	1 (0.6)	0	1 (0.3)
Gastrointestinal disorders				
Nausea	0	0	2 (1.1)	2 (0.6)
Vomiting	0	0	2 (1.1)	2 (0.6)
Abdominal pain	0	0	1 (0.6)	1 (0.3)

System Organ Class Preferred Term	Placebo N=175 n(%)	Lumateperone 28 mg N=176 n(%)	Lumateperone 42 mg N=177 n(%)	Pooled Lumateperone N=353 n(%)
Psychiatric disorders				
Anxiety	0	1 (0.6)	0	1 (0.3)
Tension	0	1 (0.6)	0	1 (0.3)
Bipolar I disorder	1 (0.6)	0	0	0
Hypomania	1 (0.6)	0	0	0
Irritability	1 (0.6)	0	0	0
Suicidal ideation	1 (0.6)	0	0	0
Eye disorders				
Vision blurred	0	0	1 (0.6)	1 (0.3)
Diplopia	1 (0.6)	0	0	0
Injury, poisoning, and procedural complications				
Toxicity to various agents	0	0	1 (0.6)	1 (0.3)
Investigations				
Platelet count decreased	0	0	1 (0.6)	1 (0.3)
Musculoskeletal and connective tissue disorders				
Back pain	0	0	1 (0.6)	1 (0.3)

Source: Applicant's Summary of Clinical Safety, Table 2.7.4-42

Clinical Reviewer Comment: The discontinuation rate due to AEs was low overall but was highest in the lumateperone 42-mg group. The most common system organ classes associated with discontinuation AEs were psychiatric disorders, nervous system disorders, and gastrointestinal disorders, which is consistent with other drugs in this class.

D. Significant Adverse Events

In the Pooled Monotherapy group, a total of eight patients (2.2%) in the lumateperone 42-mg group and four patients (2.2%) in the lumateperone 28-mg group had severe AEs compared with three patients (0.8%) in the placebo group. See Table 32 for details. In Study 402, severe AEs reported for the lumateperone group include: three reports of headache and one report each of blurry vision, anxiety, insomnia, and vomiting.

Table 32: Incidence of Severe Adverse Events— Pooled Monotherapy Group

System Organ Class Preferred Term	Placebo N=374 n(%)	Lumateperone 28 mg N=180 n(%)	Lumateperone 42 mg N=372 n(%)	Pooled Lumateperone N=552 n(%)
Patients with ≥1 severe TEAE	3 (0.8)	4 (2.2)	8 (2.2)	12 (2.2)
Gastrointestinal disorders				
Dry mouth	1 (0.3)	0	1 (0.3)	1 (0.2)
Toothache	0	0	1 (0.3)	1 (0.2)
General disorders and administration site conditions				
Fatigue	0	1 (0.6)	0	1 (0.2)
Infections and infestations				
Influenza	0	0	1 (0.3)	1 (0.2)
Sinusitis	0	0	1 (0.3)	1 (0.2)

System Organ Class Preferred Term	Placebo N=374 n(%)	Lumateperone 28 mg N=180 n(%)	Lumateperone 42 mg N=372 n(%)	Pooled Lumateperone N=552 n(%)
Injury, poisoning, and procedural complications				
Anemia postoperative	0	1 (0.6)	0	1 (0.2)
Procedural hemorrhage	0	1 (0.6)	0	1 (0.2)
Metabolism and nutrition disorders				
Increased appetite	0	0	1 (0.3)	1 (0.2)
Nervous system disorders				
Akathisia	1 (0.3)	1 (0.6)	0	1 (0.2)
Headache	0	1 (0.6)	1 (0.3)	2 (0.4)
Somnolence	0	0	2 (0.5)	2 (0.4)
Psychiatric disorders				
Aggression	1 (0.3)	0	0	0
Insomnia	1 (0.3)	0	2 (0.5)	2 (0.4)
Anxiety	0	0	1 (0.3)	1 (0.2)
Panic attack	0	1 (0.6)	0	1 (0.2)
Suicidal ideation	0	0	1 (0.3)	1 (0.2)
Suicide attempt	0	0	1 (0.3)	1 (0.2)
Tension	0	0	1 (0.3)	1 (0.2)
Respiratory, thoracic, and mediastinal disorders				
Epistaxis	0	0	1 (0.3)	1 (0.2)

Source: Applicant's Summary of Clinical Safety, Table 2.7.4-27

E. Treatment Emergent Adverse Events and Adverse Reactions

In the Pooled Monotherapy group, the most commonly reported AEs were headache, somnolence, dizziness, nausea, and dry mouth. These AEs are similar to the known adverse reactions associated with lumateperone for the treatment of schizophrenia. See Table 33 for the Pooled Monotherapy group (Studies 401-A and 404) and for AEs associated with the adjunctive trial, Study 402.

Table 33: Adverse Events Reported in ≥2% of Lumateperone-Treated Patients and that Occurred at Greater Incidence than Placebo in the Pooled Monotherapy Group (Studies 401-A and 404 Combined)

	Lumateperone 42 mg (n=372)	Placebo (n=374)
Headache	14%	8%
Somnolence[a]	13%	3%
Dizziness[b]	8%	4%
Nausea	8%	3%
Dry mouth	5%	1%
Diarrhea	4%	2%
Vomiting	4%	0%
Abdominal pain[c]	2%	1%
Upper respiratory tract infection	2%	1%

[a] Somnolence, sedation
[b] Dizziness, dizziness postural
[c] Abdominal discomfort, abdominal pain, abdominal pain upper and lower.
Source: Clinical reviewer generated table from Applicant's Study 401 and 404 databases combined, reviewed filtering the study database by Part A, safety flag, and the on treatment flag, removing follow-up visit AEs, and filtering duplicate patients; results consistent with Applicant-generated table.

The clinical reviewer compared the pooled AEs for Group 1 to the pooled AEs described in the lumateperone PI AE table (based on three clinical efficacy trials of inpatients with schizophrenia: Studies 005, 301, and 302). We noticed that the lumateperone PI adverse reaction table does not include the adverse reaction of headaches. However, per the NDA 209500 original review, the incidence of headache in the pooled analyses was 20% for lumateperone 42 mg (n=406), and 14% for placebo. The pooled analyses were consistent with the individual study analyses: the incidence of headache in Study 005 was 20% in the lumateperone 42 mg group (n=84) compared to 13% in the placebo group (n=85); Study 301 21% in the lumateperone 42 mg group (n=150) versus 15% in the placebo group (n=149); and, in Study 302, 21% in the lumateperone 42-mg group (n=174) and 17% in the placebo group (n=174). The reviewer for the current supplements contacted the original NDA 209500 clinical reviewer who stated that the Applicant did not feel that headache was due to the study drug, so it was not included in the PI adverse reaction table.

See Table 34 for the common adverse events reported in Study 402. Results are similar to other studies of lumateperone.

Table 34: Adverse Events Reported in ≥2% of Lumateperone-Treated Patients and that Occurred at Greater Incidence than Placebo in Study 402 (Adjunctive Therapy)

Preferred Term	Lumateperone 28 mg (N=180)	Lumateperone 42 mg (N=177)	Placebo (N=175)
Headache	14%	11%	11%
Somnolence[a]	7.4%	11%	3.4%
Dizziness[b]	10%	11%	23%
Nausea	5.7%	8.5%	4.0%
Dry mouth	2.3%	4.5%	0.6%
Vomiting	0.6%	4.0%	0
Diarrhea	1.1%	3.4%	1.7%
Upper respiratory tract infection	1.7%	2.8%	1.1%
Nasopharyngitis	2.8%	0.6%	2.9%
Anxiety	2.8%	1.1%	2.9%
Increased Blood Prolactin	0.6%	2.3%	0
Vision Blurred	0	2.8%	0.6

[a] Somnolence, sedation, hypersomnia
[b] Dizziness, dizziness postural
Source: Reviewer generated table from Study 402 AE dataset

During the 6-month OLE Study 401-B, the AEs occurring at ≥ 5% incidence were headache, dry mouth, dizziness, nausea, somnolence, anxiety, and irritability, similar to what was observed in the Pooled Monotherapy and Study 402 groups.

Clinical Reviewer Comment: The most common AEs reported in the lumateperone bipolar depression studies were similar across trials and similar to the AEs reported during the original NDA schizophrenia clinical trials for lumateperone. Increased blood prolactin was observed and can occur with this class of drugs. I reviewed the original NDA 209500 review of prolactin labs, and they did not observe an increase in blood prolactin compared to placebo. However, none of the studies describe if they measured free prolactin, so it is unclear how to interpret the findings. Currently there are no guidelines for measuring or monitoring blood prolactin during routine administration of antipsychotic drugs; therefore, no clinical recommendations will be suggested for the prescribing information at this time. See also the mean prolactin findings for this sNDA in the next section.

F. Laboratory Findings

Glucose (mg/dL): In the Pooled Monotherapy group, the mean (SD) change from baseline to end of treatment was slightly higher for the pooled lumateperone group (0.7, SD 16.23) compared to placebo (0, SD 14.94), but this difference is not clinically meaningful. Rates of shifts from normal to high glucose values were similar between the lumateperone 42-mg and placebo groups (9.5% and 8.9%, respectively). One patient (0.5%) in the lumateperone 42-mg

group and two patients (1.1%) in the placebo group shifted from baseline hemoglobin A1c <6.5% to ≥ 6.5% (source: Applicant's SCS Section 2.7.4.8.2.3).

The mean (SD) change in glucose was higher for placebo in Study 402 (2.1 (12.26)) compared to lumateperone 42 mg (1.4 (13.88)).

Lipids: In the Pooled Monotherapy group, the mean changes from baseline for fasting total cholesterol and triglycerides were similar in patients treated with lumateperone and placebo. Among patients in the lumateperone 42-mg group, the incidences of shifts from normal to high in total cholesterol (12%) and triglycerides (13%) were similar to placebo (15% and 10%, respectively). The incidence of shifts in LDL cholesterol in the lumateperone 42-mg group (9.3%) was higher relative to placebo (4.6%). In the 6-month OLE Study 401-B, the percentages of patients with a shift from normal to high were similar for total cholesterol, triglycerides, and LDL cholesterol, respectively (source: Applicant's SCS Section 2.7.4.8.2.3).

Hematology: In the Pooled Monotherapy group, the mean changes from baseline in hematological parameters were similar between groups for white blood cell parameters. There were some small differences in hematocrit between groups (mean (SD) change in hematocrit was -0.57 (2.65) for pooled lumateperone compared to and placebo = -0.05 (2.77); , but no dose response was observed for the mean values (Source: Applicant's ISS Appendix Table 7.1.1.1.1. and 7.1.1.1.2.). We note that seven male patients (4.7%) and three female patients (2.2%) in the lumateperone 42-mg group had hematocrit values that met the outlier criterion. We did not observe differences between treatment groups in the number of outliers for other hematological parameters (e.g., hemoglobin, leukocytes, neutrophils, platelets). During Study 402 (where lithium or valproate were also ongoing), the incidence of outliers was similar when comparing lumateperone 42 mg to placebo .

No obvious dose response was noted on any of the hematological parameters.

Regarding AEs of decreased hematocrit: In Study 401-A, patient (b) (6) , a 42-year-old female in the lumateperone 42-mg group with a history of anemia was flagged for an outlier hematocrit value. Her hematocrit values trended low at screening (hemoglobin and hematocrit values of 10.2 g/dL and 33%, respectively), and her hematocrit decreased from 32% on Day 8 to 28% on Day 44. The patient continued treatment including the Part B OLE and her hematocrit resolved by Day 150.

In Study 402, patient (b) (6) a 57-year-old male receiving lumateperone 42 mg, with no reported hematological comorbidities and had a baseline (Day 1) platelet count of 131 × 109/L, which lowered on Day 8 to 117 × 109/L; reference range: 125 to 375 ×109/L). Although the patient's platelet counts did not meet the pre-specified outlier criterion for decreased platelets, the patient was discontinued from the study after receiving study medication for 36 days. At the Safety Follow-up Visit (Day 51), the platelet count was 99 × 109/L. The clinical reviewer reviewed the associated patient narrative. The patient is described as taking valproate since at least 9 months before the study start. Valproate is commonly associated with dose-related

thrombocytopenia (source: Depakote prescribing information), and therefore, we cannot rule out the possible effect of valproate on platelet count for this patient.

During the 6-month OLE Study 401-B, no patient met outlier criteria for leukocytes, platelets, or neutrophils; few patients met outlier criteria for hematocrit, hemoglobin, and eosinophil/leukocytes.

Clinical Reviewer Comment: *Overall, there was no clinically meaningful trend in changes to glucose or lipids. There were small changes related to hematocrit, with a few associated AEs. However, the incidence of hematocrit-related AEs was low, occurred in the placebo group as well, and did not occur in other hematological parameters. The one patient with an AE of decreased hematocrit also had a history of anemia, and that anemia resolved even with ongoing lumateperone treatment. Another patient had a decreased platelet count that could possibly be related to study drug; however, we could not rule out the effect of the concomitant valproate. Lastly, we note that the nonclinical findings from the original NDA 209500 report no concern for nonclinical hematological effects nor any clinical trial concerns related to hematological findings. In summary, there does not appear to be a meaningful hematological safety signal associated with these supplemental NDA submissions.*

Liver Safety: No patient met Hy's Law criteria (Source, ISS Table 7.6.1) for the bipolar depression clinical trials (i.e., no patients had concurrent elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3× upper limit of normal (ULN) and total bilirubin ≥ 1.5 × ULN). Mean changes from Baseline were similar for placebo and lumateperone for ALT, AST, alkaline phosphatase, and total bilirubin.

There was one patient ([redacted] (b) (6), 19-year-old male in Study 401-A, lumateperone 28-mg group) who had an elevation of ALT that increased on the first study day and by Day 8 was ≥ 3 × ULN. By Day 29, ALT returned to normal (the patient remained on study drug throughout this period and completed the treatment). One placebo patient also had an elevated AST (≥ 3 × ULN). Another patient in Study 402, Patient [redacted] (b) (6), a 44-year-old male who was taking concomitant valproate 1000 mg, had baseline ALT = 13 U/L and AST = 20 U/L. On Day 9, ALT and AST values increased to 1035 U/L (> 20 × ULN) and 578 U/L (> 10 × ULN), respectively, which lowered to mildly elevated by Day 22.

During the 6-month OLE Study 401-B, no patient met outlier criteria for ALT or AST, or alkaline phosphate increases.

Creatine Phosphokinase: In the Pooled Monotherapy group, there were no clinically significant changes from baseline in mean CPK (in U/L) in the lumateperone 42-mg group compared with the placebo group; however, the lumateperone 28-mg group did have elevations of 62.4 (SD 565.07), see Table 32.

Table 35: Mean Changes from Baseline to the End of the Treatment Period in Creatine Kinase—Pooled Monotherapy Group

Creatine Kinase (U/L)	Placebo (n=374)		Lumateperone 28 mg (n=180)		Lumateperone 42 mg (n=372)		Pooled Lumateperone (n=552)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	356	148.7 (230.8)	168	151.1 (154.0)	337	150.5 (225.1)	505	150.7 (204.0)
Change from Baseline at Endpoint	356	12.3 (334.4)	168	62.4 (565.1)	337	-0.2 (230.6)	505	20.6 (377.0)

Source: Applicant's Summary of Clinical Safety, Table 2.7.3-69

The incidence of patients who met the outlier criterion for increased CK (≥ 5× ULN) was similar in the lumateperone 42 mg and placebo groups (2.1% and 2.5%), respectively.

Clinical Reviewer Comment: Elevated hepatic enzymes and elevated creatine phosphokinase are known adverse reactions that are listed in the lumateperone PI common adverse reaction table. Although it is reassuring that the mean changes and AEs were not as common in the bipolar depression trial compared to the schizophrenia trials, the information will continue to be represented in the PI as a known adverse reaction and prescribers and patients can monitor as needed.

Prolactin: The mean prolactin elevation was higher in the placebo group (1.06 ug/L) compared to the lumateperone group (-0.17 ug/L) when looking at data for all bipolar depression studies during the randomized phase. One patient (0.3%) in the lumateperone 42-mg group and two patients (0.6%) in the placebo group met the outlier criterion for increased prolactin (≥ 5× ULN; source, ISS table 7.2.1). When considered in total, these elevated prolactin findings are not enough suggest an association between lumateperone and elevated prolactin (see adverse event table results discussion above for additional details). Additionally, during the original NDA 209500, lumateperone was not described as associated with a mean increase in prolactin.

Other: Across all treatment groups, the mean changes in renal laboratory parameters were minimal and similar across all treatment groups. Mean changes in electrolytes and other laboratory parameters were minimal and similar across all treatment groups. No clinically meaningful postbaseline changes were observed in urine pH or specific gravity results across the treatment groups (source: Applicant's SCS and Study CSRs).

Clinical Reviewer Comment: The Applicant reported some abnormal laboratory results related to liver safety and creatine phosphokinase; these findings appear consistent with the known

adverse reactions that occurred with lumateperone during the schizophrenia phase 3 trials--specifically: 1) the Caplyta PI describes that the adverse reaction of "creatine phosphokinase increased" was reported in 4% of patients receiving lumateperone 42 mg compared to 1% of patients receiving placebo, and, 2) the PI also describes that the adverse reaction of "hepatic transaminases increased" was reported in 2% of patients receiving lumateperone 42 mg compared to 1% of patients receiving placebo. The presence of valproate (which is known to cause liver-related AEs) may have been a factor in some cases. Therefore, these laboratory changes are consistent with expected AEs.

G. Vital Signs

Mean changes in blood pressure (BP), pulse rate, and the incidence of vital sign-related AEs were small and similar across treatment groups in all the studies for these supplements. In the Pooled Monotherapy group, the frequencies of meeting prespecified parameters for orthostatic hypotension for lumateperone 28 mg, 42 mg, and placebo were 15%, 9.6%, and 10%, respectively. In Study 402 and the open-label extension, the incidence of meeting prespecified orthostatic hypotension parameters was lower (7%) than that observed in the placebo group (18%). However, the Applicant explains that orthostatic vital signs were not consistently obtained as part of the vital sign assessment in Study 402, and therefore the results across studies may not be consistent and are not conclusive.

Across all studies, there was one AE of orthostatic hypotension in the lumateperone 28-mg group (reported in Study 401-A). Comparatively, during the original NDA 209500, the incidence of orthostatic hypotension AEs for lumateperone and placebo in patients with schizophrenia were 0.7% and 0%, respectively.

In the Pooled Monotherapy group, the mean changes from baseline and the proportion of patients with an increase in weight ≥7% from baseline to end of study were similar in the lumateperone groups compared to placebo. The mean change from baseline for weight (in mean kg (SD)) for the Pooled Monotherapy group was 0.16 (2.15), 0.06 (0.67), and 0.19 (1.98) for lumateperone 28 mg, and lumateperone 42 mg, and placebo, respectively; in Study 402, 0.01 (1.42), 0 (1.68), and 0.23 (1.95) for lumateperone 28 mg, and lumateperone 42 mg, and placebo, respectively. Mean changes from baseline and the proportion of patients with an increase in weight ≥7% from baseline to end of study were similar in the lumateperone groups compared to placebo. In the 6-month OLE, the mean change in body weight was -0.01 kg (SD 3.1) at Day 175, although interpretation of this result is limited due to the study design and dropouts. No patients in the lumateperone 42-mg group experienced increased weight ≥ 7% compared with five patients (1.4%) in the placebo group. No patient in the lumateperone 42-mg group who was in either underweight or normal weight baseline categories met the outlier criteria for postbaseline weight changes (source: Applicant's SCS Table 2.7.4-102).

Clinical Reviewer Comment: Atypical antipsychotics are known to cause orthostatic hypotension and syncope. However, the incidence of orthostatic hypotension was higher in the placebo

group compared to the lumateperone 42 mg group in Study 402. The Applicant was asked to add their orthostatic hypotension findings to the lumateperone PI.

Atypical antipsychotics are also commonly associated with weight gain. However, weight gain appeared minimal for lumateperone relative to placebo for both short-term and the 6-month OLE Study 401-B results.

H. Electrocardiograms (ECGs)

For the Pooled Monotherapy group, the mean postbaseline changes in ECG parameters were generally small and similar in all treatment groups (e.g., change in heart rate, in beats per minute was 1 for pooled lumateperone and -0.08 for placebo; the QTcF interval in milliseconds (msec) was -0.44 for the pooled lumateperone group and -0.05 for the placebo group (source: Applicant's SCS, Table 2.7.4-115). The incidence of patients who met the ECG criteria of QTcF > 450 msec (or 480 msec for study 402 or the OLE) was low (0.9% for placebo, 2.4% for lumateperone 28 mg, and 1.2% for lumateperone 42 mg) without a clear dose response; no patient had a QTcF > 500 msec (source: Applicant's SCS, Table 2.7-116).

In Study 402, with lithium or valproate ongoing, results were similar to the Pooled Monotherapy group (e.g., change in heart rate was -0.38 for placebo and -0.14 for pooled lumateperone; the change in QTcF was 0.85 for placebo and 0.20 for pooled lumateperone (source, Applicant SCS Table 2.7-117). No patient in either lumateperone dose group had ECG interpretations that shifted from normal or clinically insignificant to clinically significant according to the Applicant. No patient in any treatment group met the ECG criterion of QTcF > 480 msec and there were no ECG-related AEs for patients in a lumateperone group.

I. QT

The Applicant submitted a thorough QT study (Study ITI-007-017) with the original NDA 209500. Based on those findings, the FDA QT Interdisciplinary Review Team (QT-IRT) suggested that the risk of QTc prolongation in the high-exposure scenarios for parent and metabolite (i.e., hepatic impairment or CYP3A4 inhibitor) should be described in the Warnings and Precautions section of the product label, with a requirement for ECG monitoring in those situations. However, the Division recommended that lumateperone should not be used in the context of hepatic impairment or concomitantly with CYP3A4 inhibitors, and therefore the product label did not include a warning for QTc prolongation.

Clinical Reviewer Comment: *ECG results including QT are unremarkable for the studies in this sNDA and show no major concerns for prolongation or arrhythmias relative to placebo.*

J. Immunogenicity

The Applicant did not submit immunogenicity data with this application or with the original NDA 209500 application. See Table 36 for the list of AEs that can be associated with immunogenicity.

Table 36: Incidence of Rash and Related Adverse Events in the Phase 3 Clinical Trials

Pooled Monotherapy Studies (Studies 401-A and 404)			
Preferred Term	Lumateperone 28 mg (n=180)	Lumateperone 42 mg (n=372)	Placebo (n=374)
Rash (any location)	1 (0.5%)	4 (1.0%)	6 (1.6%)
Pruritus	1 (0.5%)	2 (0.5%)	2 (0.5%)
Study 402			
Preferred Term	Lumateperone 28 mg (n=176)	Lumateperone 42 mg (n=177)	Placebo (n=175)
Rash (any location)	0	0	1(0.6%)
Pruritus	1(0.2%)	0	0
Atopic dermatitis	0	1(0.5%)	0
Drug eruption (rash)	0	1(0.5%)	0

Source: Clinical Reviewer generated table from Applicant's AE databases for Studies 401-A, 402, 404.

Clinical Reviewer Comment: There were a few AEs associated with pruritis and rash, but the number of AEs was similar in the individual lumateperone treatment groups compared to placebo. The AE of atopic dermatitis and drug eruption could be due to study drug, but these AEs occurred in Study 402, which included ongoing lithium and valproate. Overall, there does not appear to be a signal for immunogenicity specific to lumateperone that requires additional monitoring or labeling.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant considered hypomania, mania, and EPS as AEs of special interest. We also evaluated suicidal ideation as an AE of special interest.

Mania/Hypomania: In the Pooled Monotherapy group, AEs of hypomania occurred in three patients (0.5%) in the lumateperone dose groups and in no patients in the placebo group. AEs of mania were reported in three patients (0.5%) in the lumateperone dose groups and in two patients (0.5%) in the placebo group. The clinical reviewer reviewed the summaries for each case of mania and hypomania and did not observe common trends (e.g., day of symptom onset) or clear correlation to study drug. Postbaseline changes in YMRS total score were small and similar in all treatment groups. In Study 402, one patient in the lumateperone 42 mg group had an AE of mania and one patient in the placebo group had an AE of hypomania.

EPS: In the Pooled Monotherapy group, the incidence of AEs that may be related to EPS was low and similar in the lumateperone 42-mg and placebo groups (1.3% versus 1.1%, respectively, when including broad preferred terms (muscle spasms, dyskinesia, extrapyramidal disorder, movement disorder, tremor, restlessness, akathisia, and muscle twitching)). There was no dose response noted for EPS. In Study 402, two patients in the pooled lumateperone group reported akathisia compared to none in the placebo group. The change from baseline scores for the

BARS, AIMS, and SAS total scores were similar for the lumateperone and placebo groups; mean changes were zero or close to zero.

Suicidal Ideation:
Pooled Monotherapy: During the double-blind treatment period, the incidence of the AE of suicidal ideation was 8% in the lumateperone 42-mg group compared with a 13% incidence among placebo patients. Among patients in the lumateperone 42-mg group, emergence of suicidal ideation was lower (4.2%) than the rate observed among placebo patients (6.6%). Emergence of suicidal behavior was observed in one patient in each treatment group.

See Table 37 for a summary of suicidal ideation and behavior assessed by the C-SSRS in the Pooled Monotherapy group.

Table 37: Overall Summary of Suicidal Ideation and Behavior as Assessed by C-SSRS—Pooled Monotherapy Group

C-SSRS Category	Placebo n(%)	Lumateperone 28 mg n(%)	Lumateperone 42mg n(%)	Pooled Lumateperone n(%)
Lifetime				
N	374	180	372	552
Suicidal ideation	136 (36.4)	85 (47.2)	130 (34.9)	215 (38.9)
Suicidal behavior	83 (22.2)	54 (30.0)	79 (21.2)	133 (24.1)
Double-blind treatment period				
N	356	166	337	503
Suicidal ideation	47 (13.2)	28 (16.9)	27 (8.0)	55 (10.9)
Emergence of suicidal ideation	21 (6.6)	17 (11.9)	13 (4.2)	30 (6.7)
Suicidal behavior	1 (0.3)	1 (0.6)	1 (0.3)	2 (0.4)
Emergence of suicidal behavior	1 (0.3)	1 (0.6)	1 (0.3)	2 (0.4)

Source: Applicant's Summary of Clinical Safety, Table 2.7.4-121

In Study 402, there was one AE of suicidal ideation in the placebo group. SeeTable 38 for a summary of suicidal ideation and behavior assessed by the C-SSRS in Study 402.

Table 38: Overall Summary of Suicidal Ideation and Behavior as Assessed by C-SSRS—Study 402 (Adjunctive)

C-SSRS Category	Placebo n(%)	Lumateperone 28 mg n(%)	Lumateperone 42mg n(%)	Pooled Lumateperone n(%)
Lifetime				
N	175	176	177	353
Suicidal ideation	38 (21.7)	33 (18.8)	51 (28.8)	84 (23.8)
Suicidal behavior	26 (14.9)	13 (7.4)	26 (14.7)	39 (11.0)
Double-blind treatment period				
N	170	168	166	334
Suicidal ideation	10 (5.9)	8 (4.8)	7 (4.2)	15 (4.5)
Emergence of suicidal ideation	4 (2.5)	3 (1.9)	1 (0.6)	4 (1.3)
Suicidal behavior	0	0	0	0
Emergence of suicidal behavior	0	0	0	0

Source: Applicant's Summary of Clinical Safety, Table 2.7.4-122

6-Month OLE Study 401-B: During the OLE, there were 10 patients who had suicidal ideation (of those, 4% were considered new onset). One patient had a serious adverse event (SAE) of suicidal ideation—Patient (b) (6), a 50-year-old male with multiple psychiatric comorbidities, reported suicidal ideation due to depression and substance use and was discontinued from the study.

The clinical reviewer reviewed the available narratives that included suicidal ideation across all phase 3 studies. There was no pattern suggestive of relationship to study drug (e.g., no consistent time to event). Concomitant substance use/abuse was reported for most cases, and it is well-established that concomitant substance use and abuse increases risk of suicidal ideation and behavior.

Clinical Reviewer Comment: Hypomania and mania occurred, but this is not unexpected given the background illness being treated. The rate of EPS is low and similar to placebo with no major difference from prior studies in patients with schizophrenia. There was no apparent dose-response for these AEs of special interest. Suicidal ideation occurred and was notably higher in the placebo group compared to the lumateperone group. Like other antidepressant medications, lumateperone' s PI will be expanded to include a boxed warning and other information about risk of suicidal thoughts and behavior.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

There was no need for COA analysis as part of this NDA submission.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant considered the incidence of AEs by subgroups. (Interpretation of these results is limited because the subgroups are small.)

Sex: Compared to men in the Pooled Monotherapy group, women experienced more headaches (18% for women and 13% for men) and nausea (9.1% for women, and 4.7% for men). Subgroup safety results for Study 402 were overall similar for sex.

Age: The Applicant reviewed AEs by age (age ≤ 40 or > 40). For the Pooled Monotherapy group, the results were generally similar when comparing AEs in the pooled lumateperone group by age, except that younger patients reported more headaches (19% versus 13% in the over 40 group) and 3.8% of older individuals reported insomnia and 2.5% reported fatigue, compared to no reports in the younger group. Subgroup results for Study 402 were overall similar for age.

Race: Subgroup results by race (White versus non-White) were similar for the Pooled Monotherapy group and Study 402. As discussed in the efficacy section, the representation of

Asians in the study was poor, and subgroup results are not likely interpretable for non-White and non-Black subgroups.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant did not submit any specific safety trials with their supplemental NDAs.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

There was no signal for human carcinogenicity in the submitted data.

Human Reproduction and Pregnancy

There was no signal for human reproductive tocxicity in the submitted data. 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. The Applicant was required to perform a lactation study under the original NDA 209500, but the results were not submitted with these supplements. Currently, breastfeeding is not recommended during treatment with lumateperone.

Pregnancy in Clinical Trials for this sNDA: There were two pregnancies in the Group 1 subjects; both were in the lumateperone 28-mg groups. The first patient electively terminated the pregnancy. The second patient discontinued from the study and suffered a spontaneous abortion 1 month later. The Applicant felt this was not due to the study drug, but it is unclear if an association to study drug can be ruled out. See Table 2 for postmarketing requirements related to pregnancy and lactation under the original NDA 209500.

Pediatrics and Assessment of Effects on Growth

The Sponsor did not conduct any studies in pediatric patients; see Section 13, Postmarketing Requirements and Commitments, for required pediatric studies and Table 2 for postmarketing requirements under the original NDA 209500.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Human abuse liability studies were not conducted for this submission. The Applicant conducted safety follow-up visits and did not observe evidence of withdrawal or rebound.

AEs related to possible abuse potential were considered AEs of special interest and included dizziness, somnolence, and feeling drunk, which occurred more frequently in the study drug groups compared to placebo; see Table 39 for percentages. Euphoric mood and aggression occurred more frequently with placebo compared to study drug. We do not have additional data to link these AEs to abuse of the study drug, and previous studies with lumateperone did

not indicate abuse potential (as expected for this drug class).

Table 39: Incidence of Adverse Events Related to Possible Abuse Potential—Pooled Monotherapy Studies

Category Preferred Term	Placebo N=374 n(%)	Lumateperone 28 mg N=180 n(%)	Lumateperone 42mg N=372 n(%)	Pooled Lumateperone N=552 n(%)
Number of patients with ≥1 abuse potential TEAE	22 (5.9)	29 (16.1)	60 (16.1)	89 (16.1)
Euphoria-related terms				
Euphoric mood	1 (0.3)	0	0	0
Feeling drunk	0	1 (0.6)	0	1 (0.2)
Dizziness	14 (3.7)	10 (5.6)	24 (6.5)	34 (6.2)
Terms indicative of impaired attention, cognition, and mood				
Somnolence	9 (2.4)	21 (11.7)	40 (10.8)	61 (11.1)
Dissociative/psychotic terms				
Aggression	1 (0.3)	0	0	0

Source: Applicant's Summary of Clinical Safety, Table 2.7.4-130

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant reports that postmarketing adverse reaction reporting is consistent with the known safety profile of lumateperone.

Expectations on Safety in the Postmarket Setting

There are no new expectations in the postmarket setting.

8.2.11. Integrated Assessment of Safety

The Applicant submitted three placebo-controlled studies for these supplemental NDAs: Studies 401-A and 404 (monotherapy) and Study 402 (adjunctive). The main AEs identified across these studies included somnolence, headache, dizziness, nausea, and dry mouth. The reported AEs were not unexpected for this drug class, and no AEs occurred at rates that were markedly different than the prior lumateperone studies for schizophrenia, including EPS. No unusual or unexpected drug interaction findings were noted in the adjunctive study. In total, the incidence of laboratory or vital sign changes (including changes in glucose, weight, lipids, ECG) were low with minimal or no clinical meaningfulness or associated with already labeled adverse reactions to lumateperone that can be monitored by physicians.

Some potential safety concerns that can be addressed with as-needed lab monitoring include the risks for increased hepatic enzymes and for creatine phosphokinase, which were identified during the original NDA 209500 review and listed in the lumateperone PI as common AEs. Additionally, the clinical reviewer noted several patients with increased blood prolactin and

decreased hematocrit, although changes in mean values were not meaningful.

Additional known drug risks and serious class-effect risks can be monitored and treated (e.g., EPS), or possibly avoided by patient selection (e.g., avoid use in pregnancy).

Overall, the safety results from study 401-A, 402, and 404 were consistent with previous studies of lumateperone in schizophrenia and showed no unexpected new safety signals for the population of patients with bipolar depression.

8.3. Statistical Issues

We did not identify statistical issues that impact the overall conclusions.

8.4. Conclusions and Recommendations

The Applicant provided results of three placebo-controlled clinical trials investigating the efficacy of lumateperone for the treatment of bipolar depression (Studies 401-A and 404 (monotherapy) and Study 402 (adjunctive therapy), as well as a single 6-month OLE, Study 401-B). Study 401-A was a negative trial with a relatively high placebo response rate (which is not uncommon for psychiatric clinical trials conducted in the United States). In alignment with FDA's pre-NDA meeting advice, we conclude that Studies 404 and 402 provide substantial evidence of effectiveness for lumateperone in the treatment of bipolar depression; also, the U.S. subgroup in the other global studies had results consistent with the overall efficacy signal in those studies. AEs across trials were similar to the known adverse reactions already described in the lumateperone PI. Other mild to moderate AEs are consistent with class-effect risks and can be monitored, treated, or prevented using clinical judgement.

9 Advisory Committee Meeting and Other External Consultations

The review team determined that no Advisory Committee Meeting was warranted for these Supplements.

10 Pediatrics

The agreed upon initial pediatric study plan (iPSP) issued by the Division of Psychiatry dated October 28, 2020, was submitted with this sNDA.

The Applicant requested a waiver for pediatric studies in patients 0 to 9 years of age with bipolar depression. These studies are impossible or highly impractical because it is extremely difficult to make a diagnosis of bipolar disorder in children younger than 10 years. The prevalence rate for individuals younger than 10 years of age is less than 0.25%.
The Applicant requested a deferral of pediatric studies in patients 10 to 17 years of age with bipolar depression until after the approval in the adult population. The primary reason for delaying the pediatric studies is to establish safety and efficacy in adults before exposing pediatric patients to lumateperone.

The Division and the Agency's Pediatric Review Committee accepted this plan.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Table 40: Submitted Prescribing Information and Updates/Approved Labeling

Section	Applicant's Proposed Changes to Previously Accepted Caplyta Label, NDA 209500	Approved Labeling Changes Under NDA 209500 S-05 and S-06[1]
1. Indications and Usage	Submitted two indications: "Depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults as monotherapy" and "Depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults as adjunctive therapy with lithium or valproate."	Combined into one sentence. "Depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate"

2. Dosage and Administration	Updated administration to be taken with or without food.	Updated administration to be taken with or without food.
3. Dosage Forms and Strengths	No changes.	No changes.
4. Contraindications	No changes.	No changes.
5. Warnings and Precautions	Updated with class language and relevant bipolar depression study findings.	Updated with class language and relevant bipolar depression study findings.
6. Adverse Reactions	Added new adverse reactions table for Study 402 and 404. Updated with bipolar depression study information and new class language.	Added new adverse reactions table for Study 402 and 404, expanded to include all relevant adverse reactions, including increased blood prolactin for Study 402. Updated with bipolar depression study information and new class language.
7. Drug Interactions	Removed UGT inhibitors from the drug interaction table based on study ITI-007-027.	Removed UGT inhibitors from the drug interaction table.
8. Use in Specific Populations	Proposed changes to pediatric and geriatric use section.	Revised the pediatric and geriatric use section based on regulatory expectations.
9. Drug Abuse and Dependence	There is no Section 9.	No change.
10. Overdosage	No change.	No change.
11. Description	Add “bipolar disorder” where appropriate.	Add “bipolar disorder” where appropriate.
12. Clinical Pharmacology	Added “bipolar disorder” to the mechanism section. Updated effect of food.	Updated the mechanism to described depressive episodes in bipolar disorder instead of only “bipolar disorder.” Updated effect of food section and removed UGT inhibitors.
13. Nonclinical Toxicology	No change.	No change.
14. Clinical Studies	Updated with information from the bipolar depression clinical trials.	Updated with information from the bipolar depression clinical trials.
16. How Supplied/ Storage and Handling	No changes.	No changes.
17. Patient Counseling	Updated based on class language.	Updated based on class language and above.
18. Medication Guide	Updated based on above.	Updated based on above.

Source: Applicant’s submitted prescribing label updated by review team
1. Only significant changes are described in the table. Refer to the prescribing information documentation for additional details

12 Risk Evaluation and Mitigation Strategies (REMS)

The review team determined that no REMS was warranted for these supplements.

13 Postmarketing Requirements and Commitment

The following post-marketing requirements will be issued in accordance with the Pediatric Research Equity Act:

NONCLINICAL STUDIES

Because the current supplements support indications that can be diagnosed in children less than 13 years of age, a juvenile animal study (JAS) will be needed. Such a study was not required for the original NDA because the indication, schizophrenia, did not include children younger than 13 years of age. The Applicant submitted the GLP 3-month rat juvenile animal study protocol for review in September 2020 and planned to complete the nonclinical study no later than 1 year later (September 2021). The final report for the JAS has not been received as of November 10, 2021.

We recommend this study as a PREA PMR for the current supplements:

- Conduct a GLP juvenile animal study to assess the toxicology of lumateperone to support clinical trials of lumateperone in the intended pediatric population ages 10 to 17 years.
  Final report submission: February 2022.

CLINICAL STUDIES (specific to the supplemental efficacy indications):

1. Conduct an open-label, multiple oral dose study to demonstrate the safety, tolerability, and pharmacokinetics of lumateperone in patients ages 10 to 17 years with major depressive episode associated with bipolar I or II disorder (bipolar depression).
   Protocol submission: May 2022
   Study completion date: May 2023
   Final report submission: November 2023

2. Conduct a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of lumateperone for the treatment of major depressive episode associated with bipolar I or II disorder (bipolar depression) in patients aged 10 to 17 years.

Protocol submission: November 2023
Study completion date: May 2027
Final report submission: November 2027

3. Conduct an open-label study to assess the long-term safety of lumateperone in patients aged 10 to 17 years with major depressive episode associated with bipolar I or II disorder (bipolar depression).
   Protocol submission: November 2023
   Study completion date: November 2027
   Final report submission date: May 2028

14 Division Director (designated signatory authority) Comments

I have reviewed this document and agree with the findings and recommendations of the review teams. See appended electronic signature.

APPEARS THIS WAY ON ORIGINAL

15 Appendices

15.1. References

1. Cerimele JM, et al. The prevalence of bipolar disorder in general primary care samples: a systematic review. *Gen Hosp Psychiatry* 2014;36(1):19-25.
2. Forte A, et al. Long-term morbidity in bipolar-I, bipolar-II, and unipolar major depressive disorders. *J Affect Disord* 2015; 178:71–8.
3. Goodwin GM, et al. Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2016; 30:495.
4. Khin, Ni A. Exploratory Analyses of Efficacy Data From Schizophrenia Trials in Support of New Drug Applications Submitted to the U.S. Food and Drug Administration. *J Clin Psychiatry* 2012; 73.6: 856–64. Web.
5. Simon GE, et al. Mood symptoms, functional impairment, and disability in people with bipolar disorder: Specific effects of mania and depression. *J Clin Psychiatry* 2007; 68:1237–45.
6. Suppes T, et al. Quetiapine for the continuation treatment of bipolar depression: naturalistic prospective case series from the Stanley Bipolar Treatment Network. *Intl Clin Psychopharmacology* 2007; 22(6), 376-81.
7. Yalin N, Young AH. Pharmacological Treatment of Bipolar Depression: What are the Current and Emerging Options? *Neuropsychiatric Disease and Treatment* 2020; Volume 16: 1459–72.
8. Yatham LN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord* 2018; 20:97.

15.2. Financial Disclosure

See below for the financial disclosure forms for Studies 401-A and 402. The Applicant described submitting a financial disclosure form for Study 404, however it was not included in the NDA submission. We sent an information request to the Applicant, and they clarified that none of the study investigators had disclosable financial arrangements and that their previous statement on the matter was in error; additionally, they noted that they took steps to minimize bias for the one U.S. investigator submitting the Form 3455.

Covered Clinical Study (Name and/or Number): 401-A

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 60		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: Yes. (b) (6), MD of (b) (6) (b) (6) states they purched common stock in Intra-Cellular Therapies valued more than USD $50,000. Sponsor of covered study: Intra-Cellular Therapies		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 402

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 111		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: Yes. (b) (6), MD of (b) (6) (b) (6) states they purched common stock in Intra-Cellular Therapies valued more than USD $50,000. Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 404

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 58		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N/A	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from Applicant)

15.3. Schedule of Events

See Table 41 to 44 for the Applicant's schedule of events for Study 401-A, 402, and 404, respectively (source for all: Applicant's corresponding CSRs).

Table 41: Appendix, Schedule of Events Study 401-A

Study Period	Screening	Baseline	Double-Blind Treatment Phase						Follow-Up (Early Discontinuation)
Visit No.	1	2	3	4	5	6	7	8	9
Study Week	-2	0	1	2	3	4	5	6	8
Study Day	Up to -14[1]	1	8 (±1)	15 (±1)	22 (±1)	29 (±1)	36 (±1)	43 (±1)	57 (±2)
Informed consent	Obtained[2]								
Review inclusion/exclusion criteria	X	X							
Screening adjudication procedures including SCID-5-CT, C-VISA™, and BPI	X								
Record demography	X								
Medical history	X								
Physical & neurological examination (incl. calculation of BMI)	X				X			X	X
Randomization		X							
Medication dispensed		X	X	X	X	X	X		
Hepatitis/HIV testing	X								
Urine drug and alcohol screening	X	X			X				
Laboratory assessments[3]	X	X	X		X			X	X
Pregnancy test	X	X			X			X	X
12-lead ECG[4]	X	X	X		X			X	X
Vital signs[5]	X	X	X	X	X	X	X	X	X
MADRS[6]	X	X	X	X	X	X	X	X	X[8]
YMRS[7]	X	X	X	X	X	X	X	X	X[8]
CSSR-S	X	X	X	X	X	X	X	X	X[8]
CGI-BP-S		X	X	X	X	X	X	X	X[8]
SDS		X			X			X	X[8]
Q-LES-Q-SF		X			X			X	X[8]
WHO-5		X			X			X	X[8]
NEO-FFI		X						X	X[8]

Study Period	Screening	Baseline	Double-Blind Treatment Phase						Follow-Up (Early Discontinuation)
Visit No.	1	2	3	4	5	6	7	8	9
Study Week	-2	0	1	2	3	4	5	6	8
Study Day	Up to -14[1]	1	8 (±1)	15 (±1)	22 (±1)	29 (±1)	36 (±1)	43 (±1)	57 (±2)
AIMS, BARS, SAS		X			X			X	X[8]
Blood draw for protein biomarkers		X	X		X			X	X[8]
Blood draw for genetic biomarkers		X							
Blood draw for pharmacokinetic assessments[9]			X		X			X	X[8]
Return of medication card and assessment of compliance			X	X	X	X	X	X	X[8]
AEs/SAEs	X	X	X	X	X	X	X	X	X
Prior/Concomitant medications	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BMI = body mass index; BPI = Bipolarity Index; CGI-BP-S = Clinical Global Impression Scale Bipolar Version Severity; C-SSRS = Columbia Suicide Severity Rating Scale; C-VISA™ = Clinical Validation Inventory for Study Administration; ECG = electrocardiogram; HIV = human immunodeficiency virus; MADRS = Montgomery-Åsberg Depression Rating Scale; NEO-FFI = Neuroticism, Extraversion, and Openness to Experience-Five Factor Inventory; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form; SAE = serious adverse event; SAS = Simpson Angus Scale; SCID-5-CT = Structured Clinical Interview for DSM-5 Disorders – Clinical Trial Version; SDS = Sheehan Disability Scale; WHO-5 = World Health Organization – Five Well-Being Index; YMRS = Young Mania Rating Scale.

[1]The Screening Period may have been extended to allow for washout of previous medication with a long half-life, with review and approval by the Medical Monitor, but not to exceed a total of a 28-day Screening Period.

[2]Informed consent was obtained before any study specific procedures were conducted.

[3]Clinical laboratory samples were to be taken after an overnight fast of at least 10 hours.

[4]ECG were to be 10-second epochs.

[5]Vital signs included: respiratory rate, oral temperature, supine blood pressure and pulse readings (after at least 10 minutes in the supine position), body weight, waist circumference, and height (height, only at screening).

Table 42: Appendix, Schedule of Events Study 402

Study Period	Screening	Baseline	Double-Blind Treatment Phase						Follow-Up (Early Discontinuation)
Visit No.	1	2	3	4	5	6	7	8	9
Study Week	-2	0	1	2	3	4	5	6	8
Study Day	Up to -14[1]	1	8 (±1)	15 (±1)	22 (±1)	29 (±1)	36 (±1)	43 (±1)	57 (±2)
Informed consent	Obtained[2]								
Placebo-response training		X[12]							
Review inclusion/exclusion criteria	X	X							
Screening adjudication procedures including SCID-CT or MINI, and the C-VISA™ (US only) and may include the BPI	X								
Record demography	X								
Medical history	X								
Physical & neurological examination	X				X			X	X
Randomization		X							
Medication dispensed		X	X	X	X	X	X		
Hepatitis/HIV testing	X								
Urine drug and alcohol screening	X	X			X				
Laboratory assessments[3]	X	X	X		X			X	X
Pregnancy test[4]	X	X			X			X	X
12-lead ECG[5]	X	X	X		X			X	X
Vital signs (incl. calculation of BMI)[6]	X	X	X	X	X	X	X	X	X
MADRS[7]	X	X	X	X	X	X	X	X	X[10]
YMRS[8]	X	X	X	X	X	X	X	X	X[10]
CSSR-S	X	X	X	X	X	X	X	X	X[10]
CGI-BP-S	X	X	X	X	X	X	X	X	X[10]
SDS[9]		X			X			X	X[10]
Q-LES-Q-SF		X			X			X	X[10]
WHO-5[9]		X			X			X	X[10]
NEO-FFI[9]		X						X	X[10]
AIMS, BARS, SAS		X			X			X	X[10]
Blood draw for protein biomarkers		X	X		X			X	
Blood draw for genetic biomarkers		X							
Blood draw for PK assessments[11]			X		X			X	

Study Period	Screening	Baseline	Double-Blind Treatment Phase						Follow-Up (Early Discontinuation)
Visit No.	1	2	3	4	5	6	7	8	9
Study Week	-2	0	1	2	3	4	5	6	8
Study Day	Up to -14[1]	1	8 (±1)	15 (±1)	22 (±1)	29 (±1)	36 (±1)	43 (±1)	57 (±2)
Return of medication card and assessment of compliance			X	X	X	X	X	X	
AEs/SAEs	X	X	X	X	X	X	X	X	X
Prior/Concomitant medications	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BMI = body mass index; BPI = Bipolarity Index; CGI-BP-S = Clinical Global Impression Scale Bipolar Version Severity; C-SSRS = Columbia Suicide Severity Rating Scale; C-VISA™ = Clinical Validation Inventory for Study Administration; ECG = electrocardiogram; HIV = human immunodeficiency virus; MADRS = Montgomery-Åsberg Depression Rating Scale; MINI = Mini International Neuropsychiatric Interview; NEO-FFI = Neuroticism, Extraversion, and Openness to Experience-Five Factor Inventory; PK = pharmacokinetic; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form; SAE = serious adverse event; SAS = Simpson Angus Scale; SDS = Sheehan Disability Scale; SIGMA = Structured Interview Guide for the MADRS; WHO-5 = World Health Organization - Five Well-Being Index; YMRS = Young Mania Rating Scale.

[1]The Screening Period may have been extended (to allow for washout of previous medication with a longer half-life or to ensure minimum exposure of at least 28 days to mood stabilizer, lithium, or valproate, which was required to have been started by the patients, under standard of care, before the start of screening) with review and approval by the Medical Monitor, but was not to exceed a total of a 28-day Screening Period.

[2]Informed consent was obtained before any study specific procedures were conducted.

[3]Clinical laboratory samples were to be taken after an overnight fast of at least 10 hours.

[4]At Visit 1 (Screening), at Visit 2 (Baseline), and, at the discretion of the Investigator at an unscheduled visit, serum and urine pregnancy tests were administered. If urine pregnancy test was negative and the associated serum pregnancy test was positive, the patient was discontinued from the study.

[5]It was recommended that ECGs were conducted before other assessments scheduled in the same time window; for example, when ECG, vital signs, and blood sample collection for PK measures were scheduled for the same visit, ECG measures were to be conducted first, followed by vital signs, and then blood sample collection. If a patient met the QTcF and/or heart rate exclusion criteria during the Screening Period (Exclusion Criteria 14j), repeat ECG testing was not permitted.

[6]Vital signs included: respiratory rate, oral temperature, supine blood pressure and pulse readings (after at least 10 minutes in the supine position), body weight, waist circumference, and height (height measured only at the Screening visit). BMI was calculated to the nearest tenth decimal place for patient eligibility at Visit 1 (Screening) and Visit 2 (Baseline). It was recommended that vital signs, waist circumference, and weight were measured after conducting the ECGs, as applicable, and prior to any other assessments, including needle sticks for laboratory or PK samples, scheduled for the same visit.

[7]A qualified rater at the site conducted the MADRS assessment. In addition to MADRS administration by a qualified site rater, at every visit following screening, each patient completed a MADRS interview. Computer-based assessments on a dedicated study device/tablet were utilized at sites that were initiated under Protocol Version 1.3 or prior versions. Paper-based assessments administered by a qualified rater were completed at sites initiated with Protocol Version 1.4 and subsequent versions; these assessments used SIGMA to collect data for scoring the MADRS.

[8]A qualified rater at the site conducted the YMRS assessment. In addition to YMRS administration by a qualified site rater, at every visit following screening, each patient completed a YMRS interview. Computer-based assessment on a dedicated study device were utilized at sites that were initiated under Protocol Version 1.3 or prior versions. Assessments completed at sites that were initiated with Protocol 1.4 and subsequent versions were paper-based.

[9]Assessment was to be completed with US patients only.

[10]Assessment was conducted as part of early discontinuation visit only.

[11]Blood samples were collected for determination of ITI-007 (IC200056 parent) concentrations in plasma. Other metabolite concentrations were also determined.

[12]Procedure was implemented based on Protocol Version 1.5.

Table 43: Appendix, Schedule of Events Study 404

Study Period	Screening	Baseline	Double-Blind Treatment Phase						Follow-Up	Early Discontinuation
Visit No.	1	2	3	4	5	6	7	8	9	10
Study Week	-2	0	1	2	3	4	5	6	8	As Needed
Study Day	Up to -14[1]	1	8 (±1)	15 (±1)	22 (±1)	29 (±1)	36 (±1)	43 (±1)	57 (±2)	As Needed
Informed consent	Obtained[2]									
Review inclusion/exclusion criteria	X	X								
Screening adjudication procedures including MINI and Enrollment Assessment Form	X									
Record demography	X									
Medical history	X									
Physical & neurological examination (incl. calculation of BMI)	X							X	X	X
Randomization		X								
Medication dispensed		X		X		X				
Hepatitis/HIV testing	X									
Urine drug and alcohol screening	X	X			X					
Laboratory assessments[3]	X	X	X		X			X	X	X
Pregnancy test	X	X			X			X		X
12-lead ECG[4]	X[4]	X						X	X	X
Vital signs[5]			X	X	X	X	X			
Vital signs (3-positional)[5]	X	X						X	X	X
MADRS[6]	X	X	X	X	X	X	X	X		X
YMRS[7]	X	X	X	X	X	X	X	X		X
CSSR-S	X	X	X	X	X	X	X	X		X
CGI-BP-S	X	X	X	X	X	X	X	X		X
Q-LES-Q-SF		X						X		X
Patient placebo questionnaire and training[8]		X						X		X
AIMS, BARS, SAS		X						X		X
Blood draw for pharmacokinetic assessments[9]			X					X	X	X
Return of medication card and assessment of compliance			X	X	X	X	X	X		X

Study Period	Screening	Baseline	Double-Blind Treatment Phase						Follow-Up	Early Discontinuation
Visit No.	1	2	3	4	5	6	7	8	9	10
Study Week	-2	0	1	2	3	4	5	6	8	As Needed
Study Day	Up to -14[1]	1	8 (±1)	15 (±1)	22 (±1)	29 (±1)	36 (±1)	43 (±1)	57 (±2)	As Needed
AEs/SAEs	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant medications	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BMI = body mass index; CGI-BP-S = Clinical Global Impression Scale Bipolar Version Severity; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; HIV = human immunodeficiency virus; MADRS = Montgomery-Åsberg Depression Rating Scale; MINI = Mini International Neuropsychiatric Interview; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form; SAE = serious adverse event; SAS = Simpson Angus Scale; YMRS = Young Mania Rating Scale.

[1]The Screening Period may have been extended to allow for washout of previous medication with a long half-life, with review and approval by the Medical Monitor, but not to exceed a total of a 28-day Screening Period.

[2]Informed consent was obtained before any study specific procedures were conducted.

[3]Clinical laboratory samples were to be taken after an overnight fast of at least 10 hours. HbA_{1c} is collected at Screening (Visit 1) and Visit 8.

[4]ECGs were collected at Visit 1, Visit 2, Visit 8/Early Discontinuation, and Visit 9. At Visit 1 (Screening) only, ECGs were collected in triplicate 10-second epochs with 5 minutes between recordings. In all cases, ECGs were conducted before other assessments scheduled in the same time window; for example, when ECG, vital signs, and blood sample collection for pharmacokinetic measures were scheduled for the same visit, ECG measures were to be conducted first, followed by vital signs, and then blood sample collection.

[5]At all visits, vital signs included: respiratory rate, oral temperature, 60-second pulse readings, blood pressure, body weight, waist circumference, BMI, and height (height only at Visit 1, Screening). Vital signs were to be taken after conducting the ECGs, as applicable, and prior to any other assessments, including needle sticks for laboratory or pharmacokinetic samples, scheduled for the same visit. At Visit 1, Visit 2, Visit 8/Early Discontinuation, and Visit 9, vital signs included blood pressure readings after at least 10 minutes in the supine position, after approximately 1 minute of sitting, immediately upon standing, and after approximately 3 minutes standing.

[6]A qualified rater at the site conducted the MADRS assessment.

[7]A qualified rater at the sites conducted the YMRS assessment.

[8]Patient placebo questionnaire and training were administered at baseline and Visit 8/Early Discontinuation; placebo training was administered only at baseline.

[9]Blood sample collection for pharmacokinetic analysis were collected for determination of ITI-007 (IC200056 parent) concentrations in plasma. Additional metabolite concentrations were also determined.

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/s/

TIFFANIE A TAYLOR
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Clinical Review Memo

Application Type	sNDA
Application Number(s)	209500 S-005 and S-006
Priority or Standard	Standard
SDN#	S-005: 0109/S-006: 0110
Submit Date(s)	February 17, 2021
Received Date(s)	February 17, 2021
PDUFA Goal Date	December 17, 2021
Division/Office	Division of Psychiatry
Established/Proper Name	Lumateperone
(Proposed) Trade Name	Caplyta
Pharmacologic Class	Atypical antipsychotic
Code name	ITI-007
Applicant	Intra-Cellular Therapies
Dosage form	Capsule
Applicant proposed Dosing Regimen	42 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate.
Clinical Review Team	Clinical Reviewer: Michelle Horner, DO Clinical TL: Jean Kim, MD, MA

The Clinical review is complete and has been added to the NDA 209500 S-005 and S-006 Multidisciplinary Review and Evaluation. The Clinical review includes or contributed to Sections 1, 2, 3, 4, 7, 8, 9, 10, 11, 13, and 15.

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/s/

MICHELLE S HORNER
12/17/2021 02:09:39 PM

JEAN S KIM
12/17/2021 02:11:56 PM

Biometrics Review Memo

Application Type	sNDA
Application Number(s)	209500 S-005 and S-006
Priority or Standard	Standard
SDN#	S-005: 224 (SN: 0109)/S-006: 223 (SN: 0110)
Submit Date(s)	February 17, 2021
Received Date(s)	February 17, 2021
PDUFA Goal Date	December 17, 2021
Division/Office	Division of Psychiatry
Established/Proper Name	Lumateperone
(Proposed) Trade Name	Caplyta
Pharmacologic Class	Atypical antipsychotic
Code name	ITI-007
Applicant	Intra-Cellular Therapies
Dosage form	Capsule
Applicant proposed Dosing Regimen	42 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate.
Biometrics Review Team	Yang (Kelly) Yang, Ph.D. (Statistical Reviewer) Peiling Yang, Ph.D. (Statistical Team Lead) HM James Hung, Ph.D. (Division Director, DB1)

The Biometrics review is complete and has been added to the NDA 209500 S-005 and S-006 Multidisciplinary Review and Evaluation. The Biometrics review contributed to Sections 8.

The efficacy results of the US Study 401-A were not statistically significant. This study compared two doses with placebo. To derive the adjusted p-values, which adjusted for multiple dose arms and the interim analysis, the applicant applied a combination function to calculate composite intersection p-values:

$$c(x_1, x_2) = 1 - \Phi\left[\sqrt{w_1}\Phi^{-1}(1-x_1) + \sqrt{w_2}\Phi^{-1}(1-x_2)\right]$$

However, the calculations should have be done through one-sided p-values instead of two-sided p-values. Regardless, the unadjusted p-values were very large, so this is clearly a negative study.

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/s/

YANG YANG
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HSIEN MING J HUNG
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Office of Clinical Pharmacology--Review Memo

Application Type	NDA Efficacy Supplement
Application/Supplement Number(s)	209,500/S05, S06
Priority or Standard	Standard
SDN#	e0109; e0110
Submission Date(s)	Feb. 17, 2021
PDUFA Goal Date	Dec. 17, 2021
Division/Office	Division of Psychiatry (DP)/Office of Neuroscience
Established/Proper Name	Lumateperone
(Proposed) Trade Name	CAPLYTA
Dosage Form	Immediate-Release Capsules
Dose Strengths (mg)	42
Indication(s)	S-005: Treatment of depressive episodes associated with Bipolar I or Bipolar II Disorder in adults as monotherapy S-006: Treatment of depressive episodes associated with Bipolar I or Bipolar II Disorder in adults as adjunctive therapy with lithium or valproate
Applicant	Intra-Cellular Therapies Inc.
OCP Review Team	Huixia Zhang, Luning (Ada) Zhuang
OCP Final Signatory	Mehul Mehta Division Director Division of Neuropsychiatry Pharmacology Office of Clinical Pharmacology (OCP)

The Office of Clinical Pharmacology (OCP) review is complete and has been added to the NDA 209500/s05-06 Multidisciplinary Review and Evaluation. OCP review included or contributed to Section 6.

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/s/

HUIXIA ZHANG
10/25/2021 04:35:13 PM

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10/25/2021 05:34:24 PM

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW MEMO

Application Number:	209500/S-005 and S-006
Supporting Document Number/s:	eCTD 0109 and 0110
Applicant's letter date:	2/17/2021
CDER Receipt Date:	2/17/2021
Product:	Caplyta (lumateperone)
Indication:	Depressive episodes associated with bipolar I or II disorder (bipolar depression), as monotherapy and as adjunctive therapy with lithium or valproate
Applicant:	Intra-Cellular Therapies, Inc.
Review Division:	Division of Psychiatry
Reviewer:	Elizabeth Green, PhD
Supervisor/Team Leader:	Ikram Elayan, PhD
Division Director:	Tiffany Farchione, MD
Project Manager:	Tiffanie Taylor, PharmD

The nonclinical pharmacology/toxicology review of NDA 209500 is complete and has been added to the multidisciplinary review and evaluation document. My review is based on the information currently in the administrative record. There were no items that needed to be reviewed for these two NDA supplements from a nonclinical perspective. If I must review information that is subsequently added to the administrative record, I will update my part of the multidisciplinary review and evaluation document accordingly.

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ELIZABETH A GREEN
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IKRAM M ELAYAN
11/05/2021 11:45:04 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209500Orig1s006

OTHER REVIEW(S)

Division of Psychiatry

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 209500/SE1/S-005 & S-006

Name of Drug: Caplyta (lumateperone) capsules

Applicant: Intra-Cellular Therapies, Inc.

Labeling Reviewed

Submission Date: February 17, 2021

Receipt Date: February 17, 2021

Background and Summary Description:

- The last approved labeling was the labeling attached to the December 20, 2019 approval letter for the original NDA 209500.
- Supplemental NDA 209500 S-005 proposes the addition of a new indication, depressive episodes associated with bipolar I or bipolar II disorder in adults as monotherapy. S-005 also includes label changes to sections 7 and 12.3 as a result of Study ITI-007-027-CSR.
- Supplemental NDA 209500 S-006 proposes the addition of a new indication, depressive episodes associated with bipolar I or bipolar II disorder in adults as adjunctive therapy with lithium or valproate.
- A final report for PMR 3760-5 to conduct a clinical pharmacokinetic trial to evaluate if UGT enzyme inhibitors alter the PK of lumateperone and its metabolites is also included in this supplemental application.
- A medication guide was included with the submission of these supplemental NDAs.

Review

Reviewed by Team:
CDTL: Jean Kim; Clinical Reviewer: Michelle Horner; Nonclinical TL: Ikram Elayan; Nonclinical Reviewer: Elizabeth Green; OCP TL: Luning (Ada) Zhuang; OCP Reviewer: Huixia Zhang; Pharmacometrics (OCP) Reviewer: Jie Liu and Atul Bhattaram; Statistics TL: Peiling Yang; Statistics Reviewer: Kelly Yang; CMC Primary Reviewer: Lin Qi; CMC Secondary Reviewer: Gurpreet Gill-Sangha; IQA Reviewer Joyce Crich; Biopharm Reviewer: Ta-Chen Wu; OPDP Reviewer: Domenic D'Alessandro; DMEPA Reviewer: Loretta Holmes; DMPP/PLT Reviewer: Shawna Hutchins; ADL: Kimberly Updegraff

- The following changes were made to the label:
    - Section 1: Combined two submitted indications into one sentence
    - Section 2: Updated administration to be taken with or without food
    - Section 5: Updated with class language and relevant bipolar depression study findings
    - Section 6: Added new adverse reactions table for Study 402 and 404, including all relevant adverse reactions (i.e. increased blood prolactin for Study 402); Updated with bipolar depression study information and new class language
    - Section 7: Removed UGT inhibitors from drug interaction table
    - Section 8: Revised the pediatric and geriatric use section based on regulatory expectations
    - Section 11: Added "bipolar disorder" where appropriate
    - Section 12: Updated the mechanism to describe depressive episodes in bipolar disorder and updated the effect of food section and removed UGT inhibitors
    - Section 14: Added information from bipolar depression clinical trials
    - Section 17: Updated based on class language
    - Medication Guide: Updated based on above changes

Recommendations

1. These supplements provide for the changes noted above when compared to the last approved labeling for Caplyta (lumateperone) capsules (AP letter dated 12/20/2019).
2. The Agency agrees with the Applicants submitted changes.
3. I recommend that an approval letter be issued for these pending supplemental applications.

Tiffanie Taylor, PharmD
Regulatory Project Manager Date

Hiren Patel, PharmD, MS, RAC
Chief, Project Management Staff Date

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/s/

TIFFANIE A TAYLOR
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HIREN PATEL
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MEMORANDUM

REVIEW OF REVISED LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 15, 2021
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 209500/S-005 and S-006
Product Name and Strength:	Caplyta (lumateperone) capsules, 42 mg
Applicant/Sponsor Name:	Intra-Cellular Therapies, Inc.
OSE RCM #:	2021-710-1 (S-005) and 2021-711-1 (S-006)
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA 1 Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised trade blister carton labeling, received on December 14, 2021 (via email), for Caplyta. The Division of Psychiatry (DP) requested that we review the revised carton labeling for Caplyta (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous labels and labeling review.[a]

2 CONCLUSION

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

[a] Holmes L. Labels and Labeling Review for Caplyta (NDA 209500/S-005 and S-006). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 Nov 03. RCM No.: 2021-710 (S-005) and 2021-711 (S-006).

APPENDIX A. IMAGE OF CARTON LABELING RECEIVED ON DECEMBER 14, 2021

Carton Labeling (not to scale)

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/s/

LORETTA HOLMES
12/15/2021 04:09:27 PM

SEVAN H KOLEJIAN
12/15/2021 06:24:09 PM

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

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

Memorandum

Date: November 17, 2021

To: Michelle Horner, M.D., Clinical Reviewer
Division of Psychiatry (DP)

Tiffanie Taylor, PharmD, Regulatory Project Manager, (DP)

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

From: Domenic D'Alessandro, PharmD, MBA, BCPS, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

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

NDA: 209500 / Supplements 05 & 06

In response to DP's consult request dated April 6, 2021, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for CAPLYTA® (lumateperone) capsules, for oral use. These supplements (S-05 and S-06) pertain to the addition of new indications of depressive episodes associated with bipolar I or II disorder in adults for monotherapy and adjunctive therapy with lithium or valproate and provide for revisions to sections 7 and 12.3 of the labeling.

PI: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DP (Kimberly Updegraff) on November 11, 2021, and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on November 15, 2021.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on September 21, 2021, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Domenic D'Alessandro at (301) 796-3316 or domenic.dalessandro@fda.hhs.gov.

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/s/

DOMENIC G DALESSANDRO
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 15, 2021
To:	Tiffanie Taylor, PharmD Regulatory Project Manager **Division of Psychiatry (DP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Domenic D'Alessandro, PharmD, MBA, CDE Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	CAPLYTA (lumateperone)
Dosage Form and Route:	Capsules, for oral use
Application Type/Number:	NDA 209500
Supplement Number:	S-005 and S-006
Applicant:	Intra-Cellular Therapies, Inc.

1 INTRODUCTION

On February 17, 2021, Intra-Cellular Therapies, submitted for the Agency's review two Prior Approval Supplements-Efficacy (PAS-005 and S-006), to the New Drug Application (NDA) for CAPLYTA (lumateperone) capsules, for oral use, to support the use of CAPLYTA (lumateperone) for the treatment of:

- Depressive episodes associated with Bipolar I or Bipolar II Disorder (bipolar depression) in adults as monotherapy.
- Depressive episodes associated with Bipolar I or Bipolar II Disorder (bipolar depression) in adults as adjunctive therapy with lithium or valproate.

The adjunctive therapy bipolar depression sNDA (S-006) was submitted under separate cover on February 17, 2021 (Sequence No.: 0110) and will cross-reference back to the information and data provided in the monotherapy bipolar depression sNDA with the exception of select Module 1 documents and Module 2.7.3 Clinical Summary of Efficacy, as indicated in the Reviewer's Guide.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry (DP) on April 6, 2021, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for CAPLYTA (lumateperone) capsules, for oral use.

2 MATERIAL REVIEWED

- Draft CAPLYTA (lumateperone) MG received on February 17, 2021, and received by DMPP and OPDP on November 11, 2021.
- Draft CAPLYTA (lumateperone) Prescribing Information (PI) received on February 17, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 11, 2021.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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11/15/2021 12:15:24 PM

Clinical Inspection Summary

Date	10/12/2021
From	Cara Alfaro, Pharm.D., Clinical Analyst Phillip Kronstein, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief/Acting Division Director Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Tiffanie Taylor, Regulatory Project Manager Michelle Horner, M.D., Medical Officer Jean Kim, M.D., Team Leader Division of Psychiatry Office of Neuroscience
NDA #	209500 S-5 and S-6
Applicant	Intra-Cellular Therapies, Inc.
Drug	Lumateperone
NME	No
Proposed Indications	Depressive episodes associated with bipolar I or II disorder in adults as monotherapy or as adjunctive therapy with lithium or valproate
Consultation Request Date	3/29/2021
Summary Goal Date	10/15/2021
Priority/Standard Review	Standard
Action Goal Date	12/17/2021
PDUFA Date	12/17/2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Hassman, Malik, Riesenberg, and Romain were inspected in support of this NDA and covered Protocols ITI-007-402 and ITI-007-404. The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

II. BACKGROUND

Lumateperone (Caplyta®) oral capsules were approved in 12/2019 for the treatment of schizophrenia in adults. The sponsor submitted two efficacy supplements (NDA 209500 S-5 and S-6) to support the efficacy and safety of lumateperone for the treatment of depressive episodes associated with bipolar I or II disorder in adults as monotherapy (S-5) or adjunctive therapy with lithium or valproate (S-6).

The sponsor submitted two Phase 3 studies, Protocols ITI-007-402 and ITI-007-404, to support the safety and efficacy of lumateperone for the treatment of depressive episodes associated with bipolar I or II disorder in adults as monotherapy or adjunctive therapy with lithium or valproate.

Protocol ITI-007-402 (adjunctive therapy)

Title: "A Phase 3, randomized, double-blind, placebo-controlled, multi-center study to assess the efficacy and safety of ITI-007 adjunctive to lithium or valproate in the treatment of patients with major depressive episodes associated with bipolar I or bipolar II disorder (bipolar depression)"

Subjects: 528

Sites: 89 sites in 5 countries; United States (46 sites) and Eastern Europe (43 sites)

Study Initiation and Completion Dates: 3/7/2016 to 7/2/2020

This was a randomized, double-blind, placebo-controlled study in subjects with bipolar depression who have had inadequate response to their depression symptoms and are currently taking lithium or valproate. Included were male or female subjects 18 to 75 years of age; diagnosis of bipolar I or bipolar II disorder per DSM-5 confirmed by SCID-5-CT; the start of the current major depressive episode is at least 2 weeks but not more than 6 months prior to screening; MADRS total score ≥20 at screening and baseline; Clinical Global Impression Scale of Bipolar Illness – Severity of Illness (CGI-BP-S) depression and overall scores each ≥4 at screening and baseline; lifetime history of at least 1 bipolar manic episode or mixed episode (bipolar I) or hypomanic episode (bipolar II); Young Mania Rating Scale (YMRS) total score ≤12 at screening and baseline; minimum of 28 days of treatment with either lithium (0.4 to 1.5 mEq/L at screening), valproate (≥25 mcg/mL at screening) and inadequate response of depressive symptoms. Excluded were subjects with a decrease in MADRS total score of ≥25% between screening and baseline visits; significant risk for suicidal behavior; hospitalization for mania within 30 days of screening; rapid cycler; or treatment-resistant bipolar depression.

The study was comprised of three phases:

Screening (2 weeks)
Screening procedures were performed to determine eligibility and discontinuation of current antidepressant treatment and/or other psychotropic medications. Subjects were to remain on lithium or valproate for the duration of the study.

Subject eligibility was determined through a formal adjudication process in which screening and baseline data was reviewed by an independent clinical review team appointed by the sponsor.

Double-blind Treatment Period (6 weeks)
Subjects were randomized (1:1:1) to one of three treatment arms, added to their current therapy (lithium or valproate):

- ITI-007 (lumateperone) 40 mg once daily in the evening
- ITI-007 (lumateperone) 60 mg once daily in the evening
- Placebo once daily in the evening

Randomization was stratified for concomitant medication (lithium or valproate) and diagnosis (bipolar I or bipolar II disorder).

Safety Follow-up Period
Subjects returned to the clinic for a safety follow-up visit at Week 8, approximately 2 weeks after the last dose of investigational product.

The primary efficacy endpoint was the change from baseline in the MADRS total score to Day 43. The key secondary efficacy endpoint was the change from baseline in the CGI-BP-S-Depression score to Day 43.

Protocol ITI-007-404 (monotherapy)

Title: "A Phase 3, randomized, double-blind, placebo-controlled, multi-center study to assess the efficacy and safety of lumateperone monotherapy in the treatment of patients with major depressive episodes associated with bipolar I or bipolar II disorder (bipolar depression) conducted globally"

Subjects: 377

Sites: 54 sites in 6 countries; United States (14 sites), Eastern Europe (37 sites), and Latin America (3 sites)

Study Initiation and Completion Dates: 3/7/2016 to 7/2/2020

This was a randomized, double-blind, placebo-controlled study in subjects with bipolar depression. The inclusion criteria were essentially the same as Protocol ITI-007-402 with the exception that diagnosis was confirmed by the M.I.N.I. International Neuropsychiatric Interview, subjects had to have a CGI-BP-S total score $\geq$4 at screening and baseline (no criteria for CGI-BP-S depression score), and subjects were not taking concomitant lithium or valproate during the study. The exclusion criteria, as noted above for Protocol ITI-007-402, also applied to this protocol.

The study was comprised of three phases:

Screening (2 weeks)
Screening procedures were performed to determine eligibility and discontinuation of current antidepressant treatment and/or other psychotropic medications. Adjudication of subject eligibility was determined by the Medical Monitor.

Double-blind Treatment Period (6 weeks)
Subjects were randomized (1:1) to one of two treatment arms:
- ITI-007 (lumateperone) 60 mg once daily in the evening
- Placebo once daily in the evening

Randomization was stratified for diagnosis (bipolar I or bipolar II disorder).

Safety Follow-up Period
Subjects returned to the clinic for a safety follow-up visit at Week 8, approximately 2 weeks after the last dose of investigational product.

The primary efficacy endpoint was the change from baseline in the MADRS total score to Day 43. The key secondary efficacy endpoint was the change from baseline in the CGI-BP-S total score to Day 43.

Rationale for Site Selection

The clinical sites were chosen primarily based on risk ranking in the site selection tool, numbers of enrolled subjects, prior complaints, and prior inspectional history.

III. RESULTS

1. **Howard Hassman, DO**
Site #405
Hassman Research Institute
175 Cross Keys Road
Centennial Center, Suite 107
Berlin, NJ 08009
Inspection Dates: 4/15/2021 – 5/3/2021

At this site for Protocol ITI-007-402, 27 subjects were screened, 10 were randomized, and 7 subjects completed the study. Three subjects discontinued the study due to protocol deviation, withdrawal by subject, and loss to follow-up. Subject (b) (6), randomized to lumateperone 28 mg, was discontinued from the study due to a protocol deviation reported as a positive urine toxicology screen for cocaine at the baseline visit. This subject was discontinued from the study after receiving study drug for 7 days. It is not known when the site received the results from the urine toxicology screen from the central laboratory, Q2 Solutions.

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 enrolled subjects 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, key secondary efficacy data (Clinical Global Impression Scale of Bipolar Illness-Severity of Illness [CGI-BP-S], and primary efficacy data (Montgomery Asberg Depression Rating Scale [MADRS]).

The MADRS and CGI-BP-S scale scores were entered by site raters into an electronic tablet, Microsoft Surface Pro 3, provided by the vendor, (b) (4) After ratings were completed and submitted, (b) (4) would email the scores to the site as an attached pdf document. The site printed out these documents and filed them in the subject study binders. Scores from these printed documents were used to verify MADRS and CGI-BP-S scores against sponsor line listings; no discrepancies were identified.

There was no evidence of underreporting of adverse events. No serious adverse events were reported for this site.

Complaint Follow-Up (C #9790)
On 9/1/2020, OSI received a complaint alleging that employees at Hassman Research Institute were asked to alter subject data to ensure eligibility in clinical trials. The complainant alleged that employees were asked to switch blood and urine samples and change blood pressure results to meet protocol eligibility criteria. The complainant did not specify a particular clinical trial.

ORA was asked to follow up on this complaint. No evidence was noted during the inspection to verify the complaint. The (b) (4) who had participated in (b) (4) covered by this inspection (Protocols ITI-007-402 (b) (4)) were no longer with Hassman Research Institute and could therefore not be interviewed.

Reviewer comments: A sensitivity analysis conducted by Biometrics in preparation for site selection for inspections noted that exclusion of this site did not change the efficacy results.

2. Mohd Malik, MD
Site #783
PsychCare Consultants Research
5000 Cedar Plaza Parkway, Suite 220-A
St. Lois, MO 63128
Inspection Dates: 5/18/2021 – 5/21/2021

At this site for Protocol ITI-007-404, 19 subjects were screened, 14 were randomized, and 13 subjects completed the study. One subject, randomized to placebo, discontinued the study

approximately one week after randomization due to loss to follow-up (per site enrollment log) although the sponsor line listing indicates that the subject withdrew due to "self-reported lack of efficacy". It is not known what the site entered into the eCRF as the reason for early discontinuation as case report forms (CRFs) for this subject were not 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 all enrolled subjects 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, key secondary efficacy data (CGI-BP-S), and primary efficacy data (MADRS).

The MADRS and CGI-BP-S scale scores were recorded by site raters on paper forms. Scores from the paper forms were used to verify MADRS and CGI-BP-S scores against sponsor line listings; no discrepancies were identified.

There was no evidence of underreporting of adverse events. No serious adverse events were reported for this site.

3. Robert Riesenberg, MD
Site #436
Atlanta Center for Medical Research
501 Fairburn Road SW
Atlanta, GA 30331
Inspection Dates: 6/21 – 6/24/2021

At this site for Protocol ITI-007-402, 17 subjects were screened, 12 were randomized, and 6 subjects completed the study. The enrollment and visit log at the site did not include reasons for the six subjects who discontinued the study. Per sponsor line listings, these subjects discontinued due to adverse events (2), protocol deviations (2, *see further information below*), loss to follow-up (1), and withdrawal of consent (1). The discontinuations due to adverse events included abdominal pain (Subject (b) (6) randomized to lumateperone 60 mg) and nausea/vomiting (Subject (b) (6) randomized to lumateperone 60 mg).

According to the sponsor, Subject (b) (6), randomized to lumateperone 40 mg, was discontinued from the study due to a protocol deviation. The protocol deviation line listing (Listing 16.2.2.2 Major Protocol Deviations) noted the deviation category as "≥ 3 consecutive missed doses of study drug". However, a description of the deviation in this data listing noted that "per sponsor request due to elevated labs, subject did not take IP (b) (6). Due to missed doses, subject was terminated". This reviewer reviewed laboratory data and found that this subject had ALT, AST, and GGT within normal limits at baseline (b) (6), with an increase to 1035 U/L, 578 U/L, and 109 U/L, respectively, noted on (b) (6) (Visit 3). An

unscheduled visit occurred on (b) (6) in which the ALT and GGT were still elevated (220 U/L, 113 U/L, respectively) but the AST had returned to normal levels. The subject's bilirubin remained within normal limits throughout. This subject continued to receive lumateperone with these elevated LFTs; his last dose was on (b) (6) Based on this information, the more appropriate category for discontinuation should have been adverse event (increase in LFTs). Since the category for discontinuation was a protocol deviation, neither a narrative nor CRFs were submitted to the NDA. The FDA field investigator did not identify this issue during the inspection, and no further information is available regarding when the clinical investigator informed the sponsor of this event or what communications the clinical investigator had with the subject regarding study drug dosing.

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 enrolled subjects 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, key secondary efficacy data (CGI-BP-S), and primary efficacy data (MADRS).

The MADRS and CGI-BP-S scale scores were entered by site raters into an electronic tablet, Microsoft Surface Pro 3, provided by the vendor, (b) (4) After ratings were completed and submitted, (b) (4) would email the scores to the site as an attached pdf document. The site printed out these documents and filed them in the subject study binders. Scores from these printed documents were used to verify MADRS and CGI-BP-S scores against sponsor line listings; no discrepancies were identified.

There was no evidence of underreporting of adverse events. No serious adverse events were reported for this site.

Reviewer comments: The information regarding the discontinuation of Subject (b) (6) due to increased LFTs was provided to the review division. The LFT data for this subject was included with the safety data in the NDA submission.

4. Josette Romain, MD
Site #784
Family Psychiatric Services
2725 Rebecca Lane, Suite 107
Orange City, FL 32763
Inspection Dates: 8/9 – 8/11/2021

At this site for Protocol ITI-007-404, 45 subjects were screened, 14 were randomized, and 11 subjects completed the study. Three subjects discontinued the study due to physician decision, loss to follow-up, and an adverse event of anxiety in Subject (b) (6), randomized to placebo.

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 enrolled subjects 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, key secondary efficacy data (CGI-BP-S), and primary efficacy data (MADRS).

The MADRS and CGI-BP-S scale scores were recorded by site raters on paper forms. Scores from the paper forms were used to verify MADRS and CGI-BP-S scores against sponsor line listings; no discrepancies were identified.

There was no evidence of underreporting of adverse events. No serious adverse events were reported for this site.

{See appended electronic signature page}

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Clinical Analyst
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Office of Scientific Investigations

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Central Document Room/NDA #209500 S-5 S-6
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OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
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OSI/DCCE/GCPAB/Reviewer/Cara Alfaro
OSI/GCPAB Program Analyst/Yolanda Patague

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.

/s/

CARA L ALFARO
10/12/2021 10:09:00 AM

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10/12/2021 10:27:35 AM

KASSA AYALEW
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LABELS AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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***

Date of This Review:	November 3, 2021
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 209500/S-005 and S-006
Product Name and Strength:	Caplyta (lumateperone) capsules, 42 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Intra-Cellular Therapies, Inc. (Intra-Cellular Therapies)
FDA Received Dates:	February 17, 2021 and September 21, 2021
OSE RCM #:	2021-710 (S-005) and 2021-711 (S-006)
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA 1 Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

Intra-Cellular Therapies, Inc. submitted two prior approval efficacy supplements on February 17, 2021 to support the use of Caplyta (lumateperone) 42 mg capsules for the treatment of:

- Depressive episodes associated with Bipolar I or Bipolar II Disorder (bipolar depression) in adults as monotherapy. (S-005)
- Depressive episodes associated with Bipolar I or Bipolar II Disorder (bipolar depression) in adults as adjunctive therapy with lithium or valproate. (S-006)

Subsequently, the Division of Psychiatry (DP) requested that we review the proposed Caplyta prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

Per the Division, both supplements will be reviewed together.

1.1 REGULATORY HISTORY

With Supplements S-005 and S-006, Intra-Cellular Therapies submitted the following container labels and carton labeling:

February 17, 2021:

- Draft 30-count Trade Carton (for 3 x 10-count blister packs)

September 21, 2021[a]:

- Draft 7-count Sample Carton
- Draft 7-count Sample Bottle Label
- Draft 30-count Trade Bottle Label

[a] We previously reviewed the draft 7-count sample carton, draft 7-count sample bottle label, and draft 30-count trade bottle label under CMC supplement S-007 [Holmes, L. Label and Labeling Review for Caplyta (NDA 209500/S-007). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Jul 12. RCM No.: 2021-742]. According to the Applicant: "*As requested in the September 10, 2021 approval letter for S-007, we are amending the content of labeling for the pending Bipolar Depression efficacy supplements, S-005 and S-006, to include the changes approved under the CMC CBE-30 supplement, S-007. Specifically, we have updated the package insert to include the bottle configuration in Section 16 How Supplied/Storage and Handling. In addition, carton and container labeling is being provided to support the approved sample and trade bottle configurations.*" We note that the container labels and carton labeling were updated to include a Medication Guide statement.

2 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
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 or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed trade carton labeling (for 3 x 10-count blister packs) may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for Intra-Cellular Therapies, Inc. Our review of the proposed trade bottle label, professional sample bottle label, professional sample carton labeling, and Prescribing Information did not identify areas of vulnerability that may lead to medication errors.

4 RECOMMENDATIONS FOR INTRA-CELLULAR THERAPIES, INC

Table 2. Identified Issues and Recommendations for Intra-Cellular Therapies, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Trade Carton Labeling			
1.	The established name does not appear to be at least ½ the size of the proprietary name.	The size of the established name does not appear to comply with 21 CFR 201.10(g)(2).	Ensure the established name is at least ½ the size of the proprietary name as required per 21 CFR 201.10(g)(2).
2.	The statement “For oral use” is not on the carton labeling.	The route of administration should be on the carton labeling.	Add the statement “For oral use” to the principal display panel of the carton labeling.

Table 2. Identified Issues and Recommendations for Intra-Cellular Therapies, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	The word "Recommended" is not included in the statement of dosage which states: "Dosage: See package insert for dosing and full Prescribing Information".	The dosage statement is not consistent with the Prescribing Information (PI), Section 2.1, which states "Recommended Dosage".	To ensure consistency, revise the statement of dosage to read "Recommended Dosage: See package insert for dosing and full Prescribing Information" per 21 CFR 201.55.
4.	The Medication Guide (MG) statement lacks prominence due to its small size.	The small size of the MG decreases its readability.	Increase the prominence of the MG statement by increasing its size. Additionally, consider moving the MG statement so that it is positioned in the area below the strength.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Caplyta that Intra-Cellular Therapies, Inc submitted on September 21, 2021.

Table 3. Relevant Product Information for Caplyta	
Initial Approval Date	12/20/2019
Active Ingredient	lumateperone
Indication	Treatment of schizophrenia in adults *Proposed:* • Depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults as monotherapy. • Depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults as adjunctive therapy with lithium or valproate.
Route of Administration	Oral
Dosage Form	Capsules
Strength	42 mg
Dose and Frequency	The recommended dosage of Caplyta is 42 mg once daily with or without food.
How Supplied	Bottles of 30 Box of 30 (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].

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 1, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms (NDA 209500, lumateperone). Our search identified four previous reviews and we considered our previous recommendations to see if they are applicable for this current review.

- Holmes, L. Labels and Labeling Review for Caplyta (NDA 209500). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2019 May 23. RCM No.: 2018-2109.

- Holmes, L. Labels and Labeling Review Memo for Caplyta (NDA 209500). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2019 Oct 28. RCM No.: 2018-2109-1.

- Holmes, L. Labels and Labeling Review for Caplyta (NDA 209500/S-007). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 Jul 12. RCM No.: 2021-742.

- Holmes, L. Labels and Labeling Review Memo for Caplyta (NDA 209500/S-007). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 Jul 12. RCM No.: 2021-742-1.

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,[b] along with postmarket medication error data, we reviewed the following Caplyta labels and labeling submitted by Intra-Cellular Therapies, Inc.

- Trade container label (30-count bottle) received on September 21, 2021
- Trade carton labeling (for 3 X 10-count blister cards) received on February 17, 2021
- Professional sample container label received on September 21, 2021
- Professional sample carton labeling received on September 21, 2021
- Prescribing Information (image not shown) received on September 21, 2021, available from \\CDSESUB1\evsprod\nda209500\0137\m1\us\draft-labeling-tracked.pdf

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

Container Labels

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LORETTA HOLMES
11/03/2021 03:18:44 PM

SEVAN H KOLEJIAN
11/03/2021 04:08:18 PM